Leveraging radical-mediated degradation of thiol-maleimide bonds for responsive and programmable hydrogels

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Thiol-Michael reactions have been leveraged extensively in the synthesis of biomaterials due to the vast design space they provide for tuning material properties. They are particularly desirable for hydrogel formation due to mild reaction conditions necessary for applications such as tissue engineering, where crosslinking must often be carried out at physiological pH and temperature.[1] One of the most commonly used classes of thiol-Michael reactions used for hydrogel synthesis leverages maleimide end groups as the Michael acceptor. Notably, the thiol-maleimide chemistry does not typically require the addition of a base catalyst or elevated temperature for complete conversion of the functional groups, as is often necessary when other Michael acceptors such as vinyl sulfones or acrylates are used. As such, the simplicity of the thiol-maleimide chemistry provides an especially facile approach for the design of materials with well-defined structures and properties.

Thiol-maleimide hydrogels are favorable for many applications owing to their generally stable network structure, allowing long-term studies.[2] However, degradability in hydrogel networks is sometimes desirable and, in certain cases, critical to their application. Integration of irreversible degradation modes into hydrogels has been especially important in tissue engineering with the advent of synthetic scaffolds, which can gradually be replaced by matrix deposition and proliferation of their encapsulated cells or host cells. The flexibility of macromer structure in synthetic thiol-maleimide hydrogels facilitates the incorporation of multiple forms of degradable bonds.[3] Notably, these hydrogels must be designed with degradation mechanisms that are sensitive to stimuli orthogonal to those necessary for network formation or other responsive properties. Some examples of degradable bonds that have been employed in thiol-maleimide materials include matrix metalloproteinase (MMP)-cleavable peptide sequences and hydrolytically cleavable bonds (i.e. esters). In these examples, degradability is invoked by including additional functional groups within the polymer network structure. However, dissociation of the Michael adducts themselves is a less explored, but versatile strategy for the design of degradable hydrogels. Retro-Michael reactions can reverse Michael adducts to their constituent thiol and alkene moieties, but the aqueous microenvironment of hydrogels typically favors Michael adduct stability. Therefore, alternative mechanisms are necessary to achieve facile degradation of these materials.

In this work, we demonstrate the formation of conventional thiol-maleimide hydrogels in the presence of a radical photoinitiator followed by degradation of the crosslinked networks upon radical generation.[4] Initial studies were conducted using photo-initiated radicals to simplify the analysis of degradation by leveraging the temporal control of light as an applied stimulus. We then extend these findings to a depth-independent redox radical initiator system. Linear starting materials were used to form polymers that enabled identification of degradation products, finding that radical-mediated degradation occurs at the thioether bond between the sulfur and beta carbon of the Michael adduct. Leveraging the spatial control of light, this degradation mechanism is used to demonstrate selective patterning of poly(ethylene glycol) (PEG)-based thiol-Michael hydrogels via primary radicals from photoinitiator. The discovery of this degradation mechanism highlights the importance of hydrogel crosslink design when incorporating multiple stimuli (radicals, pH, etc.) for orthogonal modulation of functionalities such as cell behavior, hydrogel mechanics, or stimuli-responsive properties. Taken together, these results illustrate the potential for radical-mediated degradation of thiol-maleimide polymers to be extended in a broad range of future biomaterial-based applications.

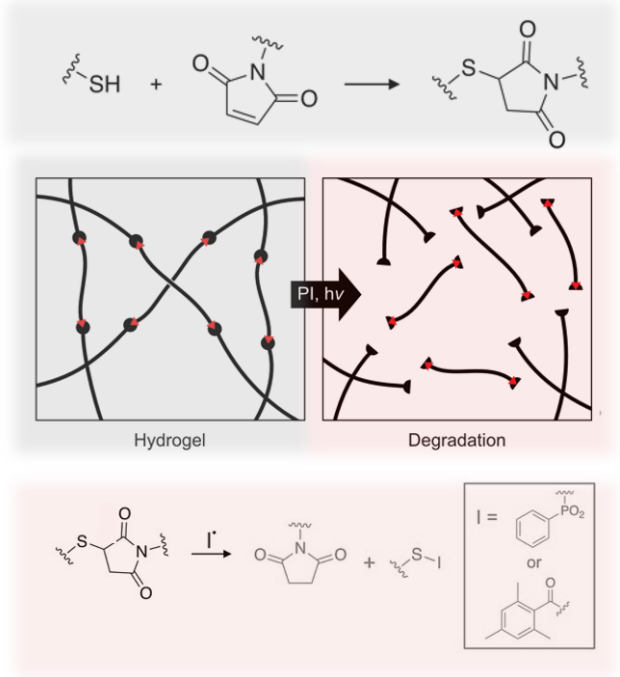

Figure 1. Hydrogels are synthesized via Michael addition using thiols and maleimides (gray) and subsequently degraded via radical-mediated mechanism.

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[3] J. Lou, D. J. Mooney, *Nature Rev. Chemistry* **2022**, 1.
[4] T. S. Hebner, B. E. Kirkpatrick, B. D. Fairbanks, C. N. Bowman, K. S. Anseth, D. S. W. Benoit, *Advanced Science* **2024**, 11, 2402191.