Hydrogels

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Programmed Degradation of Hydrogels with a Double-Locked Domain

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Abstract: *The ability to control the degradation of a material is critical to various applications. The purpose of this study was to demonstrate a concept of controlling degradation by using a double-locked domain (DLD). DLDs are molecular structures with two functional units that work cooperatively under environmental stimulation. One unit is triggered to transform without cleavage in the presence of the first stimulus, but this transformation enables the activation of the other unit for cleavage in the presence of the second stimulus. A DLD is presented that is activated to transform through intramolecular reconfiguration when exposed to light. After this transformation, the light-triggered DLD can undergo rapid cleavage under acid treatment. When this DLD is used as the crosslinkers of hydrogels, hydrogels undergo rapid degradation after sequential exposure to light irradiation and acid treatment. Reversing the order of light irradiation and acid treatment or only using individual stimulation does not lead to comparable degradation. Thus, this study has successfully demonstrated the great potential of using DLDs to achieve programmable degradation of materials.*

Control of degradation is an important mission in the field of materials science. It has been extensively studied for applications such as drug delivery,[1] tissue engineering,[2] surgery,[3] coating[4] and packaging.[5] To control degradation, it is necessary to integrate responsive molecules into materials as crosslinkers, structural units, or side groups. A variety of responsive molecules have been synthesized for molecular cleavage in response to environmental stimuli such as pH,[6] light,[7] temperature,[8] redox potential,[9] and ions.[10] Many of these molecules have been successfully applied to the synthesis of degradable materials. Recent effort has been further made in integrating different types of responsive molecules into one system to advance the ability to control the degradation of materials.[11] However, these responsive molecules work independently rather than cooperatively, providing no additional temporospatial specificity or accuracy in the control of degradation. To date no material with a double-locked domain (DLD) has been developed.[12] Materials with DLDs would have the ability to undergo rapid degradation after sequential exposure to two stimuli, whereas individual stimulation or reversing the order of the two stimuli will not induce rapid degradation. The development of materials of this kind is expected to advance the diversity, flexibility, and specificity of controlling the functions of materials in a temporospatial manner.

The purpose of this work was to develop a concept of controlling the degradation of materials by using a DLD. Figure 1 shows this concept and a comparison with traditional designs. With traditional designs, a molecular bond undergoes cleavage after exposed to a specific stimulus. By contrast, when a DLD is exposed to a specific stimulus, one of its functional units undergoes molecular transformation but not cleavage. This transformed unit enables the other unit to be activated for cleavage in the presence of another specific stimulus. We used light- and pH-responsive chemical bonds as an example (Figure 1c) to synthesize DLDs and hydrogels to demonstrate the concept.

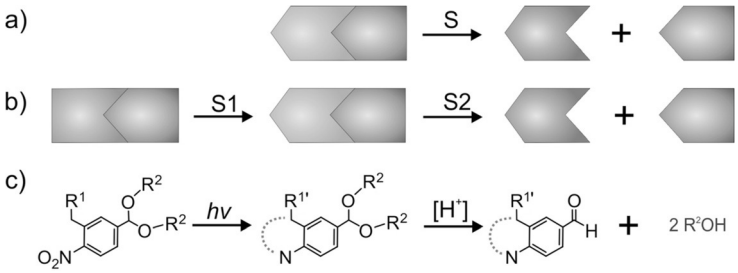

Figure 1. Schematic illustration of the principle of controlling molecular cleavage and degradation. a) Traditional design for triggered molecular cleavage in the presence of one specific stimulus (S). b) A DLD for molecular transformation and cleavage after sequential treatment with two stimuli (S1 and S2). c) An example of a DLD as presented herein to show molecular transformation and cleavage after the DLD is sequentially exposed to light irradiation and acid treatment.

The synthetic route and molecular structures of three DLDs are shown in Figure 2a. We first examined the molecular stability and responsiveness of DLD-1 to light and acid (Figure 2b) due to it simple molecular structure. DLD-1 has two domains, including *o*-nitrophenyl ethanol (ONPE) and acetal groups. On the one hand, it was hypothesized that acetal used as a substituted group of ONPE would not inhibit the photo responsiveness of ONPE. On the other hand, the acetal group would be inert to low pH since ONPE has a *p*-substituted nitro group to withdraw electrons strongly. Thus, DLD-1 would be responsive to light but not low pH in its original state. However, when DLD-1 is

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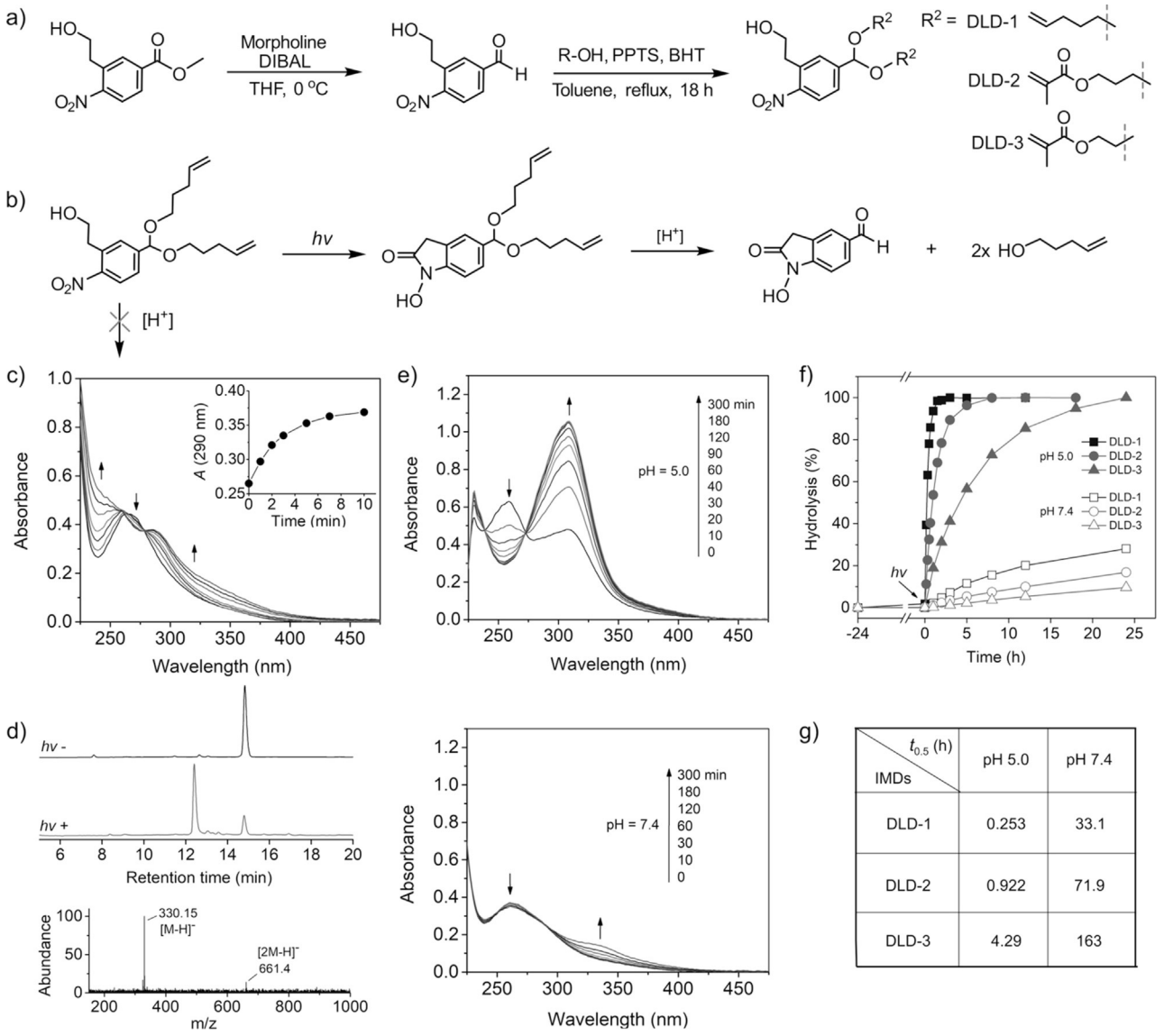

IMDs \ $t_{0.5}$ (h)	pH 5.0	pH 7.4
DLD-1	0.253	33.1
DLD-2	0.922	71.9
DLD-3	4.29	163

Figure 2. Synthesis and characterization of DLDs. a) Synthesis of the DLDs. b) Structural transformation of DLD-1 during stimulation. c) UV/Vis absorption spectra of DLD-1 upon light irradiation. The inset shows the time-dependent change in absorbance at 290 nm. d) HPLC–MS analysis of DLD-1 before and after light irradiation. e) Time-dependent UV/Vis absorbance change of light-triggered DLD-1 after incubated in the pH 5.0 (up) or pH 7.4 (bottom) solution. f) Hydrolysis kinetics of light-triggered DLDs at pH 5.0 or pH 7.4. g) Half-lives of light-triggered DLDs at pH 5.0 or pH 7.4.

exposed to light, it was expected that photoirradiation would lead to intramolecular photocyclization of OPNE.[13] This would lead to a reduction of the nitro group to form electron-abundant oxindole as a new substituted group of acetal. As a result, the acetal group would become pH-sensitive and thus light-triggered DLD-1 would be responsive to acid treatment for hydrolysis.

To test the hypothesis, the responsiveness of DLD-1 to environmental stimulation was first studied using UV/Vis spectroscopy. DLD-1 exhibited one characteristic UV/Vis absorption peak at 272 nm. Without light irradiation, this peak barely changed with time when the pH value of the DLD-1 solution was above 4 (Figure S1 in the Supporting Information). These results demonstrate that without exposure to light irradiation, DLD-1 is highly stable in an acidic environment with the pH value above 4. However, the exposure of the DLD solution at pH 7.4 to UV light (302 nm, 3 $mW\,cm^{-2}$) led to a decrease in absorption at 272 nm and a concomitant increase in absorption at both 245 nm and 293 nm (Figure 2c). These changes occurred within one minute of light irradiation and increased with time, clearly showing a fast responsiveness of DLD-1 to light irradiation. We also used HPLC to analyze the solution of DLD-1. Consistent with the UV/Vis spectra, the HPLC analysis shows one typical peak of DLD-1 before light irradiation (Figure S2) but two peaks after light irradiation (Figure 2d). As revealed by mass spectroscopy, the product of photolysis at the new peak has a molecular weight of 331.15 $g\,mol^{-1}$, which exactly matches the molecular structure of the oxindole-acetal intermediate product (Figure 2b).

After demonstrating the photoresponsiveness of DLD-1, we studied its pH sensitivity after light irradiation. Density functional theory computations suggested that the formation of oxindole is accompanied by a significant rearrangement of the electron density (Figure S3) and this change is favorable for the hydrolysis of the acetal group in response to an acidic environment. Indeed, light-triggered DLD-1 (i.e., the oxindole-acetal intermediate product) in the solution of pH 5.0 exhibited a fast change in the UV/Vis absorption spectrum (Figure 2e). As time proceeded, the absorption at 259 nm decreased, whereas the absorption at 309 nm increased with a slight blue shift. This spectral change is consistent with the HPLC analysis (Figure S4), showing the fast hydrolysis of the acetal group. In contrast to the fast change observed at pH 5.0, the oxindole-acetal intermediate product exhibited a much smaller change at pH 7.4 during the same time window (Figure 2e, bottom panel), thus suggesting that its hydrolysis in a neutral environment is slow. Taken together, these results show that DLD-1 can undergo fast hydrolysis after sequential exposure to light irradiation and acid treatment.

Next, we studied the effect of molecular structure on the hydrolysis kinetics. In principle, there are two general routes for changing the structure of DLD. One is to change R^1 and the other is to change R^2 (Figure 1c). When R^1 is changed, it is possible to change the ability of the compound to undergo intramolecular photocyclization and the responsiveness to light irradiation. However, once the oxindole structure forms, it will favor the responsiveness of R^2 to an acidic environment for hydrolysis. There are a variety of pH-labile chemical bonds such as acetal/ketal, hydrazone, imine, and *cis*-acotinyl bonds.[14] Among them, acetals have attracted significant attention recently since they are biocompatible and relatively easy to synthesize.[15] Acetals also exhibit a wide spectrum of responsiveness to pH variation.[16] Thus, in this proof-of-concept study, we changed the structure of R^2 and synthesized three acetals to understand the effect of molecular structure on the hydrolysis of the DLD after light irradiation (Figure 2a). This understanding should provide basic knowledge for the synthesis of a material with desired degradation kinetics.

Three DLDs were synthesized with primary alcohols that have different lengths of carbon chain (Figure 2a). We expected that variation of the molecular structure of R^2 may not affect the light responsiveness of DLD since R^2 is away from the conjugated system. Indeed DLD-2 and DLD-3 both exhibited fast responses to light irradiation (Figures S5 and S6) similar to DLD-1 (Figure 2c). This confirms that structural variation at the R^2 position does not affect the photoresponsiveness of the DLD. We further examined the responsiveness of DLD-2 and DLD-3 to pH after light irradiation. These two molecules both exhibited a rapid change in UV/Vis absorbance at pH 5.0 (Figures S5 and S6). These results show that the two acetals could undergo hydrolysis after DLD-2 and DLD-3 were sequentially exposed to light irradiation and acid treatment.

While all three DLD molecules were responsive to light irradiation and acid treatment, their hydrolysis profiles were significantly different (Figure 2f). DLD-1 exhibited the fastest hydrolysis kinetics, with half-lives of 0.25 h and 33.1 h at pH 5.0 and pH 7.4, respectively (Figure 2g). DLD-3 exhibited the lowest hydrolysis kinetics, with half-lives of 4.29 h and 163 h at 5.0 and pH 7.4, respectively (Figure 2g). DLD-2 fell in between DLD-1 and DLD-3. This difference is attributed to the structural variation of R^2. In comparison to the R^2 group of DLD-1, that of DLD-2 has an electron-withdrawing ester attached to C3 of the alcohol, whereas that of DLD-3 has both the ester group and a shorter carbon chain that further enhances the electron-withdrawing ability (Figure 2a). This observed effect of R^2 on the hydrolysis of DLD is consistent with a previous report showing the pH sensitivity of acetals.[6b] Taken together, these results demonstrate the feasibility of tailoring the hydrolysis kinetics through the molecular design of R^2.

Hydrogels are crosslinked networks of hydrophilic polymers with a large amount of water.[17] They are viscoelastic with structural similarity to natural tissues. They can be developed in different forms such as particles, films, coatings, and slabs.[18] Thus, hydrogels are one of the most commonly studied materials for various applications, particularly biomedical applications such as bioseparation, biosensing, drug delivery, and regenerative medicine.[12,17,18] Great efforts have been made in developing responsive hydrogels. After the synthesis of the three DLD molecules and the demonstration of their responsiveness to light irradiation and acid treatment, we used DLD-2 to synthesize a hydrogel to further test the hypothesis, that is, the utility of DLDs to control the programmable degradation of materials (Figure 3a). The hydrogel was exposed to four different treatments, including acid treatment (pH 5.0, 12 h), light irradiation (15 min, pH 7.4), acid treatment (pH 5.0, 12 h) followed by light irradiation (15 min, pH 7.4), and light irradiation (15 min, pH 7.4) followed by acid treatment (pH 5.0, 12 h). After these treatments, the morphology of hydrogels was examined by SEM. In comparison to the fresh hydrogel without specific treatment, the hydrogels treated under the first three conditions did not exhibit significant macroporosity (Figure 3b). By contrast, after sequential exposure to light irradiation and acid buffer, the entire hydrogel exhibited a macroporous structure (Figure 3b).

We further monitored the degradation of the hydrogels using UV/Vis and FT-IR spectroscopy. As shown in Figure S7a, light irradiation led to an increase in the absorption at 335 nm, that is a characteristic absorption of the oxindole compound, and a concomitant change in the color of the hydrogel. This indicates light-activated formation of the acetal-oxindole intermediate. Figure S7b shows that incubation of the light-irradiated hydrogel in a solution of pH 5 led to a fast release of oxindole to the solution, thus demonstrating the acid-catalyzed hydrolysis of the acetal unit. In contrast, the hydrogel without light activation did not show any noticeable degradation in acidic solution (Figure S7b). The degradation of the hydrogel was further confirmed by FT-IR spectroscopy (Figure S7c). We also prolonged the duration of stimulation and treated the hydrogel sequentially with UV for 60 min and acid (pH 5) for 12 hours, finding that the whole hydrogel underwent significant degradation and shape change (Figure S7d). Altogether, these data clearly demonstrate that

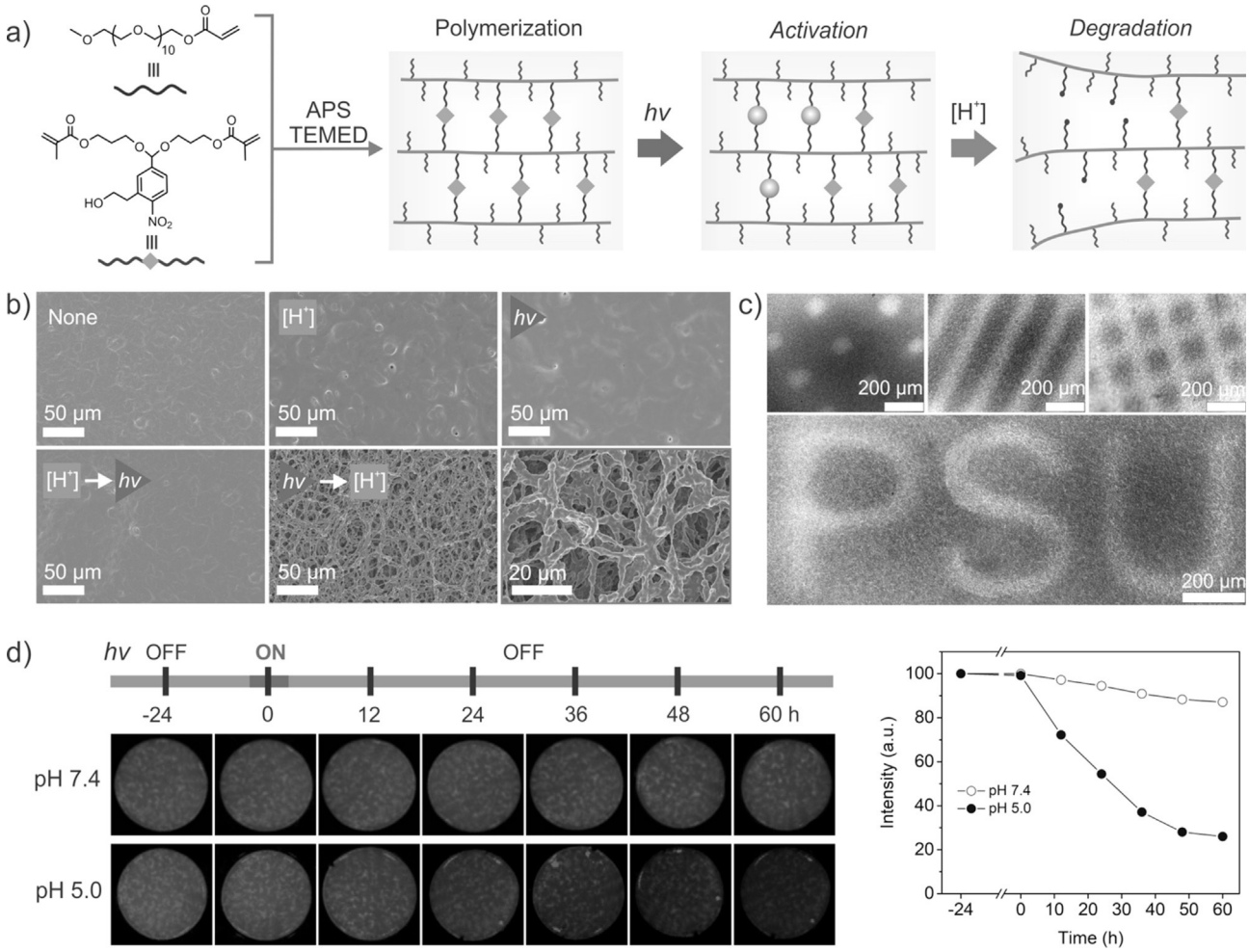

Figure 3. Evaluation of hydrogel degradation. a) Schematic illustration of hydrogel synthesis and degradation. b) SEM images of hydrogels treated under different conditions. c) Images of hydrogels after sequential exposure to patterned light irradiation and incubated in a buffer solution of pH 5.0. d) Representative fluorescence images of hydrogels (left) and intensity–time relationship (right). The hydrogels were sequentially exposed to light irradiation and a buffer solution of pH 5.0 or 7.4.

hydrogels with a DLD can undergo fast degradation after sequential exposure to light irradiation and acid treatment, whereas reversing the order of the two stimuli or only using individual stimulation does not lead to fast degradation.

We further studied the feasibility of controlling degradation spatially. The hydrogels were covered with photomasks, exposed to light irradiation, and immersed in a solution of pH 5.0. Depending on the patterns of the photomasks, the hydrogels exhibited different patterns, including dots, lines, grids, and letters (Figure 3c). These results show that while the hydrogels were uniformly exposed to acid stimulation, their acid degradation could be spatially and heterogeneously controlled.

Since the permeability of a hydrogel is directly correlated to the pore size, the velocity of molecular transport increases with the increase in pore size. Thus, to further confirm the SEM imaging analysis, we evaluated the release of Cy3-labeled streptavidin from the hydrogels. Without light irradiation, the fluorescence intensity of the hydrogel barely changed during 24 h incubation in a solution of either pH 7.4 or pH 5.0 (Figure 3d). After the hydrogel was exposed to light irradiation, its fluorescence intensity quickly decreased with time in the solution at pH 5.0. After 60 h, the fluorescence intensity of the hydrogel at pH 5.0 decreased to 23 % whereas that at pH 7.4 decreased to 86 % (Figure 3d). These results demonstrate that the transport of Cy3-labeled streptavidin was significantly increased after the hydrogel was sequentially exposed to light irradiation and acid treatment, thus confirming that the permeability and pore size of the hydrogel increased. These results also demonstrate that the degradation of hydrogels with a DLD can be temporally controlled.

In contrast to traditional designs with which each stimulus induces the cleavage of one bond for degradation, the molecular design presented herein requires the cooperation of two stimuli for the control of degradation. While this work is focused on providing a proof-of-concept for programmable control of degradation, this concept may find new applications that cannot be satisfied by traditional designs. For instance, a light-pretreated hydrogel that initially possesses uniform integrity and properties can automatically acquire heterogeneous structures when its microenvironment

becomes acidic. Such a transformation in response to an environmental change may not be easily realized by using traditionally designed light- and/or pH-responsive materials. Furthermore, quite a few organs and organelles naturally have an acidic environment, including skin, stomach, caecum, vagina, and endosome/lysosome.[19] For instance, the pH of the skin surface is around 5.[19a] The skin is also directly exposed to the environment. There is a potential to design materials for implantation and temporospatial control of drug delivery on the skin using stimulation with light and acid. However, it is important to note that UV penetration into deeper regions of a tissue is limited. This limitation may be overcome by using near infrared (NIR) light that can penetrate tissues more deeply than UV light and upconversion nanoparticles that can convert NIR photons into UV light.[7a] These potential applications will be explored in the future work.

In summary, we have successfully demonstrated the ability to control the degradation of hydrogels with DLDs as the functional crosslinkers. These hydrogels undergo degradation after they are sequentially exposed to two stimuli. They can maintain high integrity when the order of the two stimuli is reversed or only one stimulus is applied. Notably, while we used light and pH as an example to demonstrate the design of hydrogels with DLDs, it is possible to rationally design molecular structures that are responsive to other cooperative stimuli such as light and enzymes. In addition to hydrogels, it is possible to extend this concept to synthesize other types of DLD-bearing materials whose degradation can be temporospatially controlled.

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Conflict of interest

The authors declare no conflict of interest.

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