

Photoresponsive Supramolecular Hydrogel Co-assembled from Fmoc-Phe-OH and 4,4'-Azopyridine for Controllable Dye Release

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Electronic Supplementary Information

Abstract Photoresponsive hydrogels have been attractive because they can provide precise spatial and temporal control for molecule release, whereas the conventional preparation of photoresponsive hydrogels generally involves complex chemical synthesis steps or specific conditions which limits their practical applications. Herein, a new photoresponsive hydrogel is facilely prepared *via* co-assembly of two simple molecules, Fmoc-Phe-OH and Azp, without chemical synthesis. The co-assembly mechanism, morphology, and photoresponsiveness of (Fmoc-Phe-OH)-Azp hydrogel are investigated by circular dichroism (CD), ultraviolet-visible (UV-Vis), fluorescence, ¹H nuclear magnetic resonance (¹H-NMR), attenuated total internal reflection Fourier transform Infrared (ATR-FTIR) spectroscopy, and scanning electron microscopy (SEM). Furthermore, the enhanced release of encapsulated sulforhodamine B (SRB) dye molecules can be achieved *via* UV light irradiation. The enhanced dye release amount can be controlled by manipulating photoirradiation time. This study provides a facile way to prepare photoresponsive hydrogel which holds great potential for controllable drug release.

Keywords Photoresponsive; Supramolecular; Co-assembly; Hydrogel; Dye release

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INTRODUCTION

Supramolecular hydrogels, due to their non-covalent interactions between gelators and resulting stimuli-responsiveness,^[1] have received considerable attention in controlled molecular release.^[2] Despite the great progress that has been made in recent years, precisely controlled release at the target site is still challenging because it requires molecule carriers to respond to the specific endogenous or exogenous stimuli.^[3,4] Among various choices of stimuli such as light,^[5,6] pH,^[7,8] ion,^[9,10] temperature,^[11–13] redox,^[14,15] electric, or magnetic field,^[16] light is especially attractive for its noncontact mode and remote control of process, which can be manipulated by highly temporal and spatial precision, as well as dose control with tunable irradiation parameters including duration, wavelength, intensity, and so on.^[17] Accordingly, how to rationally design and facilely prepare photoresponsive hydrogels could be the key to overcome the challenges inherent in conventional delivery systems.

So far, most reported photoresponsive supramolecular hydrogels incorporate photocleavable^[18,19] or photoisomeriz-

able^[20–22] components that lead to light-mediated changes in the properties of the hydrogel. For example, Stupp's group synthesized a peptide amphiphile (PA) molecule containing photocleavable 2-nitrobenzyl group which underwent a sol-to-gel transition in response to photoirradiation at 350 nm.^[23] Hamachi *et al.* developed a zwitterionic amino acid tethered amphiphilic hydrogelator with a light-responsive unit (–C=C–).^[24] The photoconversion from the *trans* to *cis* form of hydrogel upon UV irradiation led to the transformation from gel into liquid state. However, due to light instability of photoresponsive units, incorporation of these photo-functional moieties into hydrogelators normally needs specific synthesis conditions or steps, which limits the practical application.^[25,26]

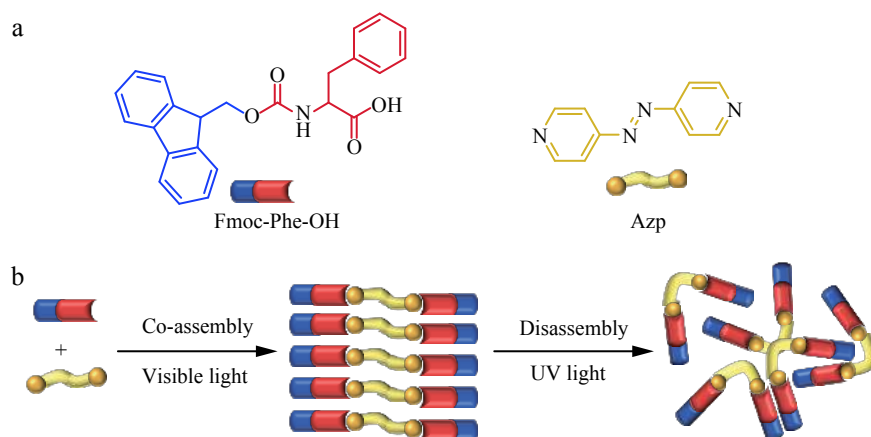
Herein, supramolecular co-assembly from two molecular building blocks is considered to simplify the photoresponsive hydrogel preparation, since it is easy to introduce functional behaviors into the hydrogel through regulation of either one of the two components and meanwhile avoids complex chemical synthesis. Based on our previous study on C₂-based gelators,^[27–29] a photoresponsive hydrogel co-assembled from *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine (Fmoc-Phe-OH) and 4,4'-azopyridine (Azp) is constructed (Scheme 1). Azp as the central core provides light responsiveness, while Fmoc-Phe-OH as side chain is responsible for gelation. Hydrogen bonding between carboxyl

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Scheme 1 (a) Chemical structure of compounds Fmoc-Phe-OH and Azp; (b) Schematic demonstration of the co-assembly and disassembly of nanofibrous networks from Fmoc-Phe-OH and Azp

and pyridine moieties readily connects these two functional units together. The π - π stacking between fluorenyl (Fmoc) groups and hydrogen bonding between amide groups render (Fmoc-Phe-OH)-Azp to assemble into nanofibers and form hydrogel. Regulation of the hydrogel's property from gel into solution state can be achieved through *trans-cis* isomerization of azo motif upon exposure to UV light. Furthermore, enhanced dye release was observed in this hydrogel irradiated with UV versus visible light, which shows the potential of this system as photoresponsive biomaterials in the field of drug delivery. Without any chemical synthesis involved, this co-assembly method to prepare photoresponsive hydrogels is not only easy to operate but also environment-friendly, paving a new way to obtain functional photoresponsive materials.

EXPERIMENTAL

Materials

N-(9-fluorenylmethoxycarbonyl)-L-phenylalanine (Fmoc-Phe-OH), 4,4'-azopyridine (Azp), and sulforhodamine B (SRB) were purchased from Sigma-Aldrich and used without further purification. Phosphate buffered saline (PBS) tablet was purchased from Sigma-Aldrich, and dissolved in Milli-Q water. Throughout the whole experiment, water was purified using a Millipore Direct Q8 system (Millipore Advantage A10 system, Schwalbach, with Millimark Express 40 Filter, Merck, Germany) to afford water with a resistivity of 18.2 M Ω ·cm.

Preparation of Hydrogel and Its Photoresponsive Property

Fmoc-Phe-OH or Fmoc-Phe-OH mixed with Azp was suspended in PBS solution and heated until the solid was dissolved, after which the hydrogel formed upon cooling down to room temperature. The molar ratio of Fmoc-Phe-OH to Azp in co-assembled hydrogel was 2:1. To test photoresponsive property, the hydrogel was exposed to UV radiation (CL-1000 series UV crosslinker, with CL-1000L Model 365 nm UV tubes, 5 $\times$ 8 W, UVP, UK). The UV light intensity was about 51.6 mW·cm⁻².

Scanning Electron Microscopy (SEM)

To further observe details of the hydrogel's inner structure, SEM was used. Samples were prepared by depositing

hydrogel (the concentration of Fmoc-Phe-OH in all samples was kept at 5.2 mmol·L⁻¹, the molar ratio of Fmoc-Phe-OH to Azp in co-assembled hydrogel was kept at 2:1) or disassembled gel on silicon wafer and dried in an oven at 35 °C at ambient pressure overnight. Before imaging, all silicon wafers were mounted on an aluminium stub and sputter-coated with gold (8–10 nm). SEM images were taken using a CamScan microscope (CS24, USA).

Circular Dichroism (CD), Ultraviolet-Visible (UV-Vis), and Fluorescence Spectroscopy

CD spectra were recorded using a Chirascan CD-spectrometer (Applied Photophysics, UK). UV-Vis spectra were recorded by a Varian Cary 50 Bio spectrometer (Mulgrave, Victoria, Australia) with the wavelength range from 200 nm to 800 nm and a scan rate of 300 nm·min⁻¹. Fluorescence study was carried out on a Varian Cary Eclipse spectrometer (Mulgrave, Victoria, Australia). The baseline was recorded with PBS solution. A quartz cuvette (Hellma Analytics, Germany) with 0.1 cm path length was used for measurements.

¹H Nuclear Magnetic Resonance (NMR) Spectroscopy

¹H-NMR spectra were recorded on a Bruker Advance 400 instrument operated at 400 MHz. D₂O was used as solvent for all ¹H-NMR measurements.

Attenuated Total Internal Reflection Fourier Transform Infrared (ATR-FTIR) Spectroscopy

All samples were dried in an oven at 35 °C at ambient pressure overnight. ATR-FTIR spectra were recorded on a Bruker TENSOR27 using the diamond lens ATR module. The samples were scanned with a resolution of 0.5 cm⁻¹ between 600 and 4000 cm⁻¹.

Dye Release

Sulforhodamine B (SRB) was used as the dye model to investigate the release property of azopyridine-based photoresponsive hydrogel. The hydrogel containing SRB dye (1 mL, 0.1 mg·mL⁻¹) was prepared by using PBS solution, then 1 mL of PBS was placed on the top of hydrogel. After desired time elapsed, 0.2 mL of the supernatant was collected and analyzed by UV-Vis spectroscopy to investigate the release amounts of SRB dye from hydrogel. SRB concentration was detected from absorbance at 565 nm. The entire process was repeated for three times.

RESULTS AND DISCUSSION

Co-assembly of Fmoc-Phe-OH and Azp

Fmoc-Phe-OH molecule itself is a thermo-reversible hydrogelator, which can self-assemble into fibers to form hydrogel upon heating and cooling (Fig. 1a). With the incorporation of Azp, assembly ability of Fmoc-Phe-OH was kept, leading to the formation of co-assembled hydrogel composed of fibrous network (Fig. 1b). It was found that the diameters of fibers in the co-assembled hydrogel increased with increase of Fmoc-Phe-OH and Azp concentrations (Fig. S1 in electronic supplementary information, ESI). To determine the critical concentration of gelators, different concentrations of Fmoc-Phe and Azp were prepared to test the formation of hydrogel which was confirmed by the “invert-vial” method (Table S1 in ESI). The critical concentrations of Fmoc-Phe-OH and Azp were 2.1 and 1.1 mmol·L⁻¹, respectively.

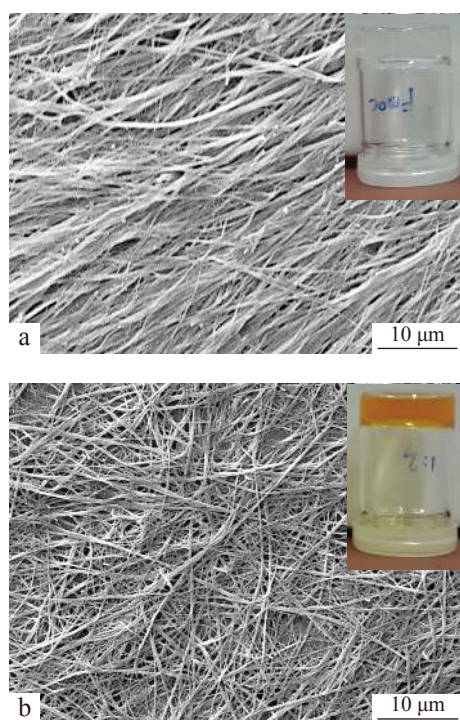


Fig. 1 SEM images of (a) Fmoc-Phe-OH and (b) (Fmoc-Phe-OH)-Azp hydrogels. Inset: digital photographs of the corresponding hydrogels. The concentration of Fmoc-Phe-OH in both samples was 5.2 mmol·L⁻¹, and the molar ratio of Fmoc-Phe-OH to Azp in co-assembled hydrogel was 2:1.

In this co-assembled hydrogel, the stacking of Fmoc-Phe-OH molecules was further demonstrated through CD and fluorescence spectra. In the CD study (Fig. 2a), the concentrations of the gelators in methanol (solution state) and in PBS (gel state) were kept constant (Fmoc-Phe-OH: 5.2 mmol·L⁻¹, Azp: 2.6 mmol·L⁻¹), as confirmed by UV-Vis spectra (Fig. S2 in ESI). The co-assembled hydrogel showed significantly increased CD intensity as compared with that of the disassembly in methanol, suggesting that the cotton effect of hydrogel originated from the assembled aggregates rather than the individual gelator molecules.^[30,31] Herein, cotton peak at 200–220 nm is consistent with $n\text{-}\pi^*$ transition from phenyl

side chain, and a second cotton band at 270–310 nm is consistent with $\pi\text{-}\pi^*$ transition from Fmoc moiety.^[32] The $\pi\text{-}\pi$ stacking interaction between Fmoc moieties was confirmed by fluorescence quenching (Fig. 2b and Fig. S3 in ESI). With the increasing concentration of gelators in PBS, samples transformed from solution state to gel state; meanwhile, the fluorescence intensity of Fmoc at 305 nm is obviously reduced. It indicates the occurrence of $\pi\text{-}\pi$ stacking between Fmoc moieties, which is likely to cause intermolecular energy transfer.^[33]

¹H-NMR was used to explore intermolecular hydrogen bonding between Fmoc-Phe-OH and Azp by monitoring the chemical shift of the heteroaromatic protons before and after co-assembly (Fig. 2c). Because of the strong electron absorbing effect of the carboxyl group in the Fmoc-Phe-OH, pyridine protons in (Fmoc-Phe-OH)-Azp were steadily shifted downfield (proton 1 of the pyridine ring was shifted from 8.91 ppm to 8.92 ppm, and proton 2 of the pyridine ring was shifted from 7.79 ppm to 7.85 ppm). It suggests that hydrogen bonding formed between the carboxyl group of Fmoc-Phe-OH and pyridine moiety of Azp.^[34]

FTIR spectra of neat Fmoc-Phe-OH and Azp powders, and (Fmoc-Phe-OH)-Azp xerogel were individually obtained to comprehend the interactions between Fmoc-Phe-OH and Azp in the co-assembly (Fig. 2d and Table S2 in ESI). The peak intensity of Fmoc-Phe-OH powder centred at 3061 cm⁻¹, which represents —OH of the carboxylic acid, decreased in the spectrum of (Fmoc-Phe-OH)-Azp xerogel. The two bands at 1719 and 1684 cm⁻¹ of Fmoc-Phe-OH powder (attributed to the carbonyl stretching vibrations of the acid and amide groups, respectively) merged into a broad band at 1693 cm⁻¹ in the spectrum of Fmoc-Phe-OH xerogel, indicating the formation of hydrogen bonds (—O—H···N) between the carboxylic acid of Fmoc-Phe-OH and the pyridyl group of Azp,^[35–37] and involvement in the intermolecular hydrogen bonding of C=O group.^[38]

According to the CD, fluorescence, ¹H-NMR, and FTIR results, the supposed interactions in the co-assembly are depicted in Fig. 3. Fmoc-Phe-OH molecules connected with Azp molecules *via* hydrogen bonding, and then the complex assembled into nanofibers through $\pi\text{-}\pi$ stacking between Fmoc and Azp groups,^[39] and hydrogen bonding between amides accompanied by hydrophobic interactions between benzene groups.

Response to UV Irradiation

As the photoisomerization property of azo motif, the gel-sol phase transitions could be triggered by photoirradiation. Upon UV (365 nm) irradiation for 3 h, the co-assembled (Fmoc-Phe-OH)-Azp hydrogel was found to gradually collapse (Fig. 4a), whereas the self-assembled Fmoc-Phe-OH hydrogel was still stable (Fig. 4b). As a control, the co-assembled hydrogel under visible light did not disassemble (Fig. 4c). Compared to the presence of nanofibers in the unbroken hydrogels (Figs. 4e and 4f), the well-organized fibrous network disappeared with the progress of gel disassembly (Fig. 4d). Next, the influence of temperature change on the gel sample was investigated. After 3 h of UV irradiation, the sample temperature increased from 20 °C to 36 °C.

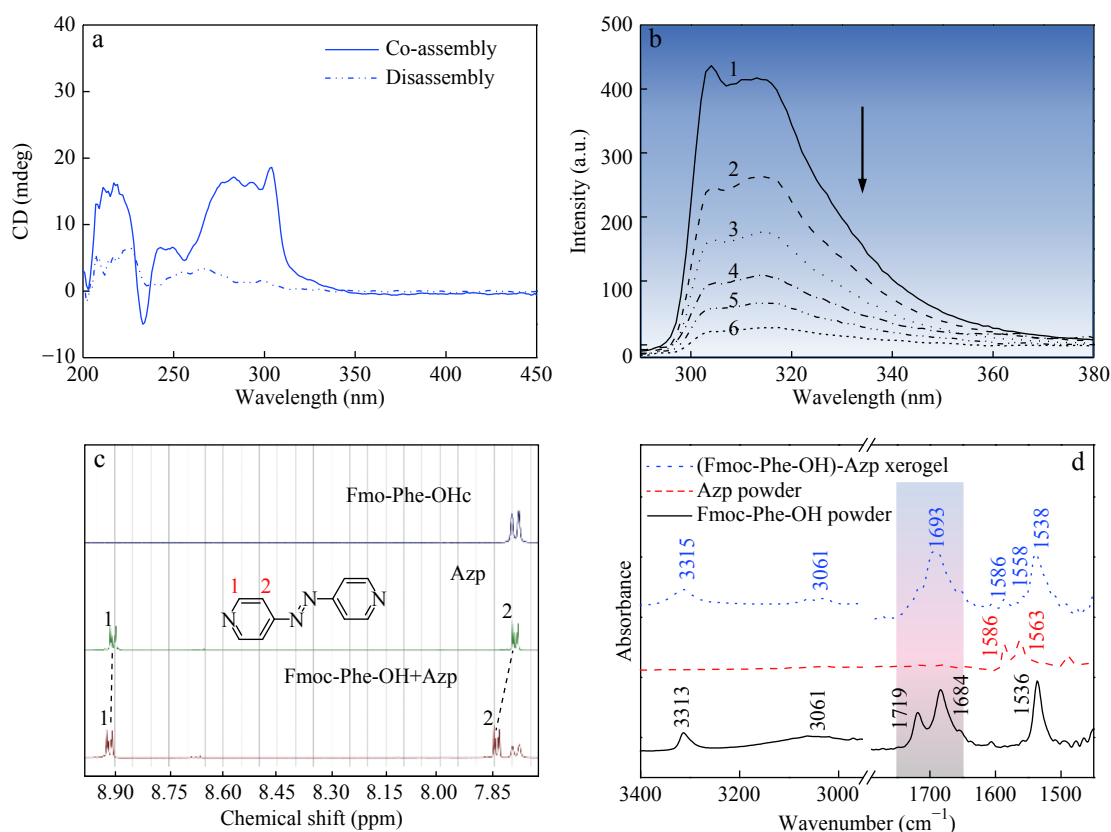


Fig. 2 (a) CD spectra of (Fmoc-Phe-OH)-Azp co-assembly in PBS (solid line) and corresponding disassembly in mesh dot line); (b) Fluorescence spectra of (Fmoc-Phe-OH)-Azp in PBS at different concentrations with $\lambda_{\text{ex}} = 263$ nm. The respective concentration of Fmoc-Phe-OH and Azp is 1.3 and 0.65 $\text{mmol}\cdot\text{L}^{-1}$ for sample 1 (solution state), 2.6 and 1.3 $\text{mmol}\cdot\text{L}^{-1}$ for sample 2 (gel state), 3.9 and 1.9 $\text{mmol}\cdot\text{L}^{-1}$ for sample 3 (gel state), 5.2 and 2.6 $\text{mmol}\cdot\text{L}^{-1}$ for sample 4 (gel state), 6.5 and 3.2 $\text{mmol}\cdot\text{L}^{-1}$ for sample 5 (gel state), 7.7 and 3.9 $\text{mmol}\cdot\text{L}^{-1}$ for sample 6 (gel state); (c) ^1H -NMR spectra of (top) Fmoc-Phe-OH, (middle) Azp, and (bottom) (Fmoc-Phe-OH)-Azp in D_2O ; (d) FTIR spectra of Fmoc-Phe-OH and Azp powders, and (Fmoc-Phe-OH)-Azp xerogel

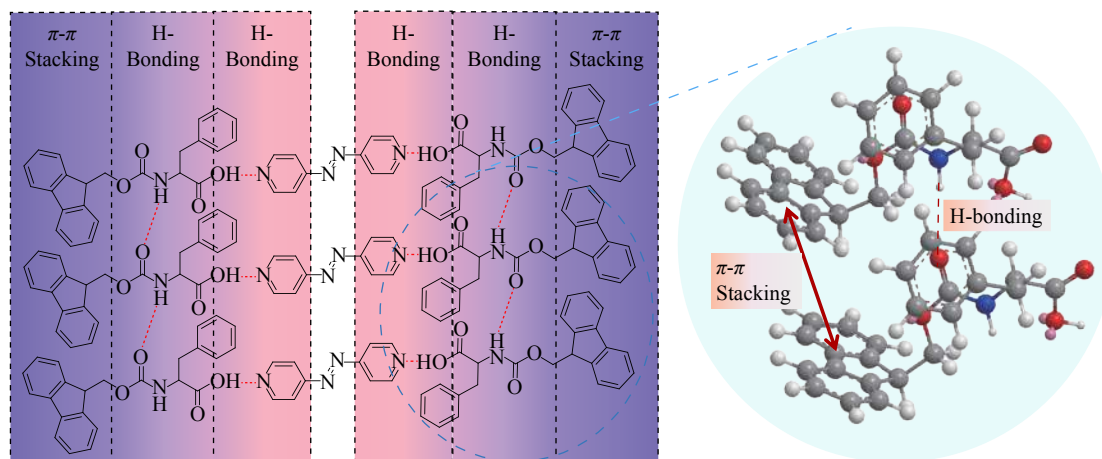


Fig. 3 Schematic representation of the co-assembly between Fmoc-Phe-OH and Azp

As a control, (Fmoc-Phe-OH)-Azp hydrogel kept in an oven at 36 °C for 3 h was still stable (Fig. S4 in ESI). It showed that the thermal effect would not induce disassembly of hydrogel herein.

The photoisomerization of Azp from *trans* form to *cis* form under UV irradiation (Fig. 5a) was further confirmed through UV-Vis spectra (Fig. 5b). Upon UV irradiation of

co-assembled hydrogel, a decrease in the strong $\pi\text{-}\pi^*$ transition at 274 nm was observed, together with 4 nm of blue shift. Meanwhile, an absorption peak of the $n\text{-}\pi^*$ band appeared notably at 450 nm. These features are typical for the *trans-cis* isomerization of Azp.^[40] Herein, the absorbance at 450 nm of unirradiated hydrogel higher than that of disassembled hydrogel should be due to the light scattering in the

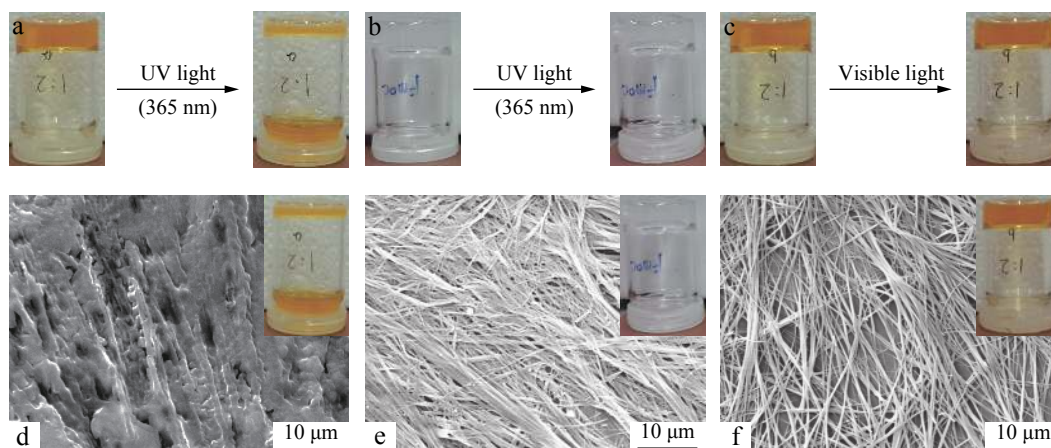


Fig. 4 Photographs of (a) (Fmoc-Phe-OH)-Azp, (b) Fmoc-Phe-OH hydrogels before and after UV irradiation, and (c) (Fmoc-Phe-OH)-Azp hydrogel under visible light for 3 h; SEM images of (d) co-assembled (Fmoc-Phe-OH)-Azp, (e) self-assembled Fmoc-Phe-OH hydrogel after UV light irradiation, and (f) co-assembled (Fmoc-Phe-OH)-Azp under visible light for 3 h

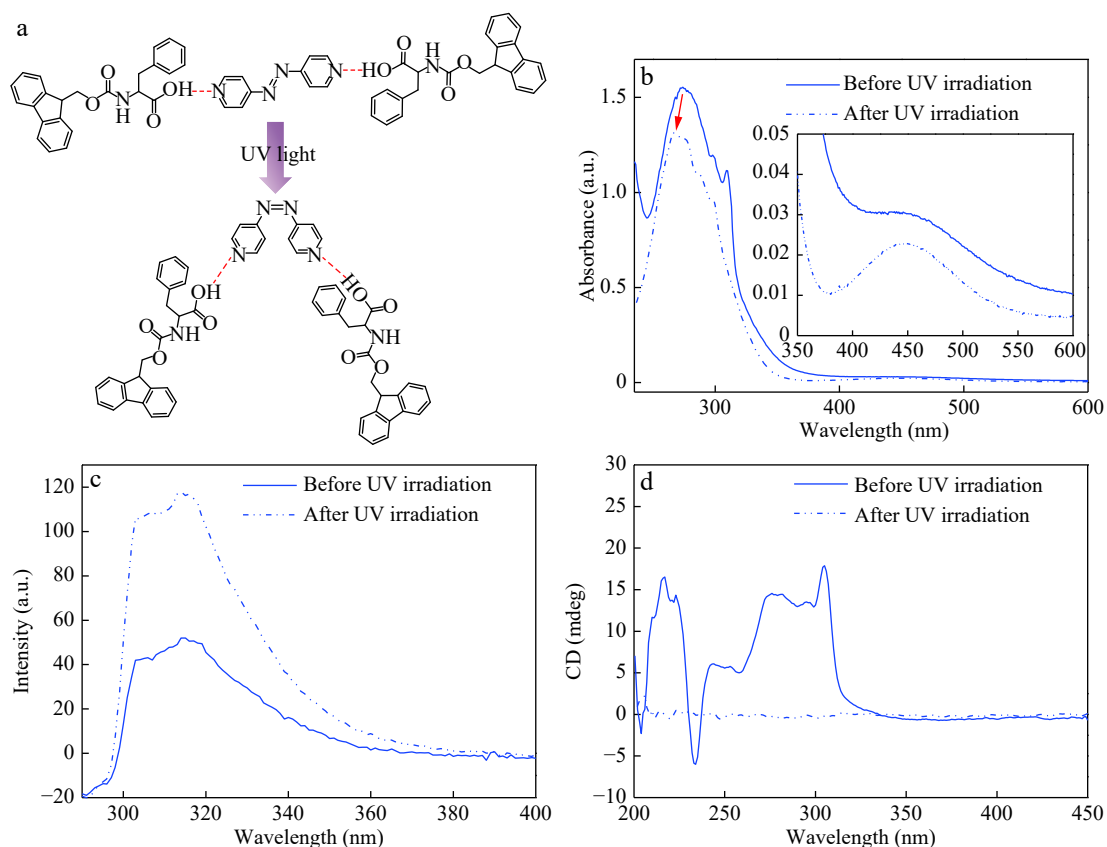


Fig. 5 (a) Chemical structures of the *trans* isomer of the (Fmoc-Phe-OH)-Azp before UV irradiation and the corresponding *cis* isomer after UV irradiation; (b) UV-Vis spectra, (c) fluorescence spectra, and (d) CD spectra of (Fmoc-Phe-OH) hydrogel before and after UV irradiation for 3 h

hydrogel. With the *trans-cis* photoisomerization of Azp, the increased fluorescence intensity (Fig. 5c) and decreased CD signal (Fig. 5d) also confirmed the disassembly of aggregates.

Dye Release

To explore the possible application of photoresponsive hydrogel for controllable release of encapsulated agents, sulforhodamine B (SRB) was selected to investigate the

release process. The co-assembled hydrogel containing SRB dyes was still stable upon 2 h of UV light irradiation, and gradually collapsed after 2 h. During the first 2 h, the release amount of SRB under UV light irradiation was 81% more than that under visible light (Figs. 6a–6c). It suggested that although the hydrogel did not disassemble in the first 2 h, the photoisomerization of Azp could accelerate dye release. Typically, the cumulative release under 3 h of UV irradiation could achieve 84% with the disintegration of hydrogel,

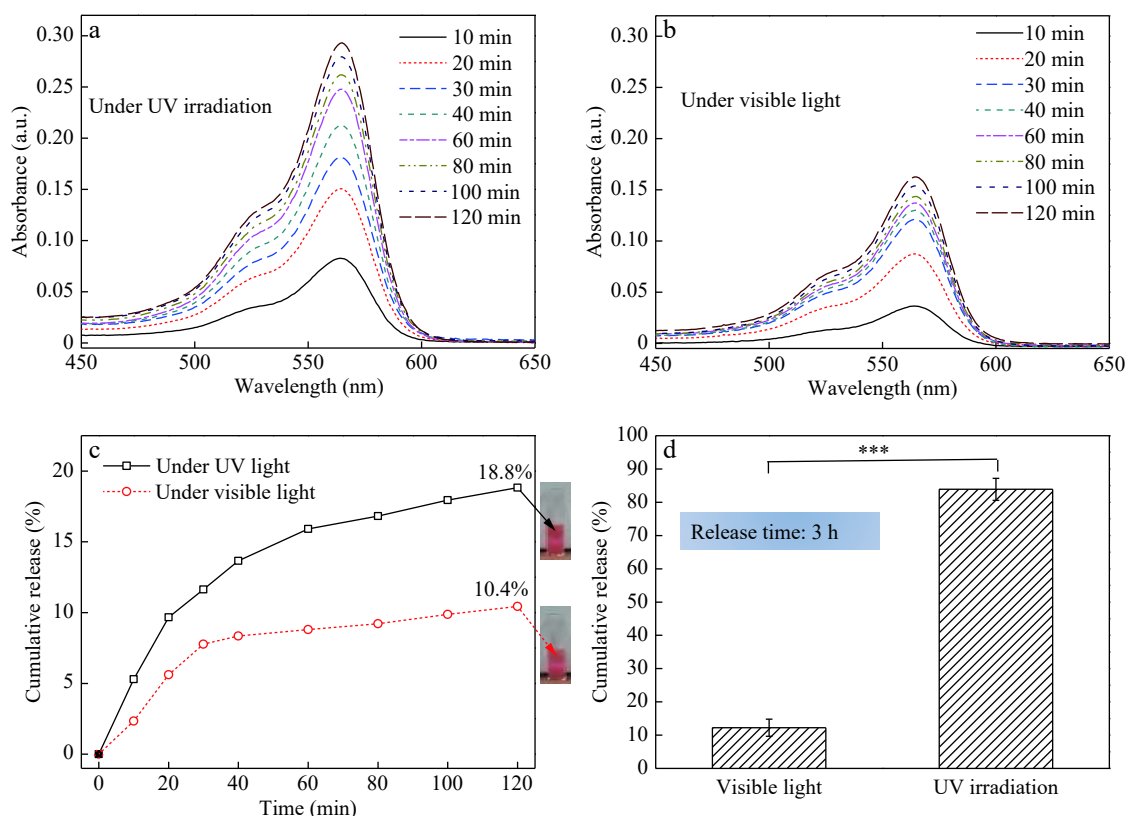


Fig. 6 UV-Vis spectra of SRB released under (a) UV irradiation and (b) visible light during the first 2 h; During (c) the first 2 h, and (d) at 3 h, released percentage of SRB dyes from (Fmoc-Phe-OH)-Azp hydrogel with and without UV irradiation. Error bars: stand error ($n = 3$), *** $p < 0.001$, one way AVONA analysis.

which is about 5.8 times higher than that under visible light (Fig. 6d). These results show that the photoresponsive (Fmoc-Phe-OH)-Azp hydrogel is a good candidate for the photocontrolled molecular release.

Response to Other Stimuli

Due to the nature of supramolecular materials, (Fmoc-Phe-OH)-Azp hydrogel could respond not only to UV irradiation but also to several other stimuli. Fig. S6 (in ESI) shows that changes of temperature, pH value, and even polarity of solvent could trigger formation or disassembly of the hydrogel.

CONCLUSIONS

In conclusion, a photoresponsive hydrogel (Fmoc-Phe-OH)-Azp was facilely prepared *via* co-assembly of two simple molecules. The co-assembled hydrogel could disassemble due to the photoisomerization of Azp from the *trans* form to the *cis* form upon UV light irradiation, resulting in the enhanced release of encapsulated agents. Moreover, this hydrogel was multi-responsive, and could respond to light irradiation, but also other stimuli such as pH, temperature, and solvent, showing great potential as smart soft materials in the biomedical field, especially as drug release system, biosensor, and so on. This co-assembly method to prepare photoresponsive hydrogel is simple, environment-friendly, and does not involve any chemical synthesis, which paves the way to the easy and quick preparation of more functional materials.

Electronic Supplementary Information

Electronic supplementary information, including UV-Vis spectra of (Fmoc-Phe-OH)-Azp co-assembly in PBS and corresponding disassembly in methanol, the calibration curve of SRB dye, and schematic representation of the multi-responsive property of supramolecular hydrogel (Fmoc-Phe-OH)-Azp, is available free of charge in the online version of this article at <http://dx.doi.org/10.1007/s10118-019-2223-2>.

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