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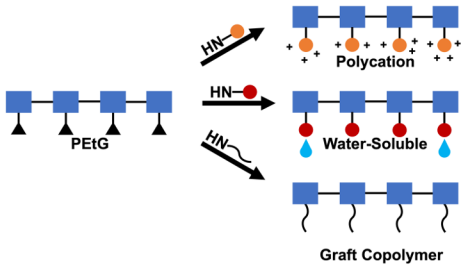


Abstract

Self-immolative polymers (SIPs) are a class of stimuli-responsive materials that undergo controlled end-to-end depolymerization in response to stimuli. Their unique degradation and amplification properties have made them of interest for a diverse array of applications including sensors, vehicles for controlled release, and transient objects. Thus far, a limited number of SIP backbones exists, each with its own advantages and limitations. We report here the preparation and study of polyglyoxylamides (PGAms) as a new class of SIPs. PGAms were synthesized by simple post-polymerization modifications of poly(ethyl glyoxylate) (PEtG). While retaining the important stimuli-responsive depolymerization properties of polyglyoxylates, PGAms exhibited

much different thermal properties, and some were even water-soluble. Furthermore, a depolymerizable PGAm analogue of poly(ethylene glycol) was prepared, demonstrating the capability to synthesize more complex PGAm graft copolymers. Overall, PGAms are a new class of SIPs with unique combinations of physical, thermal, and degradative properties that provide avenues for novel applications.

Introduction

Stimuli-responsive polymers are a class of materials that can undergo changes in their physical or chemical properties when exposed to specific stimuli. They have been explored for a wide range of applications from smart coatings to drug delivery systems.[1-4] For example, thermo-responsive polymers such as poly(*N*-isopropylacrylamide) undergo entropically-driven aggregation and precipitation above their lower critical solution temperatures.[5] This property has been exploited for the development of hydrogel valves in microfluidic channels[6] and for the controlled release of drugs.[7-8] In other cases, stimuli lead to polymer degradation. For example, polyacetals undergo selective degradation at acidic pH. Various polyacetals have been reported[9-11] and have shown promise for targeted drug delivery *in vivo*.

Self-immolative polymers (SIPs) are a recently developed subset of stimuli-responsive degradable polymers that undergo end-to-end depolymerization in response to stimuli. Most SIPs possess stabilizing end-caps at their termini that can be cleaved off by specific stimuli. Cleavage initiates a cascade of reactions resulting in the conversion of the polymer into small molecules (Figure 1a–c).[12] Since their introduction in 2008,[13] significant developments have been reported including the introduction of backbones such as polycarbamates,[13-14] poly(benzyl ether)s,[15] and polyacetals[16-17] that depolymerize by different mechanisms such as eliminations,[13, 15]

cyclizations,[18] combinations of eliminations and cyclizations,[14, 19] or based on low polymer ceiling temperatures.[16-17] Additionally, various end-caps have been incorporated onto SIPs, enabling their depolymerization to be initiated by different stimuli including light,[20-21] heat,[22-23] changes in redox[21, 24-25] or pH[25-26] conditions, and in response to the activity of specific enzymes.[13, 27] Furthermore, the utility of SIPs in applications such as transient plastics,[16, 28] degradable microcapsules,[26, 29] drug delivery vehicles,[21, 30-32] microscale pumps,[33] and sensors[34-38] has been demonstrated.

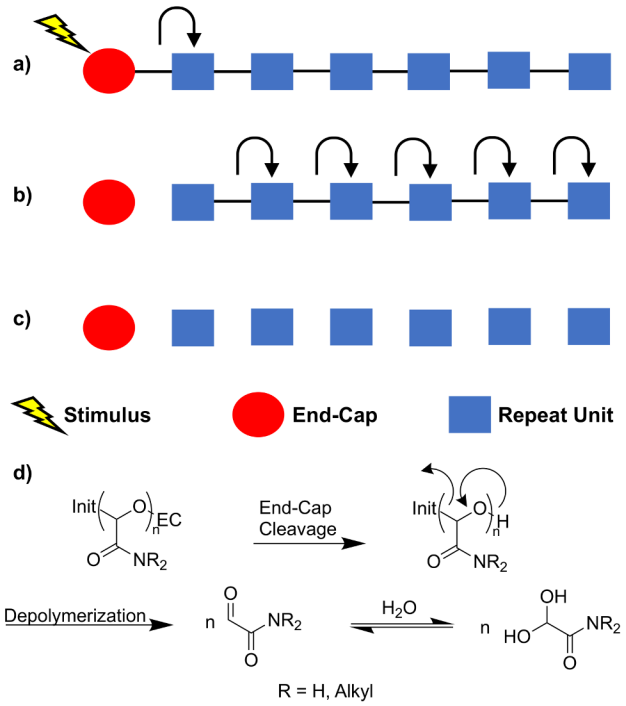


Figure 1. a) SIPs are stabilized with an end-cap that can be cleaved off in the presence of a particular stimulus; b) Removal of the end-cap leads to a cascade depolymerization of the polymer chain; c) The depolymerization products include the end-cap and repeat units of the polymer, which may be the original monomers or derivative products depending on the depolymerization mechanism; d) A polyglyoxylamide depolymerizes upon cleavage of the end-cap (Init = polymerization initiator; EC = end-cap).

Our group reported polyglyoxylates as a class of SIPs.[17] Polyglyoxylates have advantages including their preparation from commercially available monomers or monomers that can be synthesized from readily available precursors such as fumaric or maleic acid. In addition, the depolymerization product glyoxylic acid hydrate is an intermediate in the glyoxylic acid cycle and is non-harmful to the environment.[39] Based on their properties and depolymerization behaviour, polyglyoxylates are finding applications in areas such as smart coatings[38, 40] and drug delivery vehicles.[30-32] Polyglyoxylates inherently have pendant ester groups at each repeat unit, and the eventual hydrolysis of these esters reveals carboxylic acids that can intramolecularly catalyze backbone acetal hydrolysis, leading to depolymerization. Thus, polyglyoxylates have a limited lifetime even in their non-triggered state, which can be advantage or limitation depending on the application. All of the previously reported polyglyoxylates have been insoluble in water.[17, 32, 39, 41-42]

The replacement of the ester pendant groups of polyglyoxylates with amides should slow side chain hydrolysis, stabilizing the polymers in their untriggered state, while at the same time yielding polymers with different physical and thermal properties that are capable of triggered end-to-end depolymerization (Figure 1d). Thus, we report here the syntheses of polyglyoxylamides (PGAms), a new class of SIPs. Several different amines were used to prepare PGAms from poly(ethyl glyoxylate) (PEtG) using mild post-polymerization modification conditions to provide an array of new properties and functions while retaining the abilities of the polymers to depolymerize in response to stimuli. For example, relative to 25 °C, the highest glass transition temperature (T_g) reported for a polyglyoxylate,[17] the measured T_g values of the studied PGAms ranged from 39–90 °C. Additionally, several of the new PGAms demonstrated water-solubility.

Finally, using amine-terminated oligo(ethylene glycol) (OEG), a PGAm analogue of poly(oligo(ethylene glycol methyl ether) methacrylate) (POEGMA), a graft copolymer analogue of poly(ethylene glycol) (PEG) that exhibits the favorable stealthy properties of PEG,[43] was synthesized.

Experimental

General procedures and additional procedures are provided in the supporting information.

Synthesis of PGAm-NMe-MMT (Representative Polyglyoxylamide Synthesis). PEtG-MMT (2.1 g) was placed in a round-bottom flask and stoppered with a rubber septum. The flask was evacuated. After charging the flask with nitrogen at atmospheric pressure, 21 mL of dry 1,4-dioxane was injected to give a 100 mg/mL polymer stock solution. From this solution, an aliquot was removed (2.5 mL, 250 mg of polymer, 2.4 mmol of ester, 1.0 equiv.) and placed into a flame-dried Schlenk flask filled with nitrogen at atmospheric pressure. An aliquot of methylamine solution (6.5 mL, 13 mmol, 5.4 equiv.) was then added to the flask. The flask was closed off from the nitrogen line and the reaction mixture was stirred for 48 h. Removal of the solvent, ethanol, and unreacted amine under vacuum gave the crude product. This product was subsequently purified by dissolution in minimal CH_2Cl_2 and precipitation in 100 mL of *n*-pentane. After decanting the liquid, the precipitate was dried under vacuum to afford 210 mg of an off-white powder. Yield: 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67–8.64 (m, 1H), 5.73 (s, 1H), 2.79 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 166.3–169.0, 94.7–98.9, 26.3. FT-IR: 3294, 3098, 2942, 1663, 1543 cm^{-1}. SEC (DMF, PMMA): M_n = 54.1 kg/mol, M_w = 77.6 kg/mol, $Đ$ = 1.4. T_g = 90 ºC.

Depolymerization of PGAm-MMTs. PGAm-NEt-MMT, **PGAm-N*n*Pr-MMT**, **PGAm-N*i*Pr-MMT**, and **PGAm-Pyrr-MMT** were each dissolved in 1.1 mL of 9:1 CD_3CN:D_2O. **PGAm-NMe-MMT** and **PGAm-DMAE-MMT** were each dissolved in 1.1 mL of 9:1 D_2O:CD_3CN. All polymer solutions were 1% w/v in concentration. Each solution was separated into two 550 µL aliquots, which were each placed into an NMR tube. In one of the two aliquots, 30 µL of glacial acetic acid was added to give a 0.9 M concentration of acid. No acid was added to the second aliquot (control). The NMR tubes were promptly sealed and stored at room temperature. Depolymerization was monitored by acquiring ^{1}H NMR spectra of the samples at specific time points and examining the integration ratios between the peaks corresponding to the polymer backbone methine protons at ~5.5–5.6 ppm and the methine proton of the monomer hydrate (depolymerization product) at ~5.0–5.3 ppm.

Depolymerization of PGAm-Ts. A 0.1 M deuterated citrate buffer was prepared by dissolving 190 mg of citric acid into 10 mL of D_2O and correcting the pH to 3.0 using NaOH. A 0.1 M deuterated phosphate buffer was prepared by dissolving 52 mg of KH_2PO_4 and 110 mg of K_2HPO_4 into 10 mL of D_2O and correcting the pH to 7.4 with KOH. **PGAm-NMe-T**, **PGAm-DMAE-T**, and **PGAm-Pyrr-T** were each dissolved in 600 µL of the pH 3.0 buffer. Additionally, the polymers were each dissolved in 600 µL of the pH 7.4 buffer. All polymer solutions were 1% w/v in concentration. Each solution was placed into an NMR tube and the tubes were promptly sealed and stored at room temperature. Depolymerization was monitored by acquiring ^{1}H NMR spectra of the samples at specific time points and examining the integration ratios between the polymer backbone methine protons at ~5.5–5.6 ppm and the methine proton of monomer hydrate (depolymerization product) at ~5.3–5.5 ppm.

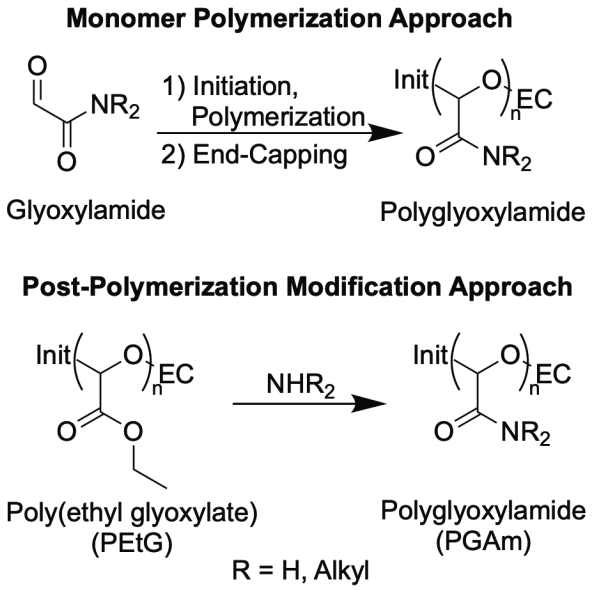
Synthesis of PGAm-OEG-T. PEtG-T (210 mg of polymer, 2.1 mmol of ester, 1.0 equiv.) was dissolved in a pressure tube using 10 mL of dry 1,4-dioxane. **OEG-NH_2** (1.2 g, 2.5 mmol, 1.0 equiv.) was subsequently added and the flask was capped. The reaction mixture was then heated at 60 °C for 9 days. The solution was concentrated, dissolved in 10 mL of $CHCl_3$, precipitated into 100 mL of Et_2O, and stirred for 20 min before allowing the precipitate to settle. The solvent was then decanted off and the purification procedure was repeated two times. The precipitate was then dried under vacuum to afford 720 mg of the product. Yield = 57%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–8.70 (m, 100H), 7.37–7.45 (s, 12H), 7.13–7.37 (m, 202H) 5.67 (s, 88H), 3.11–3.93 (m, 4270H). $^{13}C\{^1H\}$ NMR ($(CD_3)_2SO$, 100 MHz): δ 71.3, 69.8, 58.0. FT-IR: 3392, 2877, 1652, 1559 cm^{-1}. SEC (DMF, PMMA): M_n = 58.5 kg/mol, M_w = 97.4 kg/mol, $Đ$ = 1.7. T_m = 23 ºC.

Depolymerization of PGAm-OEG-T. PGAm-OEG-T was dissolved at 1% w/v at pH 3.0 and pH 7.4 and depolymerization was monitored by ^{1}H NMR spectroscopy using the deuterated buffers and techniques described above in "Depolymerization of PGAm-Ts". Additionally, **PGAm-OEG-T** was dissolved in 5.0 mL of each buffer to create 0.5% w/v solutions at pH 3.0 and pH 7.4. These solutions were promptly sealed in vials and stored at room temperature. At specified time points, 300 μL of the solution was removed, filtered, and then directly injected for analysis by aqueous SEC. The chromatograms were monitored for changes in the polymer elution time and refractive index intensity over time.

Results and Discussion

Synthetic Approaches to Polyglyoxylamides. There are two potential approaches for synthesizing PGAms (Scheme 1). The first is the monomer polymerization approach, where

glyoxylamide monomers are synthesized and purified before being polymerized. While ensuring amide moieties at each repeat unit, the limitation of this approach is that each unique glyoxylamide would need to be synthesized and purified independently. The second approach to synthesize PGAms is the post-polymerization modification of polyglyoxylates. This approach has several advantages including the ease of synthesis of the PEtG precursor from commercially available monomer, the one-step amidation reaction of PEtG, and the ability to create a small library of different PGAms from a single batch of PEtG, allowing all of the PGAms to have the same degree of polymerization (DP_n) for structure-property comparisons. Post-polymerization modification by amidation has been noted to be an effective method when used to replace ester pendant groups on polymers.[44] Therefore, to synthesize self-immolative PGAms for study, post-polymerization modification was pursued.

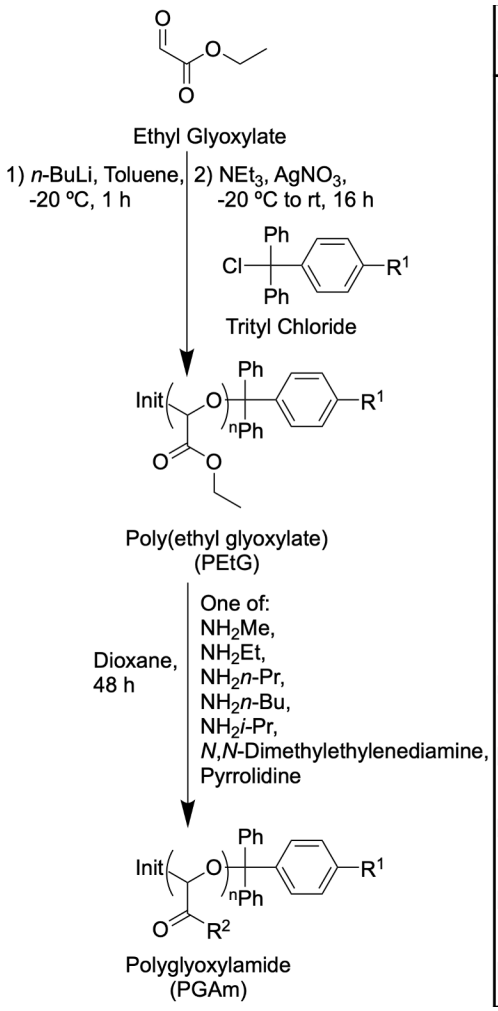


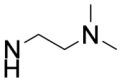
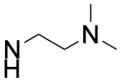
Scheme 1. Synthetic approaches for obtaining PGAms.

Synthesis of 4-Monomethoxytrityl End-Capped PEtG for Post-Polymerization Modification. To synthesize different PGAms via post-polymerization modification, a PEtG precursor with an

appropriate stimuli-responsive end-cap was needed. First, PEtG with a 4-monomethoxytrityl end-cap (**PEtG-MMT**) was targeted (Scheme 2). This end-cap was selected because prior work has shown it to serve as an acid-sensitive end-cap for PEtG.[25] In addition, unlike many other reported end-caps that are conjugated to the PEtG terminus by a carbonate or carbamate linkage,[17, 25, 30] the trityl moiety connects to the polymer via an ether linkage. An ether linkage is not susceptible to cleavage in the post-polymerization modification conditions as it does not possess a carbonyl moiety for nucleophilic attack by the amines.

PEtG-MMT was synthesized by a modified version of our previously reported method (Scheme 2).[45] *n*-Butyl lithium was used to initiate an anionic polymerization of ethyl glyoxylate in toluene at -20 °C. In addition to 4-monomethoxytrityl chloride as an end-cap and triethylamine (NEt_3), $AgNO_3$ was added as Ag^+ can scavenge Cl^- ions, thereby enhancing the end-capping yield. Purification resulted in a colourless tacky solid. Analysis by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopic methods confirmed the structure of the polymer by comparison with previous reports (Figures S1, S15, and S29).[17, 25] Size-exclusion chromatography (SEC) in *N*,*N*-dimethylformamide (DMF) relative to poly(methyl methacrylate) (PMMA) standards suggested that **PEtG-MMT** had a number average molar mass (M_n) of 51.8 kg/mol and a dispersity ($Đ$) of 1.4. Because of the polymer's high molar mass, end-group analysis by ^{1}H NMR spectroscopy could not be used to determine the DP_n of the **PEt-MMT** or any of the PGAms subsequently synthesized from it. However, thermogravimetric analysis (TGA) confirmed that the polymer was effectively end-capped as it was stable to 170 °C, whereas uncapped PEtG was previously demonstrated to degrade at 84 °C during TGA.[17]



Polymer	R_1	R_2
PEtG-MMT	OMe	N/A
PGAm-NMe-MMT	OMe	NHMe
PGAm-NEt-MMT	OMe	NHEt
PGAm-N*n*Pr-MMT	OMe	NH*n*-Pr
PGAm-N*n*Bu-MMT	OMe	NH*n*-Bu
PGAm-N*i*Pr-MMT	OMe	NH*i*-Pr
PGAm-DMAE-MMT	OMe	
PGAm-Pyrr-MMT	OMe	
PEtG-T	H	N/A
PGAm-NMe-T	H	NHMe
PGAm-NEt-T	H	NHEt
PGAm-DMAE-T	H	
PGAm-Pyrr-T	H	

Scheme 2. Synthesis of PGAms (MMT = 4-monomethoxytrityl, T = trityl).

Synthesis of 4-Monomethoxytrityl End-Capped Polyglyoxylamides (PGAm-MMTs). To perform the post-polymerization modification, **PEtG-MMT** was dissolved in dry 1,4-dioxane, then reacted with a 5-fold molar excess of amine for 48 h to afford the corresponding **PGAm-MMT** (Scheme 2). Different primary amines including methylamine, ethylamine, *n*-propylamine, *n*-butylamine, and isopropylamine were used to investigate basic structure-property relationships among simple PGAms. Pyrrolidine was used as a secondary amine. Other secondary amines such as dimethylamine and diethylamine were also investigated in preliminary work but led to

incomplete conversion, suggesting that the ring structure of pyrrolidine is important for its reactivity. *N*,*N*-Dimethylethylenediamine was selected to introduce pendant pH-sensitive tertiary amine groups to the polymer. The polymers were first isolated by the removal of the volatile amines, ethanol, and solvent from the reaction mixtures under vacuum. The crude polymer residues were subsequently dissolved in minimal CH_2Cl_2 and precipitated in *n*-pentane. Decanting off the liquid and drying the precipitate under vacuum afforded the purified polymers.

The purified polymers were characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy to confirm that complete conversion to the amides had occurred (Figures S2–S8, S16–S22). Comparison of the ^{1}H NMR spectrum of **PEtG-MMT** to spectra of the **PGAm-MMTs** revealed several key differences (Figure 2). First, the peak corresponding to the backbone methine protons changed from a sharp multiplet at δ ~5.6 ppm in **PEtG-MMT** into a broad singlet in the **PGAm-MMTs**. In addition, the peaks corresponding to the ester CH_2 and CH_3 protons at δ 4.21 and 1.28 ppm respectively disappeared and new peaks corresponding to the functional groups on the amide appeared. For example, in the spectrum of **PGAm-NEt-MMT**, two new peaks at δ 3.25 and 1.13 ppm corresponding to the amide CH_2 and CH_3 protons respectively were observed. Finally, in all cases except for **PGAm-Pyrr-MMT** (tertiary amide), a broad multiplet appeared within the range of 7.50–9.50 ppm corresponding to the NH protons of the amide pendant groups. In the FT-IR spectra (Figure S29) the **PGAm-MMTs** had a characteristic C=O amide stretch at ~1650 cm^{-1}, in contrast with **PEtG-MMT**, which had a characteristic C=O ester stretch at ~1750 cm^{-1}. In addition, **PGAm-MMTs** synthesized from primary amines had peaks at ~3200 cm^{-1} corresponding to the N–H stretch of the amide pendant groups.

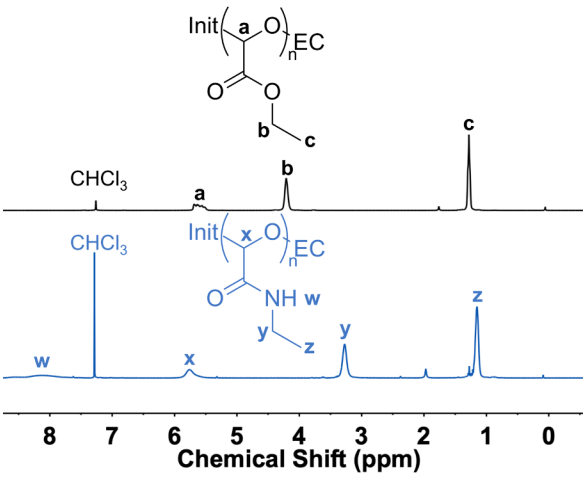


Figure 2. Comparison of the ^{1}H NMR spectra of **PEtG-MMT** (top) and **PGAm-NEt-MMT** (bottom) ($CDCl_3$, 400 MHz).

While spectral data confirmed successful conversion of the pendant esters to amides, SEC analysis was used to compare the sizes of the polymers (Figure 3). As discussed above, post-polymerization modification of **PEtG-MMT** from the same batch of polymer has the advantage of creating different polymers with the same DP_n and distribution of chain lengths. Indeed, all of the polymers, including **PEtG-MMT**, had similar $Đ$ values (Table 1). Furthermore, most of the polymers had very similar M_ns of ~60 kg/mol. The exception to this was **PGAm-Pyrr-MMT**, which had a measured M_n of 27.4 kg/mol. It is likely that **PGAm-Pyrr-MMT** has a smaller hydrodynamic volume in the DMF eluent than the rest of the polymers, which may relate to its unique tertiary amide structure. To confirm this, multi-angle laser light scattering (MALLS) was used with SEC to obtain the absolute molar masses of **PEtG-MMT** and **PGAm-Pyrr-MMT** (Table 1). In contrast to SEC, this MALLS analysis revealed the expected higher M_n for **PGAm-Pyrr-MMT** relative to the precursor polymer **PEtG-MMT**. Overall, spectral and SEC analyses confirmed that the post-polymerization modification of PEtG to form various PGAms via amidation is an easy and practical synthetic approach that does not cause significant polymer

degradation. Regarding solubility, three of the polymers (**PGAm-NMe-MMT**, **PGAm-DMAE-MMT**, and **PGAm-Pyrr-MMT**) were water-soluble at room temperature. This may provide access to different applications than polyglyoxylates, all of which so far have been water-insoluble.[17, 32, 39, 41-42]

Table 1. Summary of the physical and thermal properties of the 4-monomethoxytrityl end-capped polymers. For the SEC results, the values in parentheses were determined using MALLS rather than conventional calibration.

Polymer	**M_n (kg/mol)**	**M_w (kg/mol)**	***Đ***	**T_o (ºC)**	**T_g (ºC)**	**Water-Soluble**[b]
PEtG-MMT	51.8 (43.2)	73.6 (67.0)	1.4 (1.6)	170	-10	No
PGAm-NMe-MMT	54.1	77.6	1.4	133	90	Yes
PGAm-NEt-MMT	56.7	83.7	1.5	137	85	No
PGAm-N*n*Pr-MMT	62.4	92.8	1.5	136	68	No
PGAm-N*n*Bu-MMT	54.2	78.2	1.4	148	58	No
PGAm-N*i*Pr-MMT	73.6	99.2	1.3	130	[a]ND	No
PGAm-DMAE-MMT	60.0	89.2	1.5	141	39	Yes
PGAm-Pyrr-MMT	27.4 (62.6)	47.3 (88.1)	1.7 (1.4)	163	78	Yes

[a]Not detected within the range of the measurement (0–100 ºC); [b]At ambient temperature

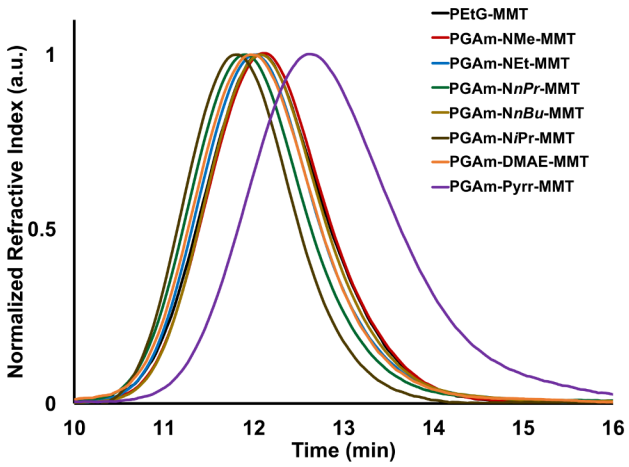


Figure 3. Overlay of the size exclusion chromatograms of the 4-monomethoxytrityl end-capped polymers.

Thermal Analysis of PGAm-MMTs. The thermal properties of the **PGAm-MMTs** were studied by TGA and differential scanning calorimetry (DSC). Based on TGA, the onset degradation temperatures (T_o) were at least 130 ºC for all of the polymers (Table 1 and Figure S33). In addition, all of the **PGAm-MMTs** underwent multi-step degradations in contrast to the one-step degradation of **PEtG-MMT**. This may relate to the varying volatilities and degradation pathways for the glyoxylamide depolymerization products in comparison with ethyl glyoxylate, which can readily evaporate above PEtG's T_o. DSC was performed up to 100–115 ºC, depending on the polymer, ensuring that the maximum temperature was at least 30 ºC less than the T_o. Notably, the T_gs of all of the **PGAm-MMTs** evaluated were much higher than that of **PEtG-MMT** (Table 1, Figures S36–S43). These higher T_g values likely result from structural features introduced by the amide pendant groups that hinder the movement of the polymer chains. For example, all of the PGAms with secondary amide pendant groups possess NH moieties that can participate in hydrogen bonding. Hydrogen bonding between polymer chains would hinder segmental motion, thus increasing the T_g. In addition, all of the PGAm pendant amide groups possess a C=N resonance

structure. The C=N bond contributes rigidity to the polymer pendant groups. Finally, polymers with more compact and rigid pendant groups (**PGAm-Pyrr-MMT** and **PGAm-N*i*Pr-MMT**) have decreased segmental motion. **PEtG-N*i*Pr-MMT** in particular possesses all three of the aforementioned factors. This polymer was solid at all temperatures that could be investigated by DSC, suggesting its T_g was greater than 100 ºC. In general, the increased T_g values of the PGAms made them glassy solids at room temperature. None of the above PGAms showed evidence of crystallization or melting in the evaluated temperature range, suggesting that they were amorphous like the polyglyoxylates. To exclude the possibility of melting temperatures outside the measured temperature range, powder x-ray diffraction was performed on the polymers. No sharp peaks attributable to the polymers were observed, confirming their amorphous structures (Figures S51–S57).

Triggered Depolymerization of PGAm-MMTs. To assess if the PGAms retained the stimuli-responsive depolymerization feature of polyglyoxylates, depolymerization experiments were performed. Their depolymerization was studied by ^{1}H NMR spectroscopy in the absence and presence of 0.9 M acetic acid as a trigger. The percent depolymerization was quantified based on the relative integrations of the peak at ~5.5–5.6 ppm corresponding to polymer backbone methine protons and the peak at ~5.0–5.3 ppm corresponding to the methine proton of the monomer hydrate depolymerization product (Figures 4a, S60–S71). **PGAm-NEt-MMT**, **PGAm-N*n*Pr-MMT**, **PGAm-N*i*Pr-MMT**, and **PGAm-Pyrr-MMT** were studied in 9:1 CD_3CN:D_2O, a solvent mixture that we have previously used to study the depolymerization of polyglyoxylates, including **PEtG-MMT**.[17, 25] The other **PGAm-MMTs** were not soluble in this solvent system. In the presence of acetic acid, **PGAm-Pyrr-MMT** underwent complete depolymerization over a period of 30–35

days, with ~10 days required for 50% depolymerization, a rate very similar to that reported for **PEtG-MMT** (Figure 4b).[25] Interestingly, **PGAm-NEt-MMT**, **PGAm-N*n*Pr-MMT**, and **PGAm-N*i*Pr-MMT** all underwent depolymerization much more rapidly, with depolymerization complete in 10–14 days and only ~3 days required for 50% depolymerization. The differentiating feature of these PGAms is their ability to hydrogen bond through their amide NH groups. We postulate that intramolecular hydrogen bonding between the oxygen adjacent to the end-cap and the final amide repeat unit can accelerate the cleavage of the end-cap on the polymer during depolymerization (Scheme 3). Such an intramolecular interaction should be favourable since the resulting hydrogen bond creates a five-membered ring. In the absence of acetic acid, all of the PGAms depolymerized much more slowly, with only ~20% depolymerization observed for **PGAm-NEt-MMT**, **PGAm-N*n*Pr-MMT**, and **PGAm-N*i*Pr-MMT** and only 4% for **PGAm-Pyrr-MMT**. Thus, these data support that PGAms undergo depolymerization in response to stimuli, confirming their self-immolative properties. In addition, the data highlight that structural features influence the depolymerization rate.

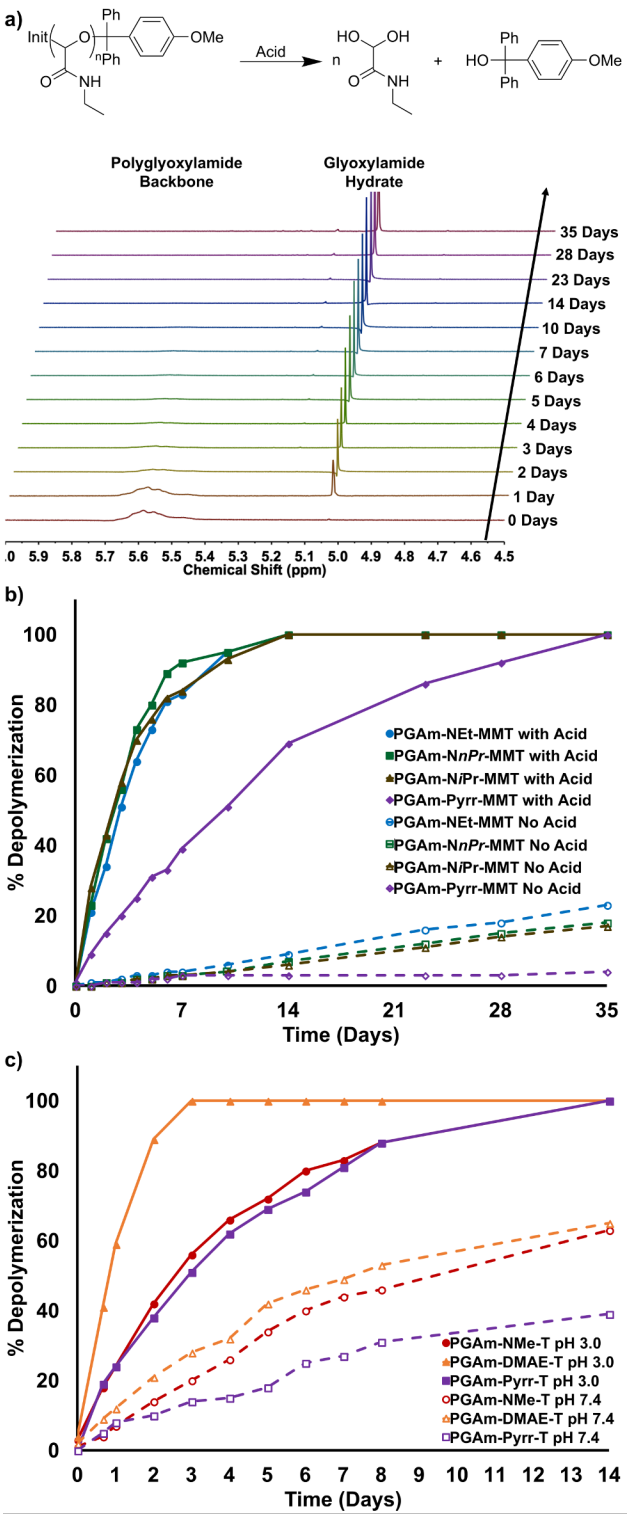
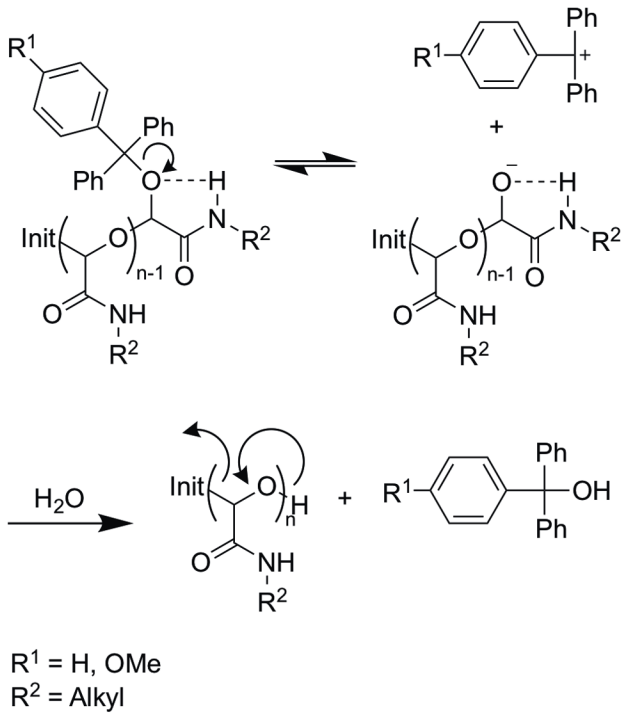


Figure 4. (a) Depolymerization of **PGAm-NEt-MMT** in 9:1 acetonitrile:water (0.1 M, pH 3.0) as a representative sample of how depolymerization was monitored using ^{1}H NMR spectroscopy

(CD_3CN, 400 MHz). As depolymerization proceeds, there is a decrease in the backbone methine proton peak at ~5.6 ppm and an increase in the methine proton peak of the monomer hydrate at ~5.0 ppm in the NMR spectra; (b) Depolymerization rates for selected **PGAm-MMTs** in 9:1 CD_3CN:D_2O with and without acetic acid (0.9 M) as a stimulus; (c) Depolymerization rates for selected **PGAm-Ts** in either citrate-buffered D_2O (0.1 M, pH 3.0) or phosphate-buffered D_2O (0.1 M, pH 7.4).



R^1 = H, OMe
R^2 = Alkyl

Scheme 3. Hypothesized hydrogen bonding mechanism that assists with the removal of the trityl end-cap. The glyoxylamide repeating unit adjacent to the end-cap is able to form a five-membered ring, accelerating the removal of the end-cap. If water is present, the end-cap is trapped and the polymer begins to depolymerize.

The high hydrophilicity of **PEtG-NMe-MMT** and **PEtG-DMAE-MMT** allowed their depolymerization to be studied in 9:1 D_2O:CD_3CN. Depolymerization was much faster in this solvent system, likely because the more polar, protic solvent accelerates the rate of cleavage of the 4-monomethoxytrityl end-cap, which follows an S_N1 mechanism. Depolymerization in the presence of acetic acid was complete for both polymers in less than 24 h (Figure S58). Unfortunately, the polymers were also rapidly degraded in the absence of acid, indicating a lack of end-cap stability in the 9:1 D_2O:CD_3CN solution. Because we wanted to further investigate the water-soluble PGAms (Table 1), this rapid background degradation in the absence of stimuli was problematic. Thus, more stable end-capped PGAms were required.

Synthesis of Trityl End-Capped Polyglyoxylamides (PGAm-Ts). To address the stability issue, we synthesized a series of new PGAms with a trityl end-cap instead of a 4-monomethoxytrityl end-cap. Since the simple trityl lacks the methoxy electron donating group, it is less labile than 4-monomethoxytrityl. First, a new polyglyoxylate (**PEtG-T**) was synthesized with the trityl end-cap by the method described above (Scheme 2). ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy were used to characterize the structure of **PEtG-T** (Figures S9 and S23). Both ^{1}H NMR spectroscopy and SEC suggested an M_n of ~9–10 kg/mol, while SEC provided a $Đ$ of 1.5. The molar mass of **PEtG-T** is likely lower than that of the analogous **PEtG-MMT** because trityl chloride reacts more slowly than 4-monomethoxytrityl chloride. Because of this, we suspect that end-capping of the polymer chains occurred at a higher temperature, allowing the chains to partially depolymerize before being end-capped and stabilized. To confirm that the discrepancy between the molar masses of **PEtG-MMT** and **PEtG-T** was caused by the end-caps used rather than other factors such as monomer purity, in an additional experiment PEtG was synthesized from the one batch of

monomer and capped with each end-cap. The resulting crude polymer mixtures were compared using SEC in tetrahydrofuran (THF) with PMMA standards (Figure S32), revealing that PEtG with 4-monomethoxytrityl as the end-cap had a larger M_n (16.5 kg/mol) than PEtG with trityl as the end-cap (6.8 kg/mol).

A subset of the PGAms (**PGAm-NMe-T**, **PGAm-NEt-T**, **PGAm-DMAE-T**, and **PGAm-Pyrr-T**) were synthesized from **PEtG-T** by reaction with the corresponding amines as described above (Scheme 2). ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy were used to confirm complete conversion of the pendant esters to amides (Figures S10–S13, S24–S27). SEC analysis was also performed for each PGAm (Table 2). Again, **PGAm-Pyrr-T** had a lower M_n than the other PGAms based on SEC (Figure S30). However, because of the lower DP_n of this polymer series, it was possible to perform end-group analysis based on ^{1}H NMR spectroscopy (Table 2). This analysis confirmed that **PEtG-T** and all of the **PGAm-Ts** had very similar DP_ns and that this was not altered in the amidation reaction. Additionally, MALLS was used with SEC to acquire the absolute molar masses of both **PEtG-T** and **PGAm-Pyrr-T** (Table 2). While this analysis gave slightly different values than those acquired from ^{1}H NMR spectroscopy, it confirmed that **PGAm-Pyrr-T** had the expected higher M_n relative to the precursor polymer **PEtG-T**. Thus, the lower SEC M_n for **PGAm-Pyrr-T** was due to conformational differences with the other polymers. Additionally, the **PGAm-Ts** were investigated using TGA and DSC (Table 2). TGA revealed an increase in the T_o values for trityl end-capped polymers relative to the 4-monomethoxytrityl end-capped polymers (Figure S34). The increase in thermal stability of the polymers corresponds to the reduced lability of the trityl end-cap in comparison to its 4-monomethoxytrityl analogue.[38] DSC revealed a decrease in the T_g values of the **PGAm-Ts** relative to their **PGAm-MMT** analogues (Table 2,

Figures S44–S48). As the T_g values of polymers are known to increase with their molar mass,[46] the decrease in the T_g values is consistent with the lower molar masses of the **PGAm-Ts**.

Table 2. Summary of the physical and thermal properties of the trityl end-capped polymers. For the SEC results, the values in parentheses were determined using MALLS rather than conventional calibration.

Polymer	**^{1}H NMR**		**SEC**				
	DP_n	**M_n (kg/mol)**	**M_n (kg/mol)**	**M_w (kg/mol)**	***Đ***	**T_o (ºC)**	**T_g (ºC)**
PEtG-T	90	9.7	8.8 (14.4)	13.5 (18.6)	1.5 (1.3)	206	-3
PGAm-NMe-T	83	7.7	8.4	14.6	1.7	172	70
PGAm-NEt-T	89	9.5	8.2	14.9	1.8	161	76
PGAm-DMAE-T	91	13.6	9.3	14.4	1.6	154	26
PGAm-Pyrr-T	96	12.7	4.0 (16.4)	9.8 (21.9)	2.4 (1.3)	169	59

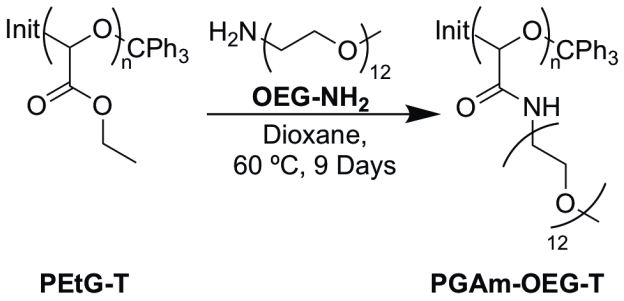
Triggered Depolymerization of PGAm-Ts. The depolymerizations of **PGAm-NMe-T**, **PGAm-DMAE-T**, and **PGAm-Pyrr-T** were studied by ^{1}H NMR spectroscopy in citrate-buffered D_2O (0.1 M, pH 3.0) and phosphate-buffered D_2O (0.1 M, pH 7.4) over a 14-day period at room temperature (Figures S72–S77). **PGAm-NEt-T** could not be studied under these conditions because it is insoluble in aqueous solutions at room temperature. Interestingly, **PGAm-DMAE-T** depolymerized more rapidly than the other polymers, with 50% depolymerization in ~24 h at pH 3.0 and complete depolymerization within 3 days (Figure 4c). **PGAm-NMe-T** and **PGAm-Pyrr-T** reached 50% depolymerization in ~3 days and required 10–14 days for complete

depolymerization at pH 3.0. At pH 7.4, the studied **PGAm-Ts** underwent depolymerization at a much slower rate than at pH 3.0, confirming their stimuli-responsive behavior. They underwent ~30–60% depolymerization over 14 days, which demonstrates a stability improvement over the PGAm-MMTs discussed above. It is anticipated that increased long-term stability could be achieved through the use of different end-caps such as benzyl ether derivatives.

Synthesis and Characterization of a Degradable Graft Copolymer Analogue of PEG. POEGMA is a graft copolymer version of PEG comprising OEG side chains on a methacrylate backbone. It possesses properties similar to those of PEG, including the ability to shield conjugated biomolecules from degradation or clearance.[43] However, POEGMA is inherently non-degradable, which may ultimately limit its applications in areas such as drug delivery. As demonstrated above, PGAms possess an acetal backbone that can undergo depolymerization. If this acetal backbone could be used to replace the methacrylate backbone of POEGMA, the resulting polymer should possess similar properties to POEGMA while at the same time undergo depolymerization when triggered by stimuli. Because the post-polymerization modification of PEtG to different PGAms with small molecule amines allowed for quantitative conversion, it was anticipated that it should be possible to graft amine-modified OEG chains to the acetal backbone.

To synthesize the graft copolymer, **PEtG-T** was dissolved in 1,4-dioxane with methoxypoly(ethylene glycol) amine (**OEG-NH_2**) (Scheme 4). We found that the use of 1.0 stoichiometric equivalent of **OEG-NH_2** per pendant ester instead of an excess for this reaction led to easier purification of the final graft copolymer (**PGAm-OEG-T**). However, in comparison with the amidation reactions involving small molecules, the use of fewer molar equivalents combined with steric hindrance associated with the relatively large **OEG-NH_2** resulted in slow conversion

of the **PEtG-T** ester pendant groups to amides. To drive the reaction, it was heated in a pressure tube at 60 ºC for 9 days. The resulting polymer was purified by multiple precipitations in Et_2O.



Scheme 4. Synthesis of **PGAm-OEG-T**.

PGAm-OEG-T was characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy to confirm that conversion was complete (Figures S14 and S28). SEC of the polymer revealed a single peak, confirming residual **OEG-NH₂** was removed during purification (Figure S31). The M_n of the polymer was 58.5 kg/mol while the $Đ$ was 1.7, very similar to the M_n of 54.7 kg/mol expected based on ^{1}H NMR spectroscopic analysis. Additionally, **PGAm-OEG-T** was analyzed via TGA and DSC (Figures S35 and S49). TGA revealed a T_o of 339 ºC, suggesting much higher thermal stability for this OEG graft copolymer than for the other **PGAm-Ts** and previously reported polyglyoxylates with various end-caps.[17, 25] The increase in thermal stability may be due to the high stability and low volatility of the OEG pendant groups as well as their ability to shield the end-cap and the acetal backbone of the main chain from thermal degradation. DSC of the polymer revealed a T_m of 23 ºC, a property conferred by the OEG side chains. No T_g was observed for the polymer over the temperature range from -70 to 200 ºC. Like POEGMA, **PGAm-OEG-T** is highly water-soluble.

The degradation of **PGAm-OEG-T** in citrate-buffered D_2O (0.1 M, pH 3.0) and phosphate-buffered D_2O (0.1 M, pH 7.4) was first examined by ^1H NMR spectroscopy (Figures S78 and S79). **PGAm-OEG-T** depolymerized much more slowly than the other **PGAm-Ts**, with ~60% depolymerization after 7 weeks in the pH 3.0 buffer and only ~10% depolymerization in the pH 7.0 buffer over the same time period (Figure S59). While **PGAm-OEG-T** can potentially hydrogen bond to the trityl oxygen as illustrated in Scheme 3, it is possible that conformational preferences prevent it from doing so. The structure-dependent depolymerization rates of the PGAms are an interesting aspect that was not noted for polyglyoxylates. To further study the depolymerization, it was also monitored by aqueous SEC for 7 weeks (Figures S80 and S81). At pH 3.0, the chromatograms showed a substantial decrease in the intensity of the polymer peak over this time period. At pH 7.4, only a small decrease in peak intensity was observed over the 7 weeks. These results indicate that the concentration of the polymer in solution was decreasing over time as the polymer depolymerized. The retention time did not increase in either case. This indicates that end-cap cleavage was the rate limiting step and that depolymerization of **PGAm-OEG-T** occurred rapidly after end-cap cleavage.

Conclusions

We have demonstrated for the first time the synthesis of self-immolative PGAms. These polymers were synthesized via a simple post-polymerization amidation of PEtG under mild conditions. Complete conversion of the esters to amide groups was demonstrated while avoiding degradation of the polymers. This allowed for the preparation of a library of different PGAms from a single batch of PEtG for property comparisons. The PGAms had much higher T_g values than polyglyoxylates, attributed to the rigidity and hydrogen-bonding capabilities of the pendant amide

groups. We demonstrated that PGAms could be triggered to depolymerize, confirming their self-immolative behavior. Furthermore, some of the PGAms were water-soluble, opening possibilities for their application in areas such as medicine. Finally, a PGAm analogue of POEGMA was synthesized and characterized, demonstrating that it is possible to easily prepare PGAm graft copolymers from amine-terminated oligomers, affording a new depolymerizable analogue of PEG. Their ease of synthesis and unique properties relative to other self-immolative polymers should make PGAms a promising new platform for applications.

Associated Content

Supporting Information

Additional experimental procedures, ^{1}H NMR, ^{13}C NMR, and FT-IR spectra, size-exclusion chromatograms, TGA and DSC thermograms, powder x-ray diffractograms, and additional depolymerization studies.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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