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FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Cucurbit[8]uril Couples Enzymatic and Supramolecular Reaction Networks for Peptide Isomerization and Recognition in Gain-of-Function Hydrogels

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Adaptive biological systems regulate molecular recognition by enzymatically converting inactive precursors into functional states. Replicating such gain-of-function behavior in synthetic supramolecular systems remains challenging because productive activation is frequently outcompeted by undesired deactivation pathways. Here, we present an enzyme-responsive depsipeptide switch[1, 2] in which cucurbit[8]uril (CB[8]) functions as a supramolecular chaperone, transiently stabilizing a latent peptide precursor and promoting its productive enzymatic transformation. The branched depsipeptide initially forms a weak binary complex with CB[8], suppressing hydrolysis and intramolecular cyclization while increasing the likelihood of trypsin-mediated cleavage. Proteolytic cleavage, followed by spontaneous rearrangement, converts the precursor into a linear peptide that binds CB[8] with high affinity to form a homoternary complex, thereby driving a transition from binary to ternary supramolecular assembly.[3] Time-resolved LC–MS, NMR spectroscopy, and isothermal titration calorimetry reveal the interplay between competing complexation and deactivation pathways and identify a tyrosine-containing depsipeptide that provides the optimal balance between hydrolytic stability and enzymatic responsiveness. Extending this strategy to hyaluronic acid conjugates enables enzyme-triggered supramolecular hydrogel reconfiguration through CB[8]-mediated intermolecular crosslinking, affording adaptive hydrogels with enhanced viscoelasticity and shear-thinning properties. This work establishes a chaperone-assisted approach for integrating enzymatic regulation with supramolecular molecular recognition, providing a versatile platform for programmable adaptive soft materials.

[1]Y. Zhu, *et al*., *Nature Communications.* **14**, 3635 (2023).
[2]S. Chagri, *et al*., *Macromolecular Bioscience.* **26**, e00427 (2026).
[3]Y. Wang, *et al*., *Advanced Materials.* **36**, 2313270 (2024).