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A Cascade Biodegradable Polymer Based on Alternating Cyclization and Elimination Reactions

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Abstract: Polymers that depolymerize by a cascade of intramolecular reactions in response to the removal of a stabilizing end-cap can allow for an unprecedented degree of control over the polymer degradation process. Described here is the development of polymers comprising *N*,*N*′-dimethylethylenediamine and 4-hydroxybenzyl alcohol linked by carbamate linkages. The polycarbamate backbone is stable in aqueous solution, but removal of a protective end-cap from the amine terminus allows the diamine to cyclize, forming *N*,*N*′-dimethylimidazolidinone and releasing the phenol, which undergoes a 1,6-elimination followed by the release of CO_2 to reveal the next amine to continue the cascade. These polymers therefore degrade by alternating cyclization and elimination reactions. First, a *tert*-butylcarbamate (Boc) group was introduced as a cleavable end-cap, and the degradation kinetics and mechanism were studied by ^{1}H nuclear magnetic resonance (NMR) spectroscopy and size exclusion chromatography. Next, to demonstrate the degradability of these polymers under biologically relevant conditions, poly(ethylene oxide) was introduced as an end-cap via an ester linkage, to provide an amphiphilic block copolymer. This copolymer was found to assemble into cascade degradable nanoparticles that were capable of encapsulating and subsequently releasing a fluorescent dye in aqueous solution. This new class of polymers therefore provides highly promising materials that can be used for the development of medical devices, drug delivery vehicles, and tissue engineering scaffolds with unique biodegradation properties.

Introduction

In recent years, there has been significant interest in the development of biodegradable polymers and in their application to areas as diverse as food sciences,[1] medical devices,[2,3] drug delivery,[4−6] and tissue engineering.[7,8] In particular, polyesters such as poly(lactic acid),[9,10] poly(glycolic acid),[11−13] and polycaprolactone[14−16] have been extensively used in biomedical applications and have also been proposed as environmentally friendly replacements for traditional plastics such as polyethylene. While the biodegradation rates of these polymers can be controlled to some extent by tuning their composition, solubility, and processing, they typically degrade by random hydrolytic cleavages throughout the backbone, a process that is relatively unregulated.[17,18] For many applications, it would be desirable to use polymers that can be degraded in a controlled manner in a specified environment or in response to a stimulus. To address this, polymers with many acetal[19−22] or disulfide linkages[23,24] in their backbones have been developed. These polymers have been demonstrated to degrade under mildly acidic and reducing conditions, respectively, but the mechanism of degradation still involves random chain scissions throughout the polymer back-

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bone, and many environmentally mediated cleavage events are required to completely degrade the polymer.

Another interesting class of molecules that is under development is stimuli responsive polymers. For example, polymers based on *N*-isopropylacrylamide (NIPAM)[25] or oligo(ethylene glycol) methacrylates[26,27] have been demonstrated to be thermally responsive, with high aqueous solubility below their lower critical solution temperature (LCST) and precipitation above the LCST. Polymers containing pendant amines or carboxylic acids are typically responsive to pH, being soluble within specified pH ranges.[28−30] In addition, hydrophobic groups and drugs have been appended to polymer backbones by pH-sensitive acetals,[31,32] hydrazones,[33] or photochemically cleavable linkages,[34,35] such that the solubilities of the polymers are significantly altered upon the removal of these groups. Other systems responsive to stimuli such as sugar concentration[36,37] and redox potential[38−40] have also been reported. These stimuli responsive polymers have increasingly been used in recent years to prepare assemblies such as micelles, vesicles, and nanoparticles that are capable of releasing molecules in response to changes in environmental conditions.[34,35,38,40–47] However, the design of systems capable of responding within the relatively narrow range of biologically accessible conditions is still a significant challenge.

A new and attractive concept for the design of materials that are both degradable and stimuli responsive is end-capped cascade degradable polymers. As illustrated in Figure 1, these polymers comprise a backbone that is stable when the end-cap

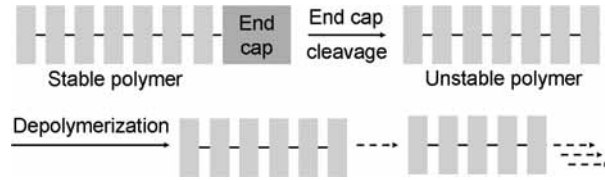

Figure 1. Schematic of a cascade degradable linear polymer, where removal of a stabilizing end-cap initiates a cascade of reactions leading to depolymerization.

is intact, but upon removal of the end-cap via a single bond cleavage, a functionality is revealed at the polymer terminus that initiates a cascade of intramolecular reactions leading to complete depolymerization from end to end. This concept was initially introduced in dendritic systems that upon removal of a focal point group were demonstrated to degrade by an intramolecular cascade, releasing multiple molecules from the dendrimer periphery.[48,49] Such systems were then further developed to provide for the simultaneous release of multiple different drug molecules, the incorporation of tumor targeting groups, and focal point groups that were sensitive to reducing conditions or enzymes.[50−53]

The application of this concept to linear cascade degradable polymers has the potential to dramatically expand their utility. Such materials may be used for the assembly of supramolecular aggregates such as micelles, vesicles, and nanoparticles or for the fabrication of medical devices or tissue engineering scaffolds, where they can impart several unique and advantageous properties. For example, the use of end-caps responsive to different conditions could allow the degradation of a single polymer to be triggered under a wide range of conditions, while the composition of the polymer backbone itself would determine the rate of degradation. By tuning the length of the polymer backbone, the time required for polymer degradation can potentially be controlled, as a longer polymer should take longer to completely depolymerize than a shorter polymer. In addition, due to the end to end degradation mechanism resulting in a controlled and gradual reduction of polymer molecular weight, the physical properties of the polymer should be retained longer during the degradation process in comparison with a traditional degradable polymer such as a polyester, where a single cleavage event may decrease the molecular weight by up to 50%. Despite these attractive features, only one cascade degradable linear polymer backbone has been reported to date.[54,55] This backbone was a polycarbamate based on 4-aminobenzyl alcohol derivatives, which degrades entirely by intramolecular 1,6-elimination reactions via iminoquinone methide intermediates. It has been demonstrated that by using enzyme sensitive end-caps this backbone can be used as an amplifying sensor,[54] or to release

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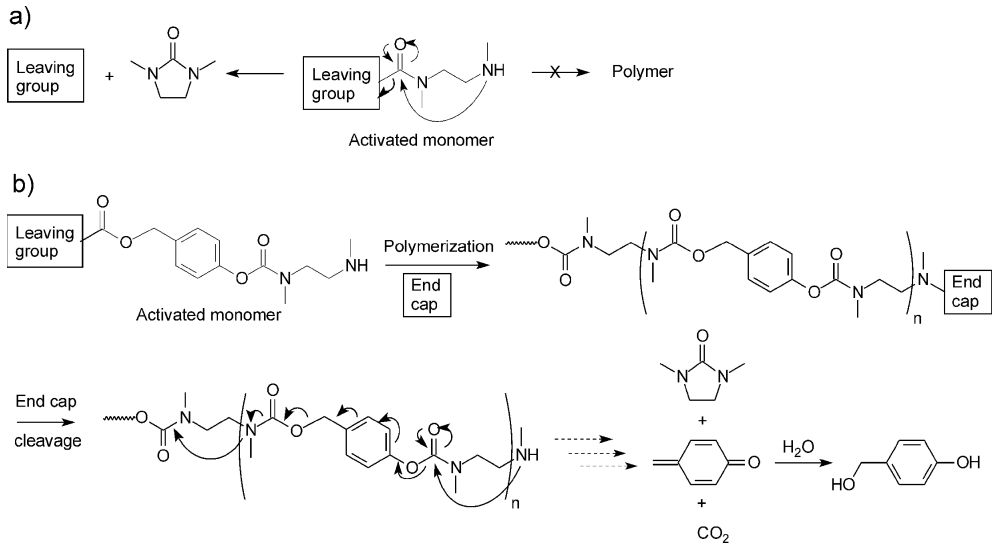

Figure 2. (a) A competing intramolecular cyclization makes the incorporation of cyclizing monomers into a cascade degradable linear polymer challenging. (b) By using alternating monomers, the activating leaving group can be moved distal to the cyclization monomer, thus facilitating polymerization. End-cap removal then allows for depolymerization by alternating cyclization and 1,6-elimination reactions.

multiple model drugs conjugated along the polymer backbone.[55] The development of alternative backbones and cascade degradation mechanisms will be necessary to tune the properties and degradation rates, opening the way for new applications of this class of materials.

Inspired by the incorporation of alternating cyclization and 1,6-elimination spacers into a dendritic system,[52] reported here is the first example of a linear cascade degradable polymer that degrades by alternating elimination and cyclization reactions. The degradation rate and mechanism were studied using nuclear magnetic resonance (NMR) spectroscopy and size exclusion chromatography (SEC), and it was demonstrated that the incorporation of a monomer that induces depolymerization by a cyclization mechanism provides an effective means of tuning the degradation rate. Furthermore, by conjugating poly(ethylene oxide) (PEO) to the terminus of the cascade degradable polymer as an end-cap, an amphiphilic block copolymer was obtained, which assembled into nanoparticles in aqueous solution. Hydrolysis of the ester linkage between the blocks initiated the cascade degradation process under physiological conditions. These nanoparticles were found to encapsulate a hydrophobic dye and release it upon depolymerization, thus demonstrating for the first time the utility of this class of molecules in the development of functional polymer assemblies and nanomaterials.

Results and Discussion

Design. The use of monomers such as hydroxybenzyl alcohol and aminobenzyl alcohol derivatives in the development of cascade degradable polymers is attractive as the presence of the free aromatic alcohol or amine functionalities that normally trigger quinone methide-mediated elimination reactions can be masked when they are activated, thus providing relatively stable polymerization monomers and synthetic intermediates. Another potential class of monomers for cascade degradable polymers are those capable of undergoing intramolecular cyclization reactions.[56] One example is a carbamate derivative of *N*,*N*′-dimethylethylenediamine, which spontaneously cyclizes to form *N*,*N*′-dimethylimidazolidinone, releasing the alcohol.[57] This spacer has been incorporated into some of the previously reported cascade degradable dendrimers,[48,52,53,58] where protecting groups can be carefully manipulated during the stepwise dendrimer synthesis; however, the synthesis of linear polymers based on this class of monomers presents a significant challenge, as the requisite activation of the monomer for polymerization introduces the possibility for an intramolecular cyclization to occur much more rapidly than the intermolecular polymerization (Figure 2a). For this work, it was proposed that by incorporating alternating *N*,*N*′-dimethylethylenediamine units with 4-hydroxybenzyl alcohol units linked via carbamates as shown in Figure 2b, the site of the monomer activation for polymerization could be moved distal to the diamine, thus significantly slowing the intramolecular cyclization, allowing effective polymerization of the activated heterodimer. Upon removal of the end-cap from the amine polymer terminus, cyclization of the diamine should occur, releasing *N*,*N*′-dimethylimidazolidinone and revealing the phenol. The phenol should then undergo a 1,6-elimination, ultimately releasing 4-hydroxybenzyl alcohol, CO_2, and another amine terminus, from which the cascade can continue until depolymerization is complete.

Monomer Synthesis. The synthesis of the target monomer began by the reaction of 4-hydroxybenzyl alcohol with *tert*-butyldimethylsilyl (TBS) chloride in the presence of imidazole to provide compound **2**, with selective protection on the aliphatic alcohol as shown in Scheme 1. The phenol of **2** was then activated using 4-nitrophenyl chloroformate to provide the activated carbonate **3**. Tri(ethylene glycol) monomethyl ether was added to the reaction mixture upon completion of the activation to quench the remaining chloroformate, which was otherwise inseparable from **3**. *N*,*N*′-Dimethylethylenediamine (**4**) was converted to the mono *tert*-butylcarbamate (Boc) protected derivative **5** by reaction with di-*tert*-butyldicarbonate, and then the other amine was reacted with the activated carbonate **3** in the presence of 4-(dimethylamino)pyridine

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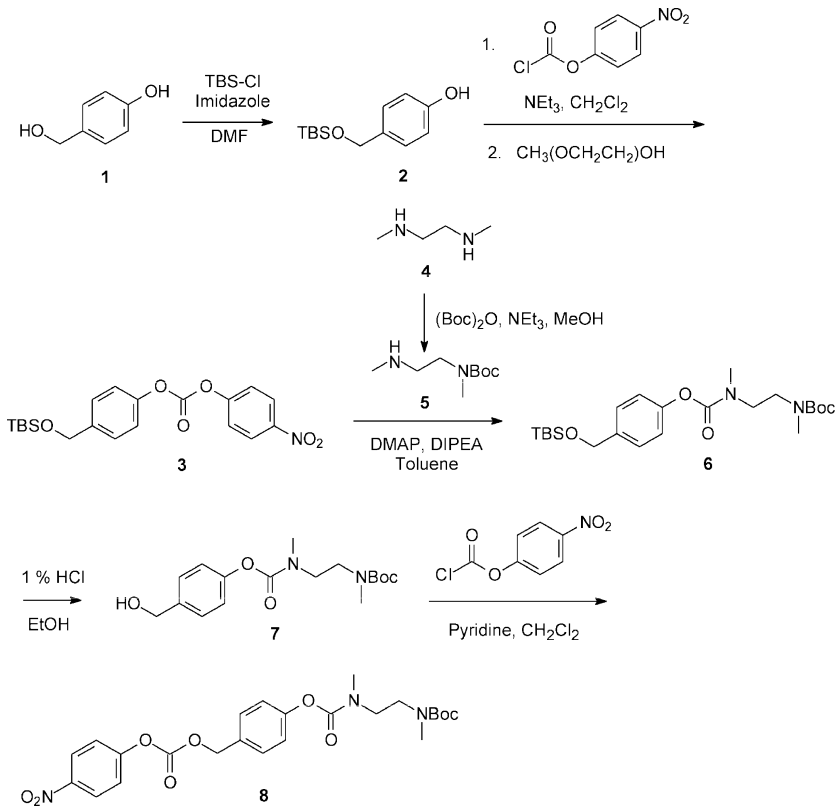
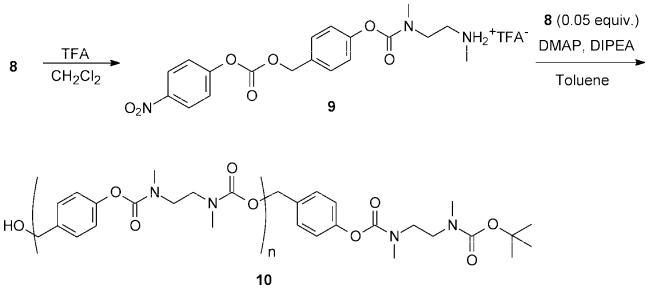
Scheme 1



Scheme 2



(DMAP) and *N*,*N*-diisopropylethylamine (DIPEA) to provide the carbamate **6**. Removal of the TBS protecting group was accomplished with 1% HCl in EtOH, conditions under which the Boc protecting group remained intact, to give **7**. Finally, the protected polymerization monomer **8** was prepared by activation of **7** with 4-nitrophenylchloroformate.

Polymer Synthesis. Removal of the Boc protecting group from compound **8** using trifluoroacetic acid (TFA) provided the monomer **9**, capable of self-condensing via reaction of the amine with the activated carbonate to form a polycarbamate, releasing *p*-nitrophenol (Scheme 2). When isolated as the TFA salt, the amine was sufficiently stable such that as long as the deprotection was performed within hours prior to the polymerization reaction it could be isolated and transferred to the polymerization conditions without premature polymerization or cyclization. Compound **8** with the Boc capped amine also served as a convenient end-cap in the synthesis of the initial model polymer. Although a Boc group cannot be readily cleaved under any known physiological conditions, it can be easily cleaved with TFA under nonaqueous conditions, allowing the depolymerization process to be studied independently of the end-cap cleavage. Thus, monomer **9** was reacted with 0.05 equiv of the end-cap **8** in the presence of DMAP and DIPEA to provide the polymer **10**. On the basis of the synthesis of **6** from **3**, it had already been determined that the reaction of the secondary amines with 4-nitrophenyl carbonates was a rapid and very high yielding process, thus favoring its use as the key polymerization reaction. Indeed, the crude polymer was isolated in a 92% yield following extraction to remove the *p*-nitrophenol, DIPEA, and DMAP, and less than 5% of the monomer had been converted into the cyclic urea byproduct as determined by ^{1}H NMR spectroscopy. This indicated that the polymerization reaction successfully competed with potential intramolecular cyclizations under the reaction conditions. It is also noteworthy that, although each monomer had a *p*-nitrophenyl end group at the beginning of the polymerization, no *p*-nitrophenyl groups were observed in the polymer product. This indicates that this group was lost during the polymerization, in the reaction medium upon completion of the polymerization, or during workup, leaving a benzylic alcohol terminus. This is not surprising considering the high reactivity of this group under these conditions.

SEC analysis of polymer **10** showed a relatively broad distribution of molecular weights (MWs) and some low MW oligomers (Supporting Information), some of which may be cyclic oligomers, consistent with the expected result for a condensation type polymerization. Therefore, to facilitate the degradation studies, the higher MW fraction was isolated in 45% yield by preparative SEC in *N*,*N*-dimethylformamide (DMF) to provide a monomer to end-cap ratio of approximately 16:1 based on ^{1}H NMR analysis. A number average molecular weight (M_n) of 17 000 and polydispersity index (PDI) of 1.58 were determined on the basis of SEC relative to polystyrene standards (Figure 3). The overestimation of the MW by SEC using a conventional calibration can be attributed to the contracted

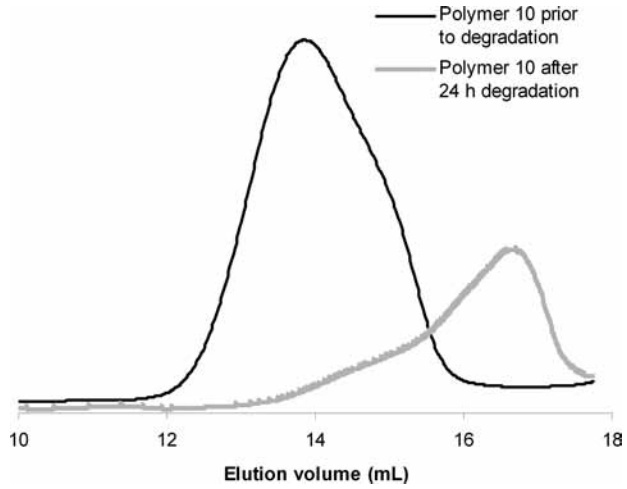


Figure 3. Size exclusion chromatograms of polymer **10** prior to degradation (after preparative SEC) and after 24 h of degradation (eluent = DMF with 10 mM LiBr and 1% (v/v) NEt_3; detection by differential refractive index).

conformation of polystyrene relative to polymer **10** in DMF as DMF is a relatively poor solvent for polystyrene.[59] Polymer **10** did not provide a light scattering signal of sufficient intensity to allow for absolute MW determination by multiangle light scattering, likely due to its relatively low MW, but the ^{1}H NMR analysis should provide an accurate measurement of the average degree of polymerization. Preparative SEC could be easily performed on 200 mg batches of polymer, which was suitable for the current study, but for scale up, it is anticipated that dialysis using a membrane with an appropriate MW cutoff can likely be used.

Degradation Kinetics for Polymer 10. While the rate of the 1,6-elimination reaction has previously been reported and was found to be very rapid,[54,55] the diamine cyclization was expected to be much slower.[52,57] As this was anticipated to be the rate-limiting step in the polymer degradation, it was important to investigate its rate under the same conditions to be used in the polymer degradation study to gain insight into the time scale expected for the depolymerization. To accomplish this, the Boc protecting group was removed from compound **7** by treatment with TFA/CH_2Cl_2, and the product was incubated in a 0.1 M phosphate buffer:acetone (3:2) at 37 °C. The appearance of *N*,*N*′-dimethylimidazolidinone and 4-hydroxybenzyl alcohol was quantified by ^{1}H NMR spectroscopy. Mass spectrometry was used to further support the identities of the proposed degradation products (Supporting Information). As shown in Figure 4a, the cyclization was complete after approximately 3 h, and fitting of the data to a first-order rate law provided a half-life of approximately 35 min, very close to that measured by Saari et al. in a fully aqueous system.[57] It is noteworthy that, although quantitative kinetic studies were not carried out in other solvents, it was found that the cyclization was generally slower in less polar solvents. The 0.1 M aqueous phosphate buffer:acetone (3:2) mixture was selected for the above kinetic study as it was found to be the most polar one capable of fully dissolving polymer **10**.

To study the degradation of polymer **10**, the polymer was treated with TFA/CH_2Cl_2 to remove the Boc end-cap, and then the polymer was incubated in 0.1 M phosphate buffer:acetone (3:2). The degree of degradation was quantified by ^{1}H NMR

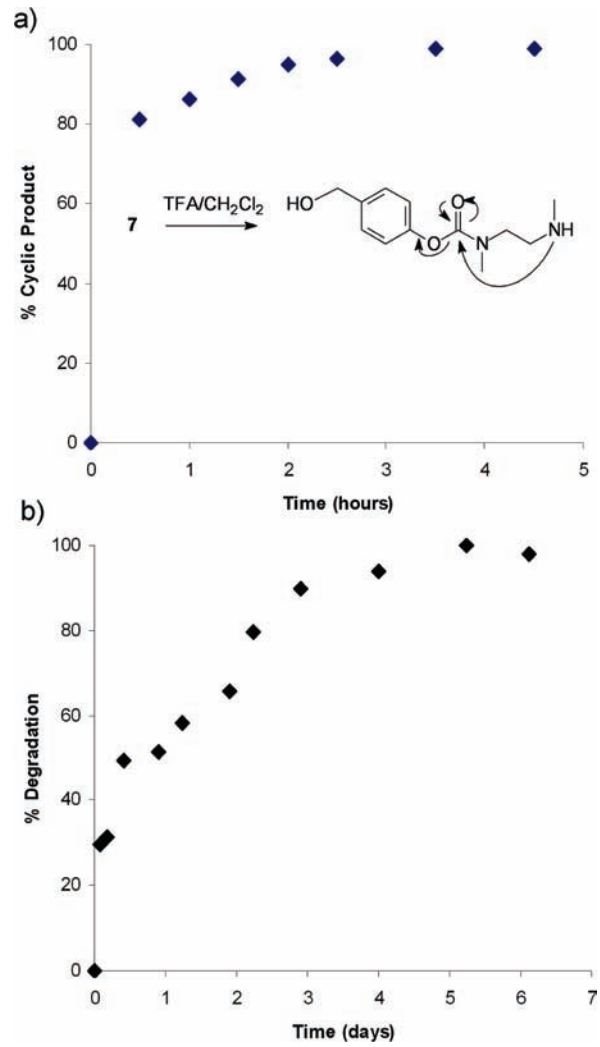


Figure 4. (a) Kinetics of cyclization of compound **7**, as measured by ^{1}H NMR spectroscopy in 0.1 M phosphate buffer (D_2O):acetone-d_6 (3:2) at 37 °C, following removal of the Boc protecting group. (b) Kinetics of depolymerization of polymer **10**, as measured by ^{1}H NMR spectroscopy in 0.1 M phosphate buffer (D_2O):acetone-d_6 (3:2), following removal of the Boc end-cap.

spectroscopy. As shown in Figure 5, peaks corresponding to 4-hydroxybenzyl alcohol and *N*,*N*′-dimethylimidazolidinone emerged as the degradation progressed. This supports that the degradation occurred by the proposed depolymerization mechanism as a degradation mechanism based primarily on random chain scission of the carbamate linkages in the polymer backbone would generate primarily *N*,*N*′-dimethylethylenediamine rather than the cyclic urea. As predicted on the basis of the half-life for the cyclization, and the approximate length of the polymer, the degradation was 50% complete in less than 1 day, and complete degradation was observed after 4−5 days (Figure 4b). In comparison, a control sample of polymer **10** in which the Boc end-cap was left intact exhibited only trace levels of degradation after 4 days (Supporting Information). The fact that the depolymerization reached completion also indicates that there was no significant amount of nondegradable cyclic polymers in this high MW fraction that was subjected to degradation. The degradation was also monitored by SEC, and it was found that after 24 h of degradation, as shown in Figure 3, there was a significant increase in the retention time of the

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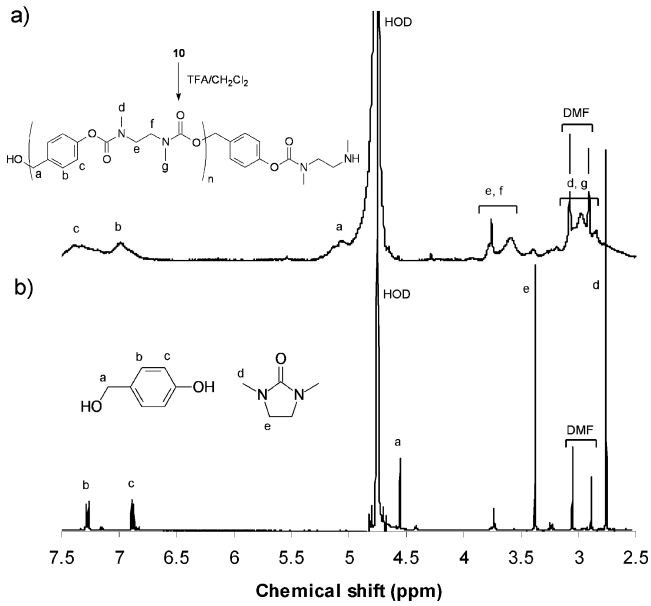
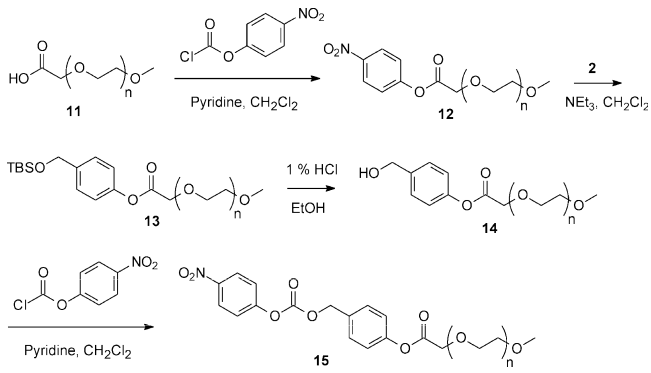
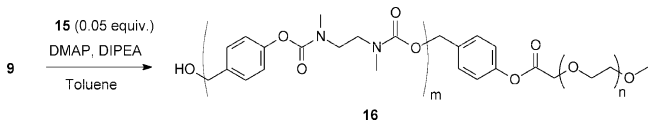


Figure 5. ^{1}H NMR spectra of (a) polymer **10** following end-cap removal in 0.1 M phosphate buffer (D_2O):acetone-d_6 (3:2) at $t = 0$ in the degradation process and (b) the same polymer solution after 5 days at 37 °C, showing complete depolymerization into small molecules.

Scheme 3



Scheme 4



polymer, corresponding to a decrease in the polymer MW. After 4 days, no polymeric material could be detected by SEC.

Synthesis of a PEO End-cap. The development of an end-cap based on PEO was motivated by the possibility of forming an amphiphilic block copolymer capable of assembling into cascade degradable aggregates in aqueous solution. In this study, an ester linkage that could readily be hydrolyzed under neutral physiological conditions was selected for the conjugation of the PEO block to the terminus of the cascade degradable block, but this concept could readily be extended to pH or redox-sensitive linkages to initiate the degradation cascade under a wide range of conditions. In contrast to a traditional polyester, only one ester cleavage should be required to initiate the degradation cascade.

As shown in Scheme 3, the synthesis of the PEO end-cap began by reaction of the commercially available acid terminated PEO monomethyl ether **11** having a MW of approximately 5000 g/mol, with 4-nitrophenyl chloroformate to provide the active ester **12**. This active ester was reacted with the phenol **2** in the presence of triethylamine to provide the ester **13**. The TBS protecting group of **13** was then removed by treatment with 1% HCl in EtOH, and the resulting alcohol **14** was activated with 4-nitrophenyl chloroformate to provide the activated end-cap **15**.

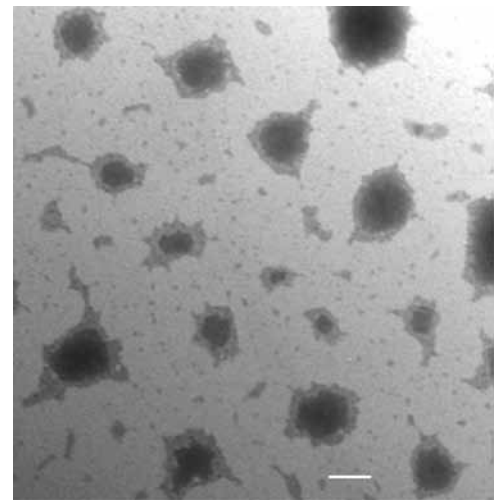


Figure 6. Transmission electron microscopy image of nanoparticles formed by the assembly of polymer **16** in water. Staining was performed with phosphotungstic acid. Scale bar = 100 nm.

Synthesis and Assembly of the PEO−Polycarbamate Block Copolymer. Polymerization of the deprotected monomer **9** with the end-cap **15** was carried out under the same polymerization conditions described above to provide the block copolymer **16** in 76% yield (Scheme 4). Like polymer **10**, this polymer was further purified by preparative SEC for kinetic studies. ^{1}H NMR analysis in $CDCl_3$ indicated that the ratio of monomer to end-cap in the resulting polymer was approximately 15:1, while an M_n of 28 700 and a PDI of 1.22 were measured by SEC relative to polystyrene standards. When polymer **16** was added to pure water or 0.1 M phosphate buffer, the polymer did not immediately dissolve, but with sonication it readily dispersed. Transmission electron microscopy (TEM) performed using phosphotungstic acid as a stain revealed the presence of nearly spherical aggregates with a relatively broad distribution of diameters ranging from less than 100 nm to a few hundred nm (Figure 6). The light corona surrounding the darker core suggests that the hydrophobic aromatic polycarbamate block forms the cores of the nanoparticles while the hydrophilic PEO coats their surfaces. TEM performed using osmium tetroxide to stain the polycarbamate block also revealed the presence of spherical aggregates (Supporting Information). Assemblies in water were also detected by dynamic light scattering (Supporting Information). The extreme broadness and very low intensities of the peaks corresponding to the hydrophobic polycarbamate block of **16** in its ^{1}H NMR spectrum in D_2O is additional evidence of the polymer's assembly (Figure 7a).

Degradation Kinetics for Polymer 16. Prior to evaluating the degradation rate of the end-capped polymer **16**, it was of interest to determine the rate at which the ester linkage of the end-cap would be hydrolytically cleaved under physiological conditions, as this was the essential first step in initiating the degradation cascade. Thus, the PEO derivative **14** was incubated in 0.1 M phosphate buffered D_2O at 37 °C, and the release of the hydrolysis product 4-hydroxybenzyl alcohol was quantified by

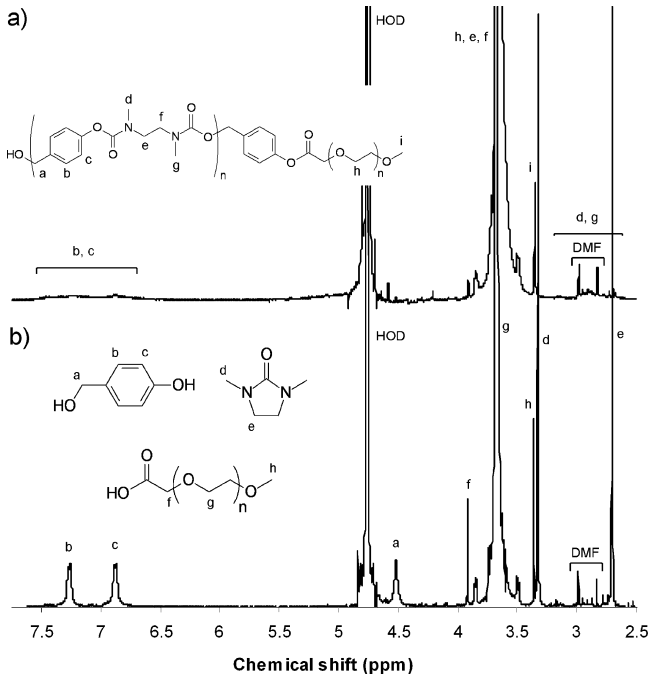


Figure 7. ^{1}H NMR spectra of (a) polymer **16** in 0.1 M phosphate buffered D_2O and (b) the same polymer solution after 29 days at 37 °C, showing complete depolymerization.

^{1}H NMR spectroscopy. As shown in Figure 8a, the hydrolysis occurred over a period of approximately 1−2 days, with a calculated half-life of 15 h.

To measure the rate of degradation of the assemblies formed from polymer **16**, the polymer was dispersed using sonication in 0.1 M phosphate buffered D_2O and incubated at 37 °C. The depolymerization was monitored by ^{1}H NMR spectroscopy. As described above for polymer **10**, peaks corresponding to 4-hydroxybenzyl alcohol and *N*,*N*′-dimethylimidazolidinone emerged as the degradation progressed (Figure 7b), and the kinetic data are shown in Figure 8b. Even taking into account the time required for the removal of the PEO end-cap via ester hydrolysis, the depolymerization rate is clearly slower than that observed for polymer **10**. This can likely be attributed to the formation of the above-described nanoparticles from polymer **16** in aqueous solution. While the depolymerization of **10** was carried out in a water:acetone mixture in which the polymer was fully dissolved, the depolymerization of **16** occurred at the hydrophobic core of the nanoparticles. A slowing of reactions with polar transition states in the hydrophobic cores of micelles has been previously reported[32,60] and is consistent with the observation that the diamine cyclization was quite dependent on the polarity of the solvent. These results indicate that the rate of the cascade degradation can be modulated not only by incorporating new monomers with different depolymerization rates, but also by modulating the hydrophobicity of the materials and controlling their assembly into nanoaggregates.

It is also of interest to note that the depolymerization kinetics for both polymer **10** and **16** are significantly slower than those of the previously reported backbone based entirely on 1,6-elimination spacers.[54,55] While a rapid depolymerization is a definite asset for the previously reported application of amplified sensing, the availability of a polymer degrading in a controlled manner, but at a slower rate, opens up many new potential applications such as drug carrier systems or biomedical devices where a more prolonged degradation or release of molecules is required.

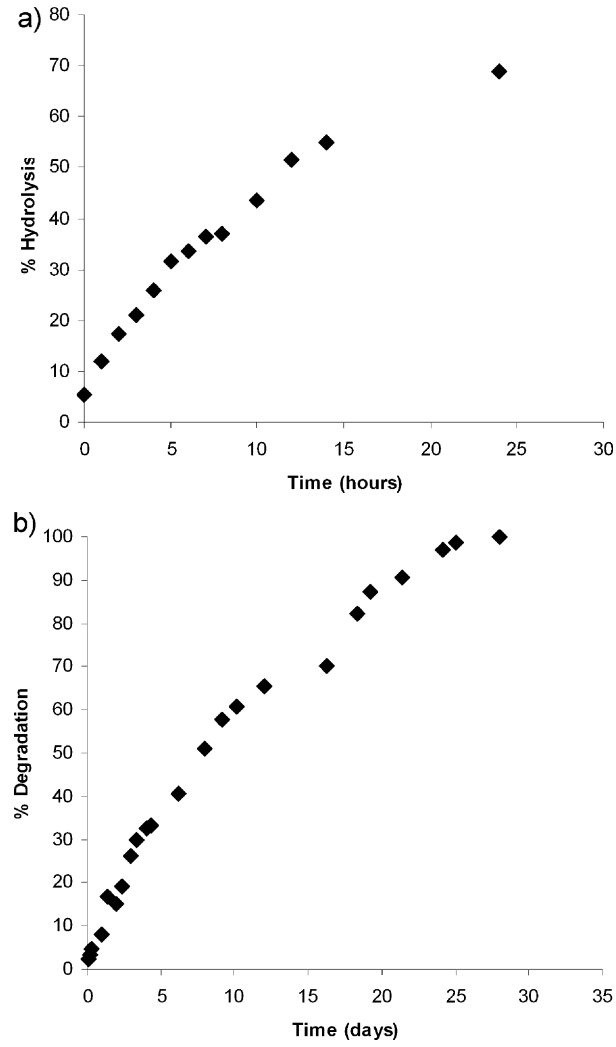


Figure 8. (a) Ester hydrolysis kinetics for the PEO derivative **14** in 0.1 M phosphate buffered D_2O at 37 °C as measured by ^{1}H NMR spectrscopy. (b) Kinetics of depolymerization of polymer **16** in 0.1 M phosphate buffered D_2O at 37 °C as measured by ^{1}H NMR spectroscopy.

Evaluation of Controlled Release Properties. To evaluate the potential utility of this new polymer system for encapsulation and controlled release applications, the dye Nile Red was encapsulated, and its release was studied. Nile Red was chosen as a hydrophobic dye because its fluorescence is negligible in aqueous solutions but is known to increase substantially in the hydrophobic compartments of polymer assemblies.[61,62] The encapsulation was performed by sonicating the polymer in pH 7.4 phosphate buffer in the presence of insoluble Nile Red. As the nanoparticles formed, Nile Red was taken up as evidenced by a ∼20-fold increase in the fluorescence of the solution in comparison with the minimal fluorescence of Nile Red, which was sonicated in phosphate buffer alone. The loaded nanoparticles were then incubated in this buffer at 37 °C, allowing depolymerization of the polymers to occur. Over a time period

(60) Chan, Y.; Wong, T.; Byrne, F.; Kavallaris, M.; Bulmus, V. *Biomacromolecules* **2008**, *9*, 1826–1836.
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(62) Krishna, M. M. G. *J. Phys. Chem. A* **1999**, *103*, 3589–3595.

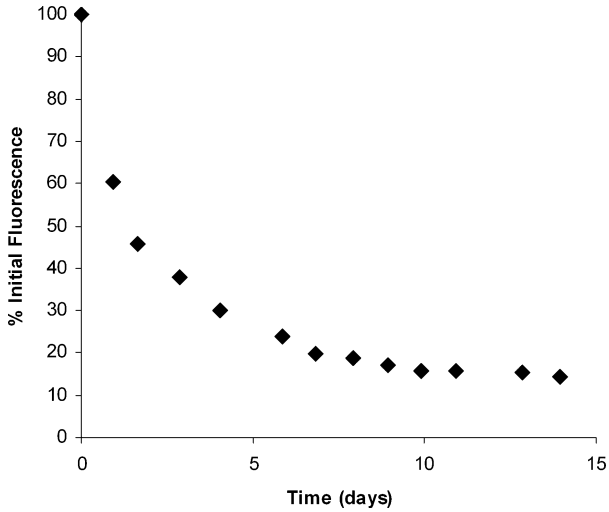

Figure 9. Fluorescence decrease of Nile Red corresponding to its release from nanoparticles comprising polymer **16**, as a function of time incubated in pH 7.4 phosphate buffer at 37 °C.

of 2 weeks, the fluorescence of the dye relative to a control solution of Nile Red decreased to less than 15% of its initial fluorescence, consistent with its release from the nanoparticles (Figure 9). The time scale of this release was similar to that of the polymer degradation. This experiment therefore suggests that nanoparticles comprising cascade degradable polymers can provide well-controlled release properties that depend on the rate of depolymerization.

Conclusions

In conclusion, a new approach was developed for the incorporation of spontaneously cyclizing monomers into linear polymers, providing a new class of cascade degradable linear polymers. This approach was based on the use of activated heterodimers as polymerization monomers, leading to polymers degrading by alternating elimination and cyclization reactions. Kinetics studies were carried out on both the monomer and the corresponding polymer, and the data supported the proposed route of degradation via end to end depolymerization. This work therefore demonstrated that cyclization spacers could be incorporated to control the rate of degradation, and as a number of different cyclization spacers have previously been reported,[56] this approach should allow for the depolymerization rate to be readily tuned according to the desired application, while the choice of the end-cap can be used to determine under which conditions the degradation will be initiated. In addition, using a PEO end-cap, an amphiphilic block copolymer was developed and was demonstrated to assemble into cascade degradable nanoparticles in aqueous solution. It was possible to encapsulate the hydrophobic fluorescent dye Nile Red into these nanoparticles and to subsequently release it over the time scale of the depolymerization. This ability of the block copolymers to form functional nanoassemblies in aqueous solution is highly promising as it opens up many new and exciting applications of the materials.

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Supporting Information Available: Details of all chemical syntheses, characterization data and ^{1}H NMR spectra for all new molecules, procedures for degradation studies, Nile Red encapsulation study and transmission electron microscopy, SEC of polymer **10** prior to preparative SEC, control NMR of polymer **10**'s degradation without end-cap removal, additional TEM image and dynamic light scattering data for assemblies formed from polymer **16**, and mass spectrometry data for degradation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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