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Light-Triggered Intramolecular Cyclization in Poly(lactic-*co*-glycolic acid)-Based Polymers for Controlled Degradation

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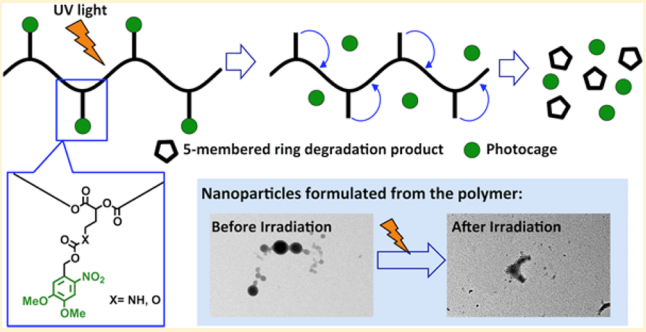
Supporting Information

ABSTRACT: Polylactide (PLA) and poly(DL-lactide-*co*-glycolide) (PLGA) are two prominent FDA-approved polymers because of their useful biodegradation into largely innocuous substances. Their hydrolytic degradation is slow and offers minimal control over degradation kinetics, especially in the minutes time scale. However, molecular engineering of their structures could allow triggered degradation. We have synthesized, by ring-opening polymerization (ROP), a series of PLGA-based polymers containing pendant nucleophiles protected with photocleavable groups. Upon deprotection, two of the polymers degrade rapidly via intramolecular cyclization into small molecules. Nanoparticles formulated from these polymers undergo rapid structural changes in response to UV light. This work introduces a novel polymeric structure to enable rapid on-demand degradation and expands the library of polymers that degrade by cyclization.

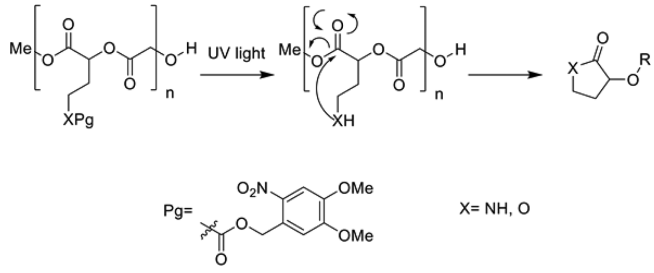


INTRODUCTION

Stable polymers that depolymerize rapidly upon application of a specific stimulus are of great interest for a variety of industrial applications, such as patterning and lithography,[1,2] and biomedical applications, such as tissue engineering,[3,4] tissue adhesives,[5,6] and drug delivery.[5,7] However, the variety of degradation kinetics of such materials remains limited; increasing the diversity of degradable polymers might allow better matching of materials to specific applications. Toward this end, we combined intramolecular cyclization, recently shown to allow triggered, rapid polymer degradation,[8−11] with a PLGA-based backbone. We chose PLGA because of its broad use in current medical materials,[12−14] its relatively rapid hydrolysis rate compared to other nonresponsive polymers (e.g., polycaprolactone), and its compatibility with ring-opening polymerization, allowing control over polymer length. Attaching stimuli-responsive groups to cyclizing side chains creates polymers that can rapidly degrade on demand and, in the absence of signal, slowly hydrolyze to minimize accumulation in biological systems.[15−17]

We designed a series of polymers including cyclizing side chains protected with photolabile groups. Irradiation exposes a pendant nucleophile and triggers intramolecular cyclization to form favorable five-membered rings (Scheme 1). An *o*-nitrobenzyl (ONB) protecting group, which degrades in response to UV light, was selected as the photocleavable moiety because this variety of protecting group is well-studied,[18,19] commonly used in similar applications,[8,20−23] and readily available. UV-degradable polymeric particles[24] and other

Scheme 1. Polymer Degradation Mechanism[a]



[a]Removal of the photolabile protecting group frees the pendant nucleophile to cleave the backbone ester and form a five-membered ring.

materials have been employed for biologically relevant purposes.[22,25−30] These polymers add a new backbone to the collection of chain-breaking polymers already described[8−10,31−40] and add light-triggered degradation to the array of properties now found in the growing field of functional hydrolytically degradable poly(*α*-hydroxyl acid)s.[41,42]

Polymeric nanoparticles composed of these polymers, when exposed to UV, should rapidly degrade and release encapsulated molecules. Upon irradiation the component polymers immediately become more hydrophilic, allowing water to

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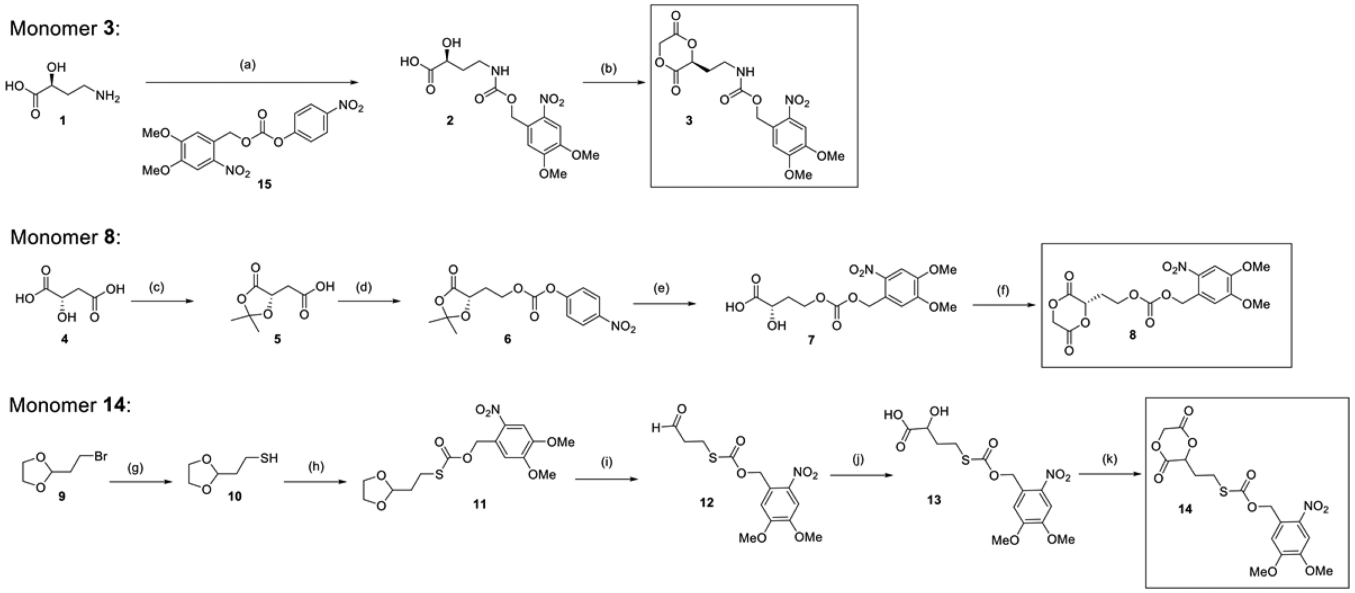
Macromolecules XXXX, XXX, XXX−XXX

Scheme 2. Synthesis of Monomers[a]



[a]Reagents and conditions: (a) **15**, Et_3N, MeCN, reflux, 61%; (b) (i) bromoacetyl bromide, Et_3N, MeCN, 0 °C; (ii) $NaHCO_3$, DMF, 45% over two steps; (c) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, CH_2Cl_2, 95%; (d) (i) borane, THF 0 °C; (ii) 4-nitrophenyl chloroformate, pyridine, CH_2Cl_2, 0 °C, 48% over two steps; (e) (i) 4,5-dimethoxy-2-nitrobenzyl alcohol, DMAP, pyridine, CH_2Cl_2, 0 °C, 68%; (ii) THF, H_2O, AcOH, 100%; (f) (i) bromoacetyl bromide, Et_3N, MeCN, 0 °C; (ii) DMF, $NaHCO_3$, 58% over two steps; (g) sodium hydrosulfide, DMF, 0 °C, 80%; (h) **15**, pyridine, DMAP, CH_2Cl_2, 0 °C, 85%; (i) THF, 1 M HCl, 98%; (j) (i) trimethylsilyl cyanide, ZnI_2, CH_2Cl_2, 0 °C, 98%; (ii) HCl (concentrated), 1,4-dioxane, 50 °C, 59%; (k) (i) bromoacetyl bromide, Et_3N, MeCN 0 °C; (ii) DMF, $NaHCO_3$, 41% over two steps.

infiltrate particles, promoting hydrolysis of the polymer backbone. The released nucleophiles also cause more rapid polymer degradation by intramolecular cyclization. Non-triggered ester hydrolysis of the PLGA-type backbone ensures complete degradation, facilitating clearance from the circulation, even without complete removal of pendant photocages.

RESULTS AND DISCUSSION

We have synthesized three polymers with different pendant nucleophiles: an amine, an alcohol, and a thiol. Preparation of a polymer series not only allows comparison of their degradation but also examination of what chemistries are compatible with cyclization. Previous intramolecularly cyclizing polymers did not include pendant alcohols as nucleophiles. Our incorporation of an alcohol thus broadens the range of chemistries that can be used to trigger degradation. Degradation by cyclization does not occur with analogous thiol nucleophiles in this series. Polymer properties were also compared in polymeric particles, which could be used for drug delivery or other applications.

The synthetic routes for the three monomers **3**, **8**, and **14** are shown in Scheme 2. The monomer with a pendant amine, monomer **3**, was readily prepared from **1**. The amine of **1** was first protected with the UV light-sensitive *o*-nitrobenzyl protecting group using triethylamine and compound **15**. Alcohol **2** was then acylated with bromoacetyl bromide and subsequently cyclized with sodium bicarbonate to give dilactone **3** in a manner similar to that outlined by Pounder et al.[43]

To obtain monomer **8**, L-malic acid (**4**) was protected to form acetal **5** following an established procedure for D-malic acid.[44] Acetal **5** was then reduced with borane to yield an alcohol that was immediately reacted with 4-nitrophenyl chloroformate to form carbonate **6**. Carbonate **6** was reacted with 4,5-dimethoxy-2-nitrobenzyl alcohol to install the light-sensitive protecting group. The acetal was then hydrolyzed to reveal the vicinal alcohol and acid of **7**. Compound **7** was cyclized to form the dilactone monomer **8** in a manner similar to that described for monomer **3**.[43]

Synthesis of monomer **14** required a distinct route because the ketal protecting group proved too labile under the conditions required to generate a thiol from compound **5**. Instead, the protected thiol was formed by a more mild substitution reaction, a nucleophilic displacement of the bromine of compound **9** with sodium hydrosulfide, to yield thiol **10**. Thiol **10** was protected with the *o*-nitrobenzyl protecting group using compound **15** to yield compound **11**, the acetal of which was hydrolyzed to yield aldehyde **12**. Aldehyde **12** was treated with trimethylsilyl cyanide and zinc iodide to yield a cyanohydrin which was then hydrolyzed to afford acid **13**. Compound **13** was reacted with bromoacetyl bromide in the same manner as the previous two monomers to afford dilactone monomer **14**.[43]

The three monomers were polymerized by organic-catalyzed ring-opening polymerization (ROP).[45−47] We could not directly follow the method used by Dove et al.[43] for this variety of monomer due to lack of a commercial source for the catalyst (−)-sparteine. Instead, we selected an alternative reported organocatalyst, triazabicyclodecene, for ROP (Scheme 3).[48] Commercially available compound **19**, 1-[3,5-bis-(trifluoromethyl)phenyl]-3-[(1*R*,2*R*)-(−)-2-(dimethylamino)-cyclohexyl]thiourea (R,R-TUC), was also included as a cocatalyst; the triazabicyclodecene alone was sufficient to catalyze ROP, but at a far slower rate. Attempts at polymerization with metal catalysts were unsuccessful because of poor solubility in compatible solvents and the high melting points (exceeding 180 °C, at which point degradation is observed) of the monomers in bulk. Weight-average molecular weights (M_w) of the polymers were determined by gel

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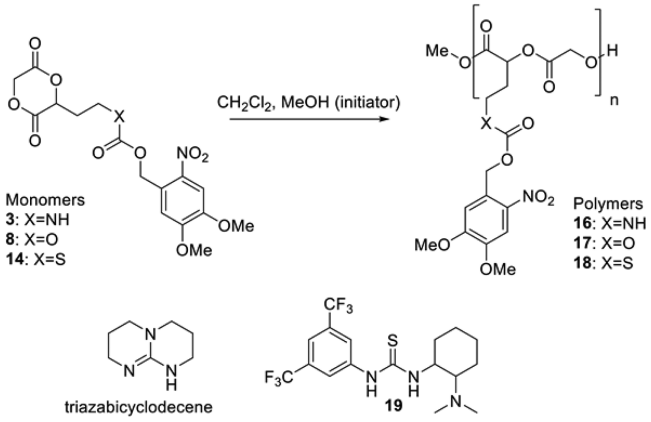
Scheme 3. Preparation of the Three Light-Degradable Polymers 16–18[a]



[a]Reagents: triazabicyclodecene was used as catalyst and **19** was used as cocatalyst.

permeation chromotography (GPC) to be 3800 Da (PDI = 1.2) for polymer **16**, 19 200 Da (PDI = 1.5) for polymer **17**, and 12 200 Da (PDI = 1.5) for polymer **18** using PMMA standards. Side reactions during ROP were a limiting factor in MW for the polymers. Polymer **16**'s MW appeared to be the most limited of the three polymers by side reactions like transcarbamation, though polymer **17** and **18** also suffered from analogous side reactions to a lesser extent. This resulted in higher PDIs and lower number-average molecular weights than predicted from monomer and initiator ratios (Table S1).

Toward characterizing the polymers' degradation, we first compared the photocleavage efficiencies of the carbamate, carbonate, and thiocarbonate photocleavable protecting groups in polymers **16**, **17**, and **18**, respectively. Polymers were irradiated with UV light (1 mW/cm^2) for the specified times, up to 18 min, and the change in absorbance at 346 nm was monitored. The peak at 346 nm, corresponding to the 4,5-dimethoxy-2-nitrobenzyl protecting group, decreased, while a new peak at 400 nm, associated with the cleaved 4,5-dimethoxy-2-nitrosobenzaldehyde, formed (Figure S5a–c).[49] The percent absorbance was plotted over time (Figure S5d). The three protecting groups are quite similar in sensitivity, though the carbonate protecting group of polymer **17** is slightly less sensitive than the other two.

We then attempted to monitor polymer degradation by gel permeation chromatography. Each polymer was dissolved in 9:1 acetonitrile/phosphate buffer pH 7.4, irradiated for 15 min (1 mW/cm^2), and then incubated at 37 °C for specified times before concentrating the samples and analyzing by GPC. The 15 min of irradiation at this concentration is only enough to cleave a minor percentage of the protecting groups, avoiding substantial changes in the polarities of polymers **17** and **18**. Even with this low level of irradiation, polymer **16** underwent a substantial change in polarity, causing interactions with the GPC columns that impeded interpretation (Figures S7a and S8a). Polymer **17** was amenable to GPC following irradiation; the initial irradiated trace (blue) shifted to longer elution times following incubation for 30 min (red) and 1 h (black) (Figure 1a). This indicates a shift to lower molecular weight fragments, consistent with intramolecular cyclization. The minor difference between the 30 min and 1 h traces suggests that the intramolecular cyclization reactions of polymer **17** are quite

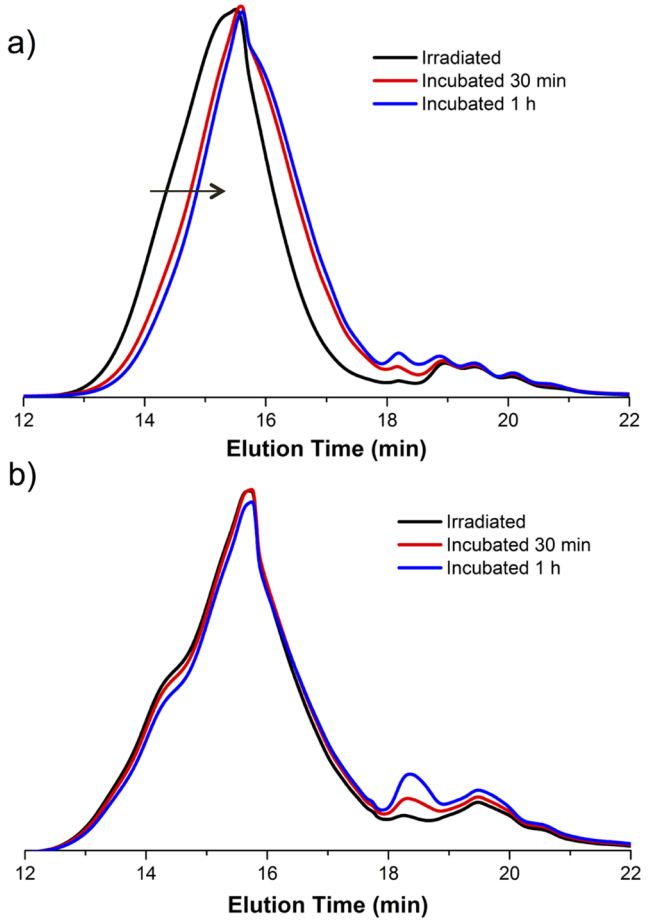


Figure 1. GPC traces of (a) polymer **17** and (b) polymer **18** following 15 min irradiation (1 mW/cm^2) and subsequent incubation for the specified times at 37 °C. Irradiation was brief to minimize side reactions.

rapid, largely completing within 30 min of incubation. This change is not associated with hydrolysis as no shift occurs in the nonirradiated control over this 1 h time scale (Figure S7b). The molecular weight of polymer **18** did not change in 1 h (Figure 1b), and changes were not apparent until after 4 h of incubation (Figure S8c). As this amount of time is compatible with hydrolysis of exposed thiocarbonate protecting groups (Figure 1b), we infer that this structure did not cyclize appreciably at this temperature, and the apparent degradation was unrelated to breaking of the polymer backbone. ^{1}H NMR spectroscopic studies on polymer **18** and model small molecules found no evidence of cyclic products at biologically relevant temperatures. This result is not surprising, as the cyclization would necessitate an enthalpically unfavorable conversion of an ester to a thioester. The reaction would be entropically favorable at higher (less biologically relevant) temperatures.

Next, we sought to confirm that cyclizations driven by the pendant amine and alcohol nucleophiles contribute significantly to the degradation of polymers **16** and **17**. While identifying small cyclic degradation products would be the most direct means of confirming the mechanism, polymers **16** and **17** are not compatible with such an approach. Small products are only formed when two adjacent protecting groups are removed, so generating sufficient quantities of such products for detection by NMR requires removal of most protecting groups. Such thorough deprotection would require intense and lengthy

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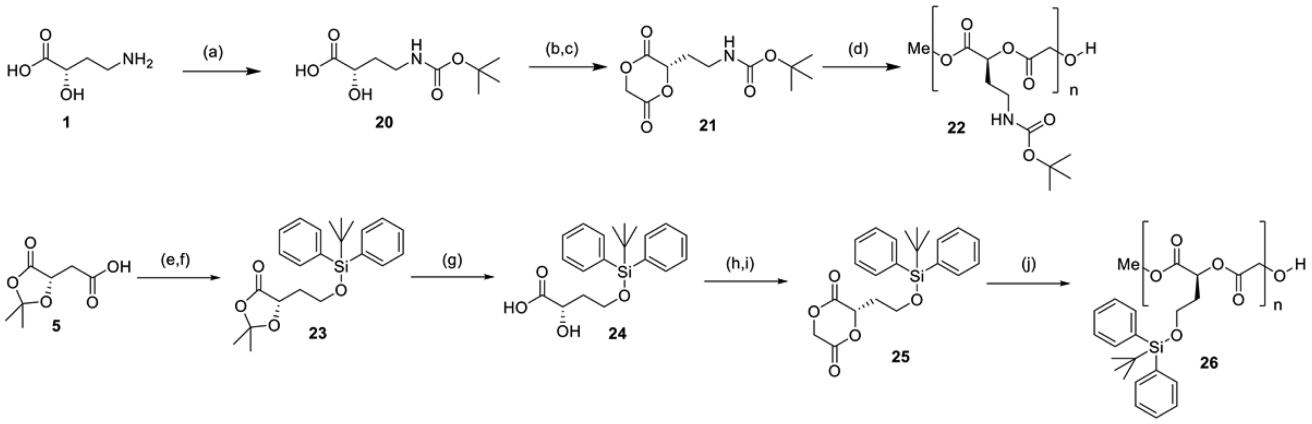
Scheme 4. Synthesis of the Model Polymer[a]



[a]Reagents and conditions: (a) Boc_2O, K_2CO_3, H_2O, 1,4-dioxane; (b) bromoacetyl bromide, Et_3N, MeCN, 0 °C; (c) DMF, $NaHCO_3$, 25% over two steps; (d) $Sn(Oct)_2$, 125 °C, 29%. Synthesis of the silyl-protected model polymer: (e) borane, THF, 0 °C; (f) TBDPSCl, pyridine, CH_2Cl_2, 59% over two steps; (g) THF, H_2O, AcOH, 73%; (h) bromoacetyl bromide, Et_3N, MeCN, 0 °C; (i) DMF, $NaHCO_3$, 15% over two steps; (j) **19**, MeOH, triazabicyclo[4.4.0]dec-5-ene, CH_2Cl_2, 48%.

irradiation, which is not practical for on-demand release. Thus, we synthesized two model polymers with conventional protecting groups that could be completely removed by chemical means (Scheme 4). Using these model polymers, **22** and **26**, the degradation products of these backbones were studied, and the presence of significant quantities of cyclic compounds was confirmed.

Model polymer **22**, analogous to polymer **16**, was prepared with a Boc in place of the light-sensitive protecting group, by a method similar to that used for polymer **16**. Boc protection of compound **1** yielded alcohol **20**, which was acylated with bromoacetyl bromide and subsequently cyclized with sodium bicarbonate to give dilactone **21**. Monomer **21** proved difficult to polymerize, possibly due to an even stronger tendency toward transcarbamation than monomer **3**. Using $Sn(Oct)_2$ as a catalyst instead of the previously used organic catalyst provided low molecular weight polymer **22** (4000 Da; PDI = 1.2).

The model polymer analogous to polymer **17**, polymer **26**, was prepared incorporating a silyl protecting group for the alcohol. Using methods adapted from the synthesis of polymer **17**, compound **5** was reduced with borane and then protected with *tert*-butyl(chloro)diphenylsilane. The bulky protecting group was chosen to minimize deprotection of the silyl protecting group in the subsequent deprotection of ketal **23** with acetic acid to yield carboxylic acid **24**. Carboxylic acid **24** was readily converted into dilactone monomer **25**, using bromoacetyl bromide, which then was polymerized using the same technique as for the photosensitive polymers.

To confirm the presence of cyclic degradation products for polymers **22** and **26**, they were deprotected with TFA and TBAF, respectively, and allowed to degrade. The deprotected materials were dissolved in deuterated buffer solutions prior to analysis by ^{1}H NMR spectroscopy. Minimal changes occurred in the spectra over time, indicating that degradation had reached near completion before samples could be analyzed by ^{1}H NMR spectroscopy, possibly during sample preparation or deprotection. Cyclic components were identified in the ^{1}H NMR spectra by comparison to predicted product spectra. Because of the nature of the ROP, the glycolic acid and the α-hydroxyl acid with a pendant nucleophile do not alternate perfectly, though certain patterns should be more likely due to steric interactions. This means that degradation could yield multiple cyclic products (Figure 2a,b).

The two most readily synthetically accessible predicted products are compounds **27** and **28**. Compound **27** was prepared using a slightly modified method for a similar lactam,[50] and compound **28** was readily obtained following a procedure developed by Denmark and Yang.[51] The peaks corresponding to these compounds were easily located in the degraded polymer spectra, confirming cyclization (Figure 2a,b). Peaks likely consistent with other cyclic products are also present in the degraded polymer spectra; the substantial difference between the methylene protons vicinal to the alcohol at 2−2.5 ppm is characteristic of those methylene protons when fixed in a ring. This evidence validates intramolecular cyclization as the major means of degradation for polymers of this backbone design upon deprotection.

The three polymers were then formulated into nanoparticles to compare their degradation in a hydrophobic assembly and their potential for light-triggered release. Nanoparticles were formulated by single emulsion, both empty (Figure 3) and encapsulating Nile red (Figure S8a−c). The degradation of empty particles was continuously monitored by DLS following irradiation for 15 s (0.181 W/cm^2) (Figure 4b). The count rate for irradiated particles composed of polymer **16** decreased more rapidly than for the other polymers in the first 30 min following irradiation. This rapid degradation likely results from the increase in hydrophilicity upon release of the amine, as well as the amine's high nucleophilicity, allowing rapid intramolecular cyclization. Particles composed of polymer **17**, NP **17**, also rapidly degrade, but with a less substantial initial drop in the first 30 min. To avoid inclusion of the initial rapid decrease, which may be a result of hydrophobicity changes, the rate of count rate decrease from 30 min to 4.5 h for NP **16**−**18** was determined (Table S2). Irradiated NPs **17** and **18** decrease in count rate roughly 2.5 times faster than nonirradiated nanoparticles and irradiated NP **18**, likely due to their ability to degrade by intramolecular cyclization. The count rate decreases at roughly the same rate in irradiated and nonirradiated NP **18**, consistent with an absence of appreciable intramolecular cyclization. Particles formulated with PLGA behaved identically when irradiated and not irradiated under these conditions (Figure 4d).

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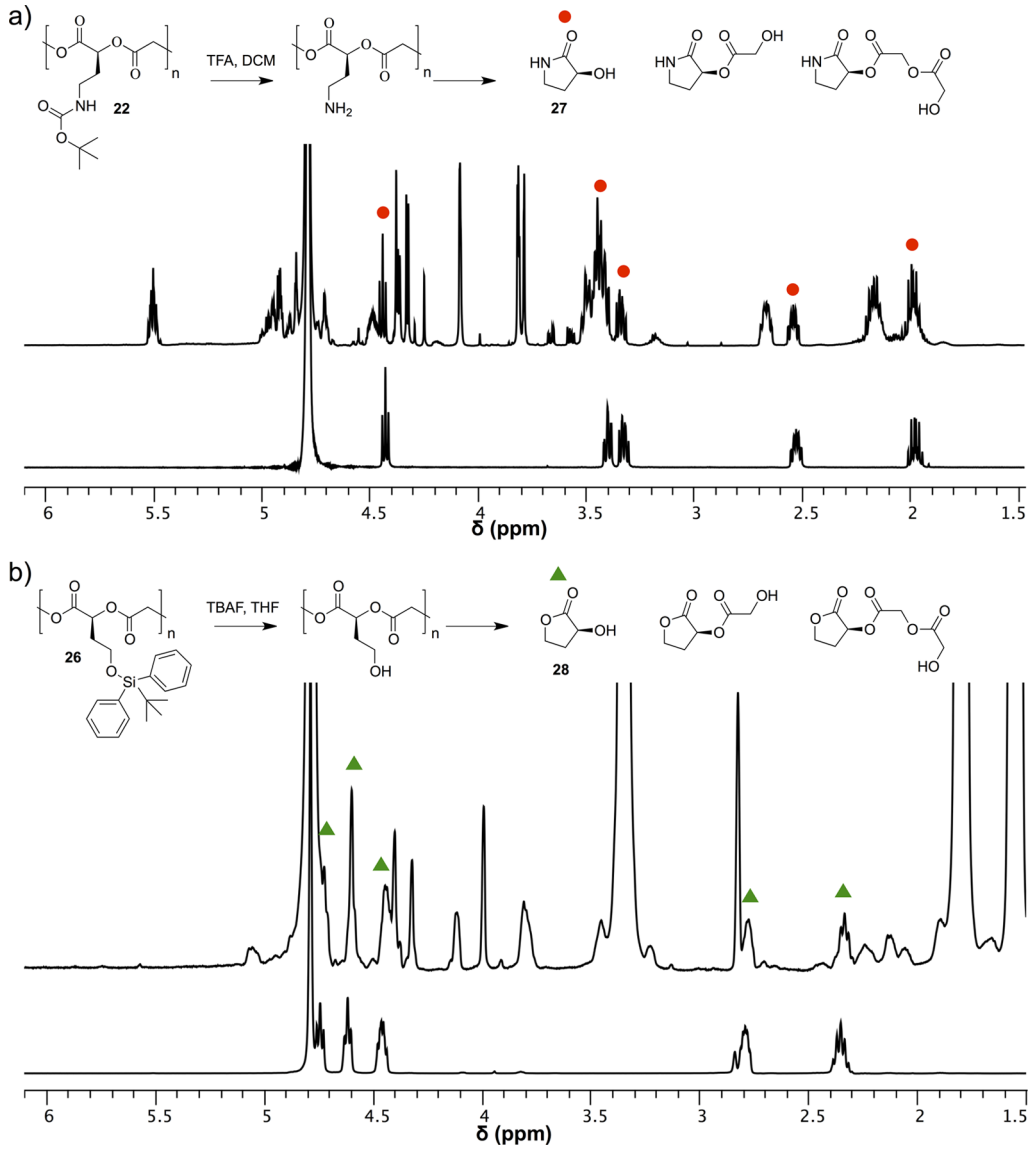

Figure 2. (a) Deprotection and subsequent degradation of model polymer **22** to likely cyclic degradation products and ^{1}H NMR spectra of degradation products of polymer **22** (upper) and compound **27** (lower). (b) Deprotection and subsequent degradation of model polymer **26** to likely cyclic degradation products and ^{1}H NMR spectra of degradation products of polymer **26** (upper) and compound **28** (lower).

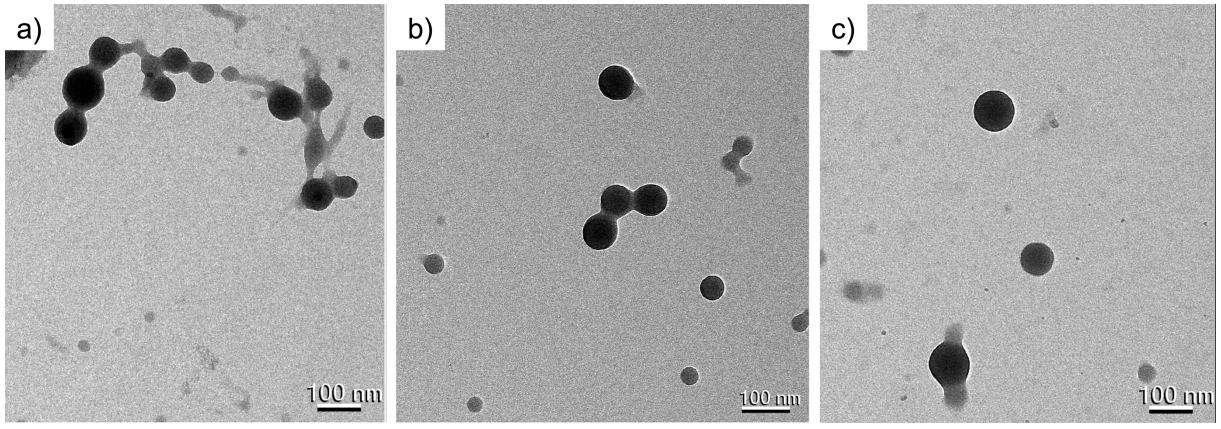

Figure 3. TEM micrographs of (a) NP **16**, (b) NP **17**, and (c) NP **18**.

To confirm NP degradation, transmission electron micrographs (TEMs) of irradiated and nonirradiated particles were also obtained. In agreement with the DLS data, particle densities of NP **16** and NP **17** were markedly lower after 15 s

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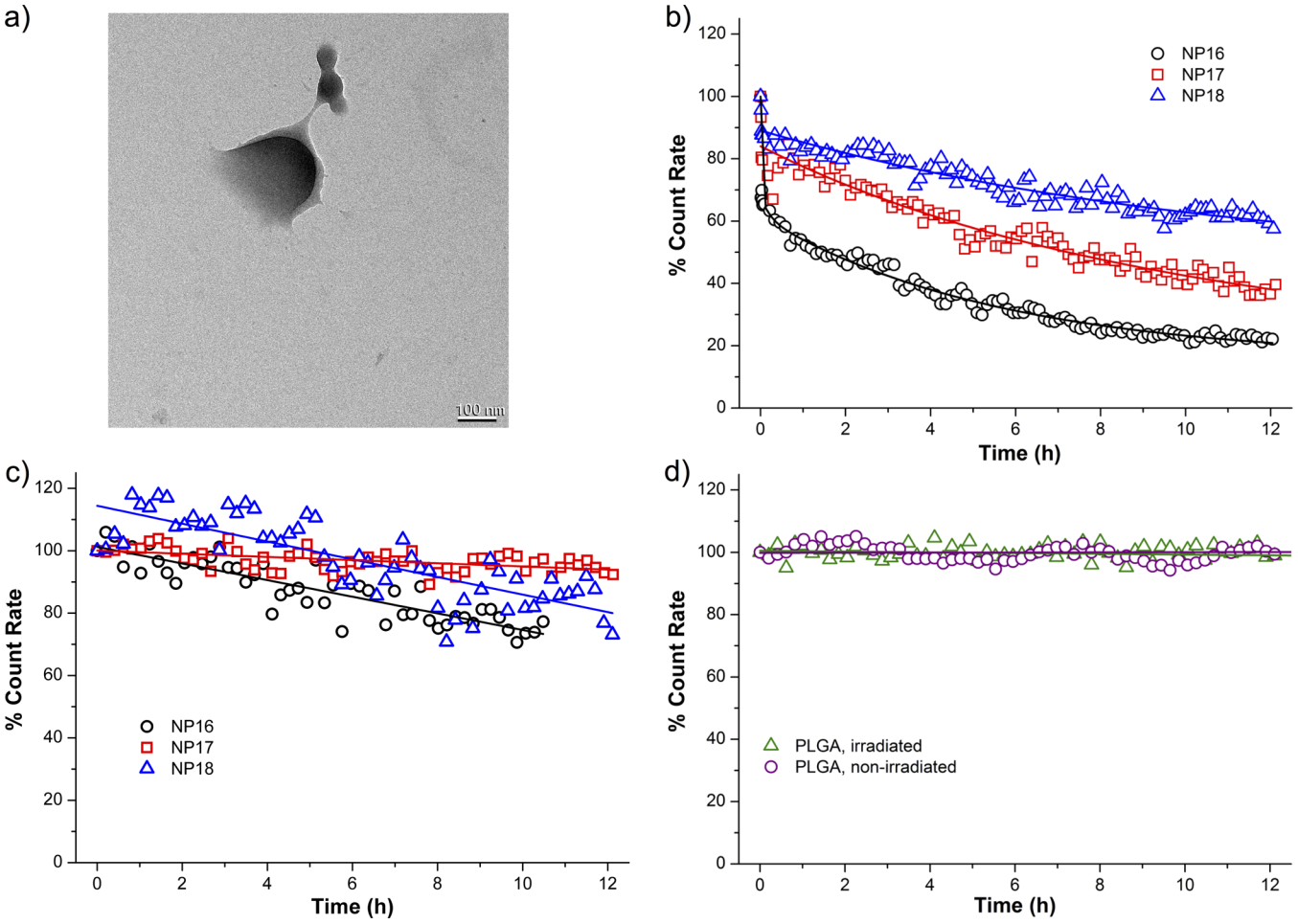

Figure 4. (a) TEM of NP **16** after irradiation at 320−390 nm (0.181 W/cm^2) for 15 s and overnight incubation at 37 °C. DLS count rate of (b, c) NP **16**, NP **17**, and NP **18** either (b) irradiated at 320−390 nm (0.181 W/cm^2) for 15 s or (c) not irradiated, then incubated at room temperature in 1X PBS (pH 7.4), and (d) PLGA particles either irradiated under the above conditions or not irradiated, then incubated at room temperature in 1X PBS (pH 7.4).

irradiation (0.181 W/cm^2) and overnight incubation at 37 °C. After irradiation NP **16** (Figure 4a) and NP **17** (Figure S4c,d) also contained substantial quantities of aggregates with no clear spherical structure, likely material from degraded particles. Irradiated NP **18** (Figure S4e,f) still had substantial numbers of intact particles, though the particles did appear to aggregate more following irradiation.

To assess utility for triggered release, particles were also formulated encapsulating the fluorescent dye Nile red (NP-NR). Nile red is fluorescent in hydrophobic environments, such as the interior of a hydrophobic nanoparticle, and is quenched by water. Upon irradiation with UV light (1 mW/cm^2), Nile red fluorescence was rapidly quenched in all three particles, but most quickly in NP-NR **16** and NP-NR **17**, which are composed of the polymers that degrade rapidly through cyclization (Figure S6d). Rapid quenching is indicative of substantial structural changes to the particles, allowing both release of Nile red and water influx. Particles are stable over at least 4 h when not irradiated (Figure S6e).

CONCLUSION

We have prepared three novel polymers with a poly(lactide-*co*-glycolide)-type backbone that contain pendant protected nucleophiles. In polymers containing pendant alcohols or amines, polymer degradation following deprotection is accelerated by intramolecular cyclization events that cause breaks in the polymer backbone. This should allow these already biodegradable polymers to be used in applications requiring triggered degradation, such as drug delivery. This backbone has the potential to support a variety of protecting groups sensitive to different triggers, providing opportunities for future investigation.

ASSOCIATED CONTENT

Supporting Information

Synthetic methods, particle formulation, and additional data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.5b00455.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

UV, ultraviolet; MeCN, acetonitrile; DMF, dimethylformamide; THF, tetrahydrofuran; DMAP, 4-(dimethylamino)-pyridine; AcOH, acetic acid; PMMA, poly(methyl methacrylate); PDI, polydispersity index; TBDPSCl, *tert*-butyldiphenylchlorosilane; TFA, trifluoroacetic acid; TBAF, tetra-*n*-butylammonium fluoride; ppm, parts per million; PBS, phosphate buffered saline.

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