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Intramolecular Cyclization for Stimuli-Controlled Depolymerization of Polycaprolactone Particles Leading to Disassembly and Payload Release

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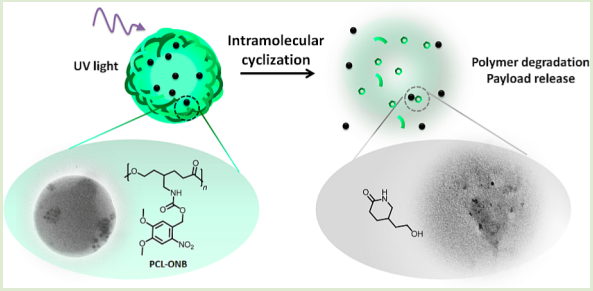
Supporting Information

ABSTRACT: Polymers capable of on-demand, controlled depolymerization are an important tool in a broad variety of applications in science, technology, and industry. We report functionalized poly(caprolactone)s (PCL)s designed to allow on-demand and complete depolymerization through incorporation of pendant protected amino groups that, on deprotection, trigger nucleophilic attack and yield a single cyclic product. Two cleavable protecting groups were used to cap PCL: light sensititve *o*-nitrobenzyl alcohol (ONB) and *tert*-butyl carbamate (Boc; for proof of concept). NMR confirmed that PCL-Boc degrades completely into the designed intramolecular cyclization products within a day upon deprotection. TEM visualization of irradiated particles made from PCL-ONB encapsulating iron oxide nanoparticles reveals complete disruption of nanoparticles and release of payload. This work demonstrates that intramolecular cyclization within the polymer backbone is an excellent route to accelerate polymer degradation by backbiting reactions into small fragments that should be easily cleared from the circulation.



While there has been enormous progress in developing novel methods to synthesize and control the synthesis and assembly of polymers during the past several decades, less effort has been devoted to designing chemical mechanisms of controlled depolymerization or polymeric particle disassembly.[1] Most reported depolymerization mechanisms of polymers or self-immolative degradation of dendrimers involve a cascade of self-elimination reactions[2−4] or hemiacetal hydrolysis.[5] However, a few degrade through such processes combined with a cyclization mechanism involving a diamine spacer and yielding urea derivatives.[6−11] In the present study, our proposed design allows the formation of particles that rapidly degrade and release encapsulated contents through triggered intramolecular cyclization reactions that cleave the polymer backbone. We choose to work with poly(ε -caprolactone)s (PCLs)[12] to take advantage of their biocompatibility, as this could facilitate applications (e.g., in tissue engineering scaffolds, sutures, or drug carriers) where triggered degradation would be useful.

Most polymers used in biomedical applications (polyesters, polycarbonates, polycarbamates, polyanhydrides, polyketals) are degraded by hydrolysis or enzymes, requiring water to interact with the polymer, so the degradation kinetics of particles, hydrogels or fibers are dictated by water accessibility.[13−19] We aim to develop new chemical mechanisms relying on intramolecular cyclization, allowing degradation without interaction with water (Figure 1). We hypothesize that such a mechanism would allow more controlled, on-demand degradation or depolymerization of hydrophobic polymer assemblies. On-demand depolymerization is achieved by incorporating light-sensitive chemistries; optical stimuli can be remotely applied for a short period of time with high spatial and temporal precision (Figure 1).[20,21]

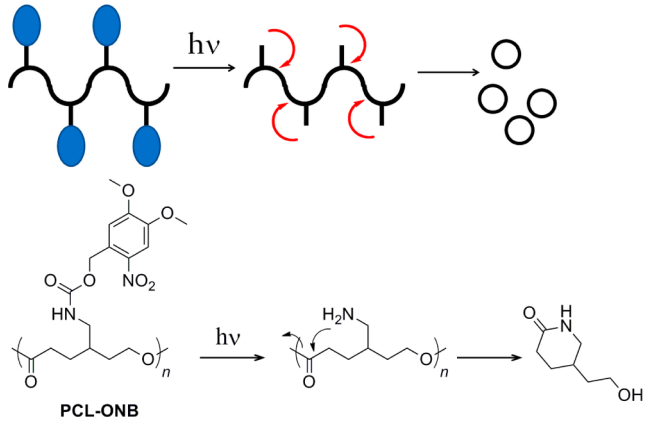


Figure 1. Illustration, structure, and mechanism of the disassembly process. Removal of the photocleavable protecting groups upon irradiation triggers intramolecular cyclization in each deprotected subunit to reach complete depolymerization of PCL-ONB.

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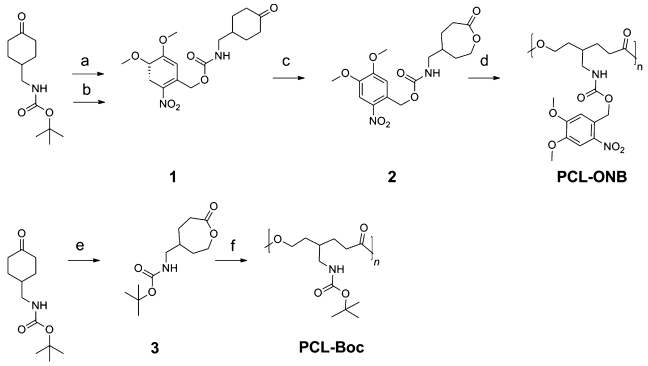
PCLs degrade slowly (half-life of one year in vivo) by hydrolysis of their ester linkages in physiological conditions,[22] limiting their applicability.[12] To speed degradation, others have copolymerized caprolactone with DL-lactide, DL-ε-decalactone δ-valerolactone, or cyclic ester amides.[23,24] While this strategy of changing hydrophobicity does accelerate degradation by reducing the polymer melting point, degradation is still too slow for triggered release. Our proposed degradation strategy is different, offering greater control and likely much faster degradation. This is the first attempt, to our knowledge, to employ PCLs for triggered degradation.

Here, we demonstrate that a PCL capable of intramolecular backbiting reactions allows triggered and fast release from a hydrophobic nanoparticle and degradation within 24 h in the absence of ester linkage hydrolysis. Release kinetics and the products formed upon degradation confirm our hypothesis. Thus, we expand the limited toolbox of polymer chemistries that rely on intramolecular mechanisms of backbone degradation.

Scheme 1 shows the 4-step and 2-step syntheses of PCL-ONB and PCL-Boc. Key steps are the introduction of the light-

Scheme 1. Synthesis of PCL-ONB and PCL-Boc Polymers[a]



[a]Reagents and conditions: (a) TFA/DCM (1/1); (b) 4,5-dimethoxy-2-nitrobenzyl (4-nitrophenyl) carbonate, DIEA, DCM (91%); (c) *m*-CPBA, $NaHCO_3$, $CHCl_3$ (86%); (d) $SnOct_2$ (32%); (e) *m*-CPBA, $NaHCO_3$, $CHCl_3$ (97%); (f) $SnOct_2$ (71%).

sensitive group through a carbamate linkage (b), the formation of a 7-membered ring by a Baeyer–Villiger oxidation using *meta*-chloroperbenzoic acid (*m*-CPBA) (c), and the ring-opening polymerization (ROP) of the cyclic ester monomer using stannous octoate ($SnOct_2$) catalyst (d). We synthesized both a light-sensitive version, in which amine groups were protected with *o*-nitrobenzyl groups, and a model Boc-protected polymer to study the mechanism of degradation. Light-sensitive polymers were formulated into nanoparticles encapsulating model payloads to examine the kinetics of release. Polymer synthesis is reported in the Supporting Information.

We compared the NMR spectrum of PCL-Boc to that of the products formed after removal of the protecting group as a function of incubation time in deuterium phosphate buffer (0.2 M) at pH 7.4 (37 °C). Spectral differences indicate that the polymer is fully degraded after 24 h into only the expected target small molecule (Figure 2).

It is noteworthy to mention that almost 80% of the polymer is degraded after only 5 h at pH 7.4 (Figure 3, blue). As expected, the kinetics are slower when the polymer is incubated

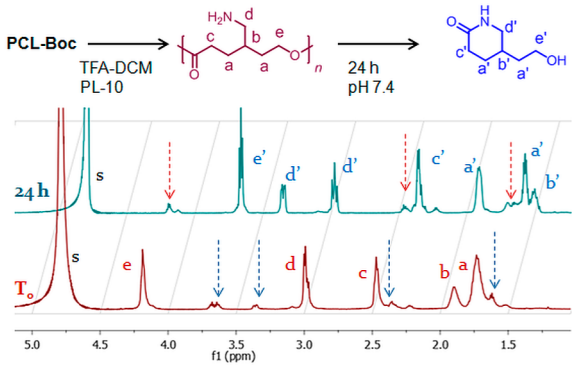


Figure 2. PCL degrades into a single product upon deprotection. ^{1}H NMR spectra of deprotected PCL in deuterium phosphate buffer (0.2 M) at pH 7.4, after deprotection (red), and after being incubated for 24 h at 37 °C (blue). Blue arrows indicate degradation products present immediately following deprotection; red arrows indicate residual traces of polymer.

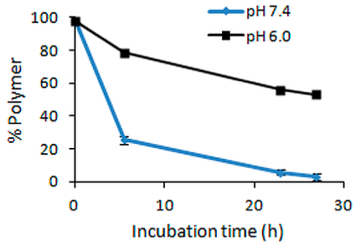


Figure 3. PCL degrades completely within 24 h at pH 7.4. Kinetics of degradation at two different pH values determined by ^{1}H NMR (7.4 and 6.0).

at acidic pH (Figure 3, black). No ester hydrolysis is observed in this time frame: our polymer design degrades so rapidly upon cyclization that water does not affect the rate of depolymerization. If the polymer underwent hydrolysis, the chemical shift for one proton in the α position of the amine would be observed upfield, likely in the range of 2.6–3.0 ppm. However, what we observe is a low field shift (3.3 ppm) in agreement with amide formation.

In addition, stability toward hydrolysis was also tested using PCL-Boc (not deprotected) by NMR and GPC. Solutions of the polymer in either 0.2 M deuterium phosphate buffer at pH 7.4/acetonitrile (2/3) or 0.2 M phosphate buffer at pH 7.4/acetonitrile (2/8), respectively, were incubated at 37 °C. There is no evidence of hydrolysis in the NMR spectrum after 5 days (Figure 4a). Aliquots removed periodically did not show any decrease in molecular weight by GPC over 12 days (Figure 4b).

Finally, we investigated whether nanoparticles consisting of this polymer release contents in response to light. We formulated particles from PCL-ONB encapsulating 10 nm super paramagnetic iron oxide (Fe_3O_4) nanoparticles (SPIONs) by single emulsion and examined them by TEM. The nonirradiated particles are intact after 24 h (Figure 5a), with SPIONs found only inside the particles, while irradiated particles are no longer visible; only chunks of material in coexistence with free SPIONs remain (Figure 5b). Notably, the time frame of 24 h is in perfect agreement with the NMR degradation study, which does not show any hydrolysis of the ester linkages. Thus, we believe that particle disruption results only from polymer degradation and not a switch in hydro-

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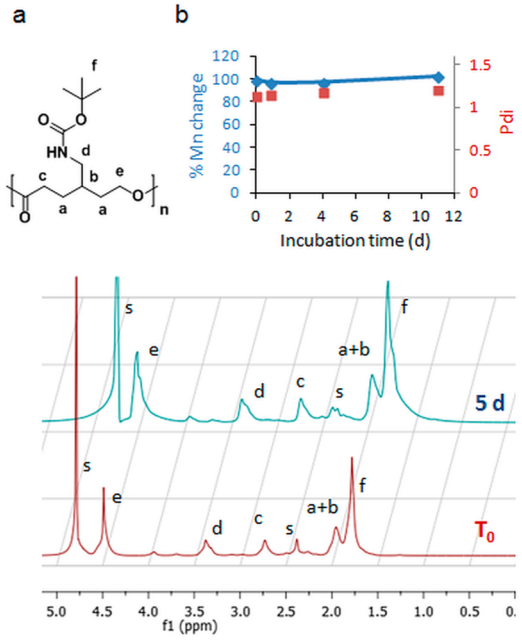

Figure 4. PCL-Boc is stable against hydrolysis over 5 d. ^{1}H NMR spectra of nondeprotected PCL-Boc in a mixture of deuterium phosphate buffer (0.2 M) at pH 7.4/acetonitrile, after preparation (T_0) and after being incubated for 5 days at 37 °C (a). Mn and Pdi of nondeprotected PCL-Boc as a function of incubation time (b).

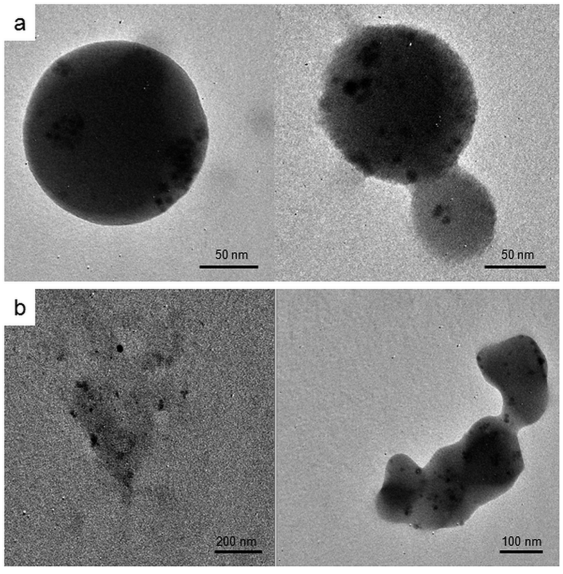

Figure 5. Irradiation triggers disruption of PCL-ONB particles. Representative TEM images of nanoparticles; either unirradiated (a) or irradiated for 5 min (b) after 24 h incubation at 37 °C in phosphate buffer (pH 7.4, 10 mM).

philicity. Additional TEM images of nonirradiated and irradiated particles are presented in Figures S1 and S2.

In conclusion, our new light-responsive polymer design demonstrates a new intramolecular cyclization mechanism as a selective route to rapid triggered depolymerization and release from nanoparticles. NMR degradation studies confirm fast degradation and validate that a single product is obtained. In addition, our PCL design degrades in a controlled manner in a day only upon deprotection, when the backbiting cyclization is possible. As far as nanoparticle degradation is concerned, while a decrease in hydrophobicity caused by the deprotection of amines cannot be eliminated, as 80% of the polymer is degraded within 5 h, we believe that degradation and release is induced primarily by cyclization. As the versatile design of this system allows easy replacement of the triggering group, the presented strategy may have a broad impact on polymer science if applied to the right platform, with well-chosen triggering groups.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for the synthesis of PCL-ONB, PCL-Boc, and intermediates, procedure for nanoparticle formulation, and additional TEM images of nanoparticles formulated from PCL-ONB. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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