

Supporting Information

Stack-Based Hydrogels with Mechanical Enhancement, High Stability, Self-Healing Property, and Thermoplasticity from Poly(l-glutamic acid) and Ureido-Pyrimidinone

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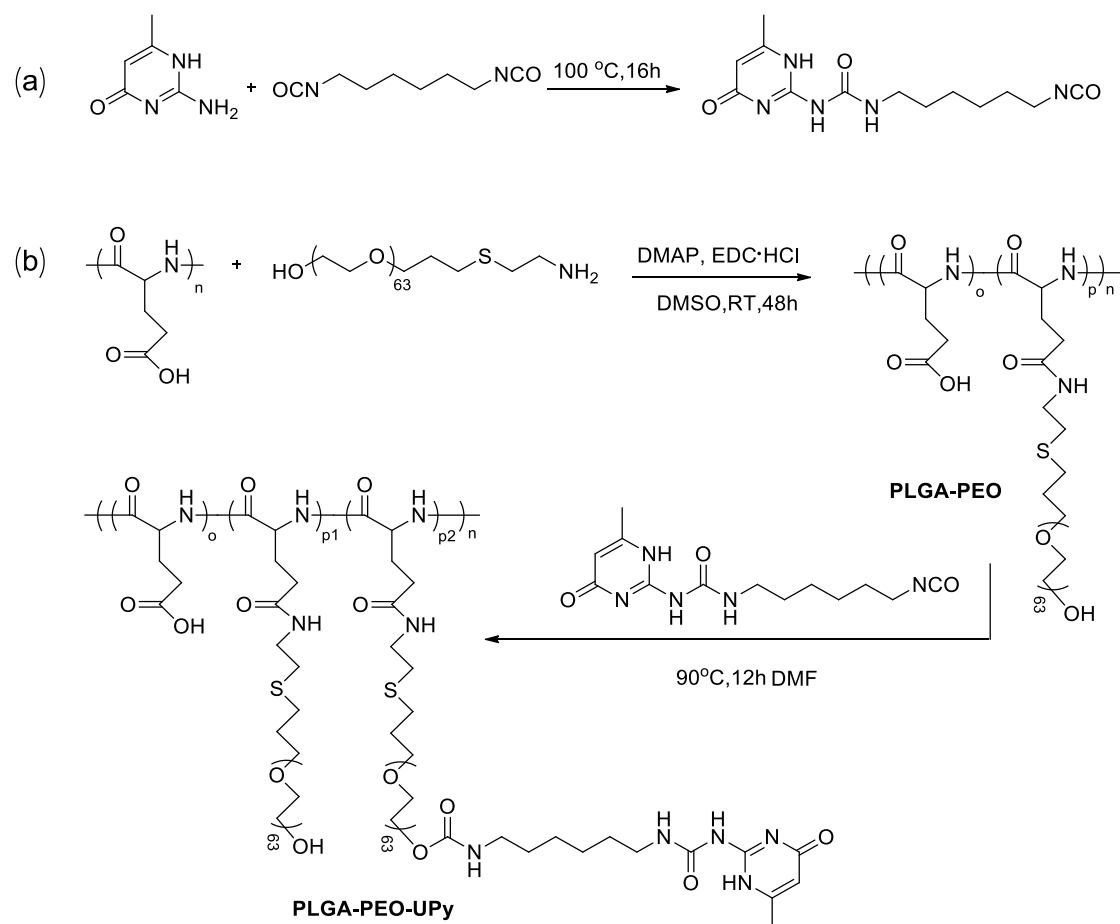


Figure S1. Synthesis of PLGA-PEO-UPy.

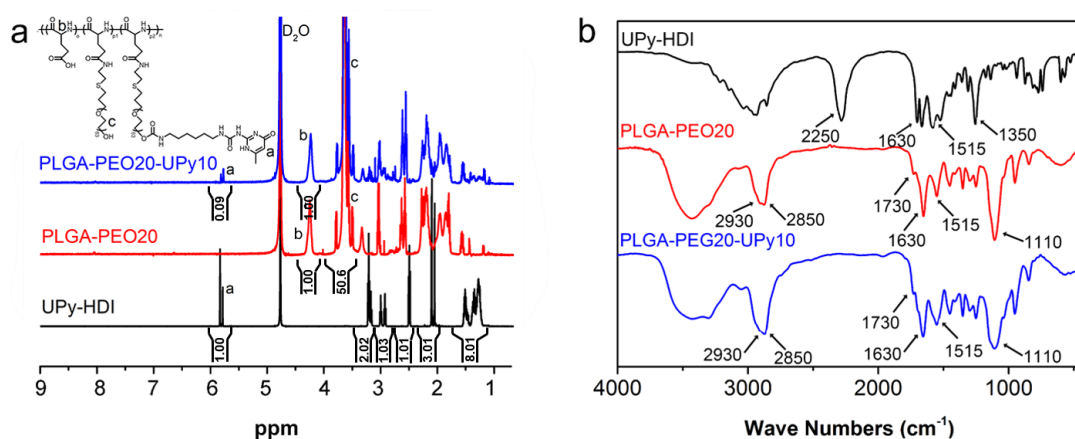


Figure S2. Characterization of polymer PLGA-PEO20-UPy10. (a) ^1H -NMR analyses and (b) FTIR curves of UPy-HDI, PLGA-PEO20 and PLGA-PEO20-UPy10.

The structures of the resultant polymers were proved by ^1H -NMR spectra, as shown in Figure S2a. The contents of PEO and UPy in resultant PLGA-PEO-UPy polymers were measured to be 20.1% and 9.7 % (marked as PLGA-PEO20-UPy10), according

to the ^1H -NMR peak integrations of the tertiary hydrogen of PLGA at δ 4.27 ppm, the secondary hydrogen of PEO at δ 3.67 ppm and the alkenyl hydrogen of pyrimidinone at δ 5.82 ppm. The results approximated the theoretical ratio. The ^1H -NMR spectrum of UPy-HDI at δ 5.82 ppm was double peak because the pyrimidinone occurred enol tautomerism in the deuterium reagent of NaOH- D_2O .

The representative FTIR analyses of UPy-HDI, PLGA-PEO20 and PLGA-PEO20-UPy10 were presented in Figure S2b. For UPy-HDI, the asymmetric stretching vibration and symmetric stretching vibration of isocyanate bond could be confirmed at the site of 2250 and 1350 cm^{-1} , respectively. For PLGA-PEO20, the characteristic absorption peaks at 1630 and 1515 cm^{-1} referred to amide I and amide II groups in PLGA, respectively.¹ The stretching vibration of carbonyl group in PLGA was described by the peak at 1730 cm^{-1} . The stretching vibration of C-H bond in PEO was marked by the peaks at 2930 and 2850 cm^{-1} , and the stretching vibration of ether linkage was pointed out by the characteristic absorption band at 1100 cm^{-1} . The peak of UPy-HDI at 2250 cm^{-1} disappeared in polymer PLGA-PEO20-UPy10, indicating that the isocyanate bond of UPy-HDI was successfully reacted with the hydroxyl group of PLGA-PEO20.

Table S1. The products of PLGA-PEO45 and PLGA-PEO72 coupled UPy pendants with different ratio.

No.	Yield	Different graft ratio	Yield
PLGA-PEO45	74.9%	PLGA-PEO45-UPy10	87.2%
		PLGA-PEO45-UPy30	85.7%
		PLGA-PEO45-UPy45	83.6%
PLGA-PEO72	67.1%	PLGA-PEO72-UPy10	74.9%
		PLGA-PEO72-UPy20	73.8%
		PLGA-PEO72-UPy50	70.5%
		PLGA-PEO72-UPy72	67.8%

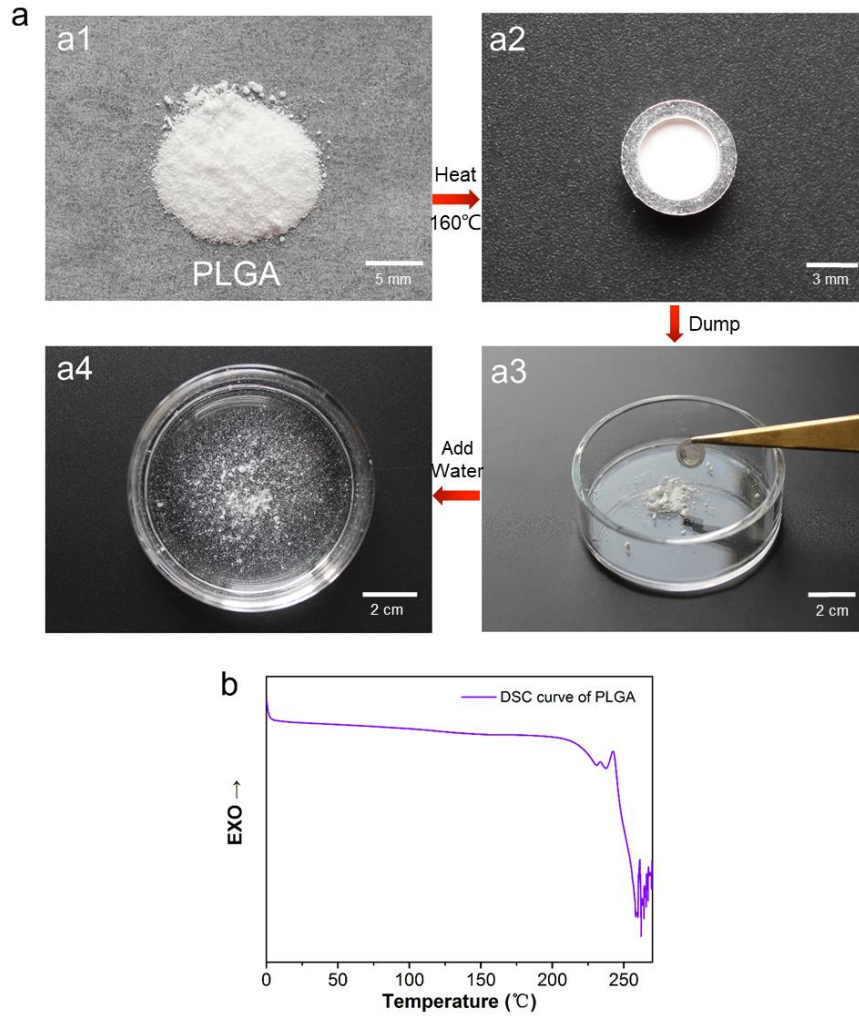


Figure S3. (a1) The photograph of the raw material polymer PLGA, (a2-a3) PLGA was annealed from 160 °C, (a4) Immersing the specimen into water. (b) DSC spectra of PLGA.

The experiments were stated as followed:

The polymer PLGA powders were pressed into lidded circular molds. Then, the samples were heated at 160 °C for 1.5 hours. The specimen of the annealed polymer PLGA was immersed into plenty of deionized water for at least 24 hours at ambient temperature (Figure S3), and no gelation occurred. The representative DSC analyses of PLGA were presented in Figure S3. There was no evident heat energy signal from room temperature to 160 °C.

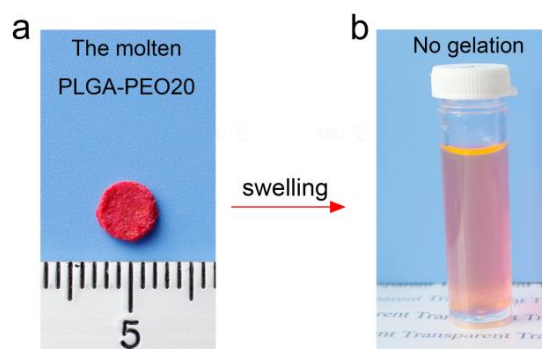


Figure S4. (a) The photographs of the annealed polymer PLGA-PEO20 from 160 °C dyed with EY. (b) Immersing the specimen into water.

The raw material PLGA-PEO20 were stained with EY (red), and then pressed into circular molds, followed by being heated at 160 °C for 1.5 hours. The specimen of the annealed polymer PLGA-PEO20 was immersed into deionized water in the capped sample vials. After 24 hours, the annealed polymer PLGA-PEO20 gradually collapsed, and no gelation occurred (Figure S4).

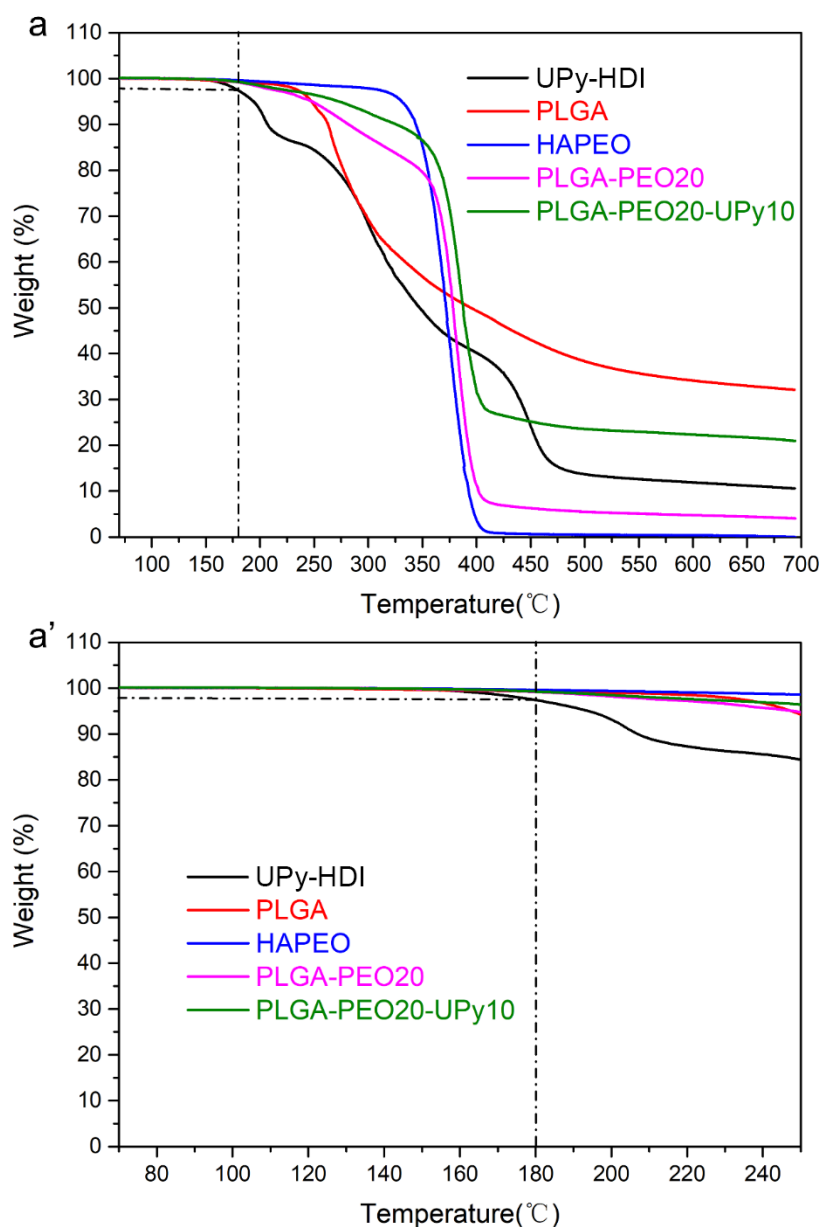


Figure S5. (a) TGA spectra of UPy-HDI, PLGA, HAPEO, PLGA-PEO20 and PLGA-PEO20-UPy10. (a') TGA spectra between 70°C-180°C.

The thermogravimetric analyzer (TGA, Q-500, TA, USA) was employed to track degradation temperature of UPy-HDI, PLGA, HAPEO, PLGA-PEO20 and PLGA-PEO20-UPy10. TGA was examined with a $10\text{ }^{\circ}\text{C min}^{-1}$ heating speed under N_2 atmosphere between $0\text{ }^{\circ}\text{C}$ and $700\text{ }^{\circ}\text{C}$. As shown in Figure S5a and S5a', the UPy-HDI had no degradation at $160\text{ }^{\circ}\text{C}$, the initial degradation of UPy-HDI appeared at $180\text{ }^{\circ}\text{C}$ with a 2.4 % pyrolysis. While the PLGA had no pyrolysis at $180\text{ }^{\circ}\text{C}$, and its pyrolysis temperature was about $230\text{ }^{\circ}\text{C}$. There was no obvious pyrolysis occurred on PLGA-PEO20-UPy10 at $180\text{ }^{\circ}\text{C}$.

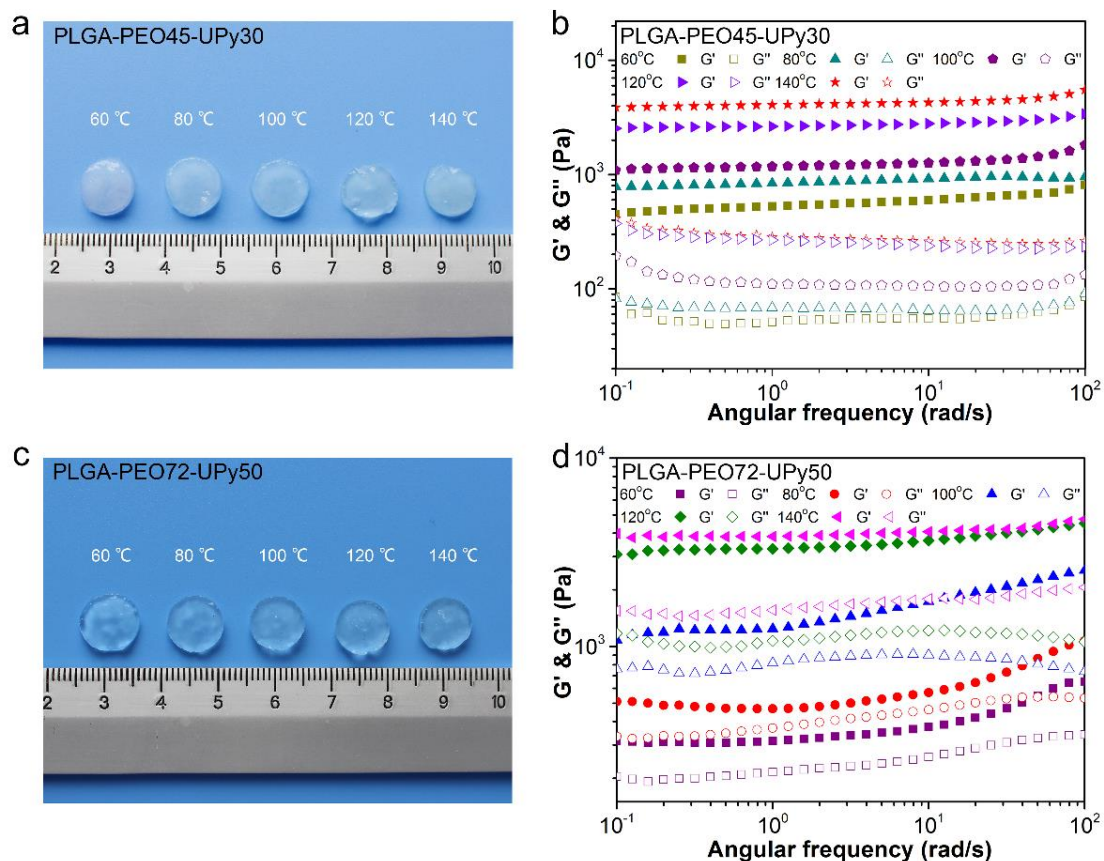


Figure S6. (a) Photographs of hydrogels derived from the pellets cooling from different melt temperatures based on PLGA-PEO45-UPy30. (b) Rheology data of PLGA-PEO45-UPy30 hydrogels. (c) Photographs of hydrogels derived from the pellets cooling from different melt temperatures based on PLGA-PEO72-UPy50. (d) Rheology data of PLGA-PEO72-UPy50 hydrogels.

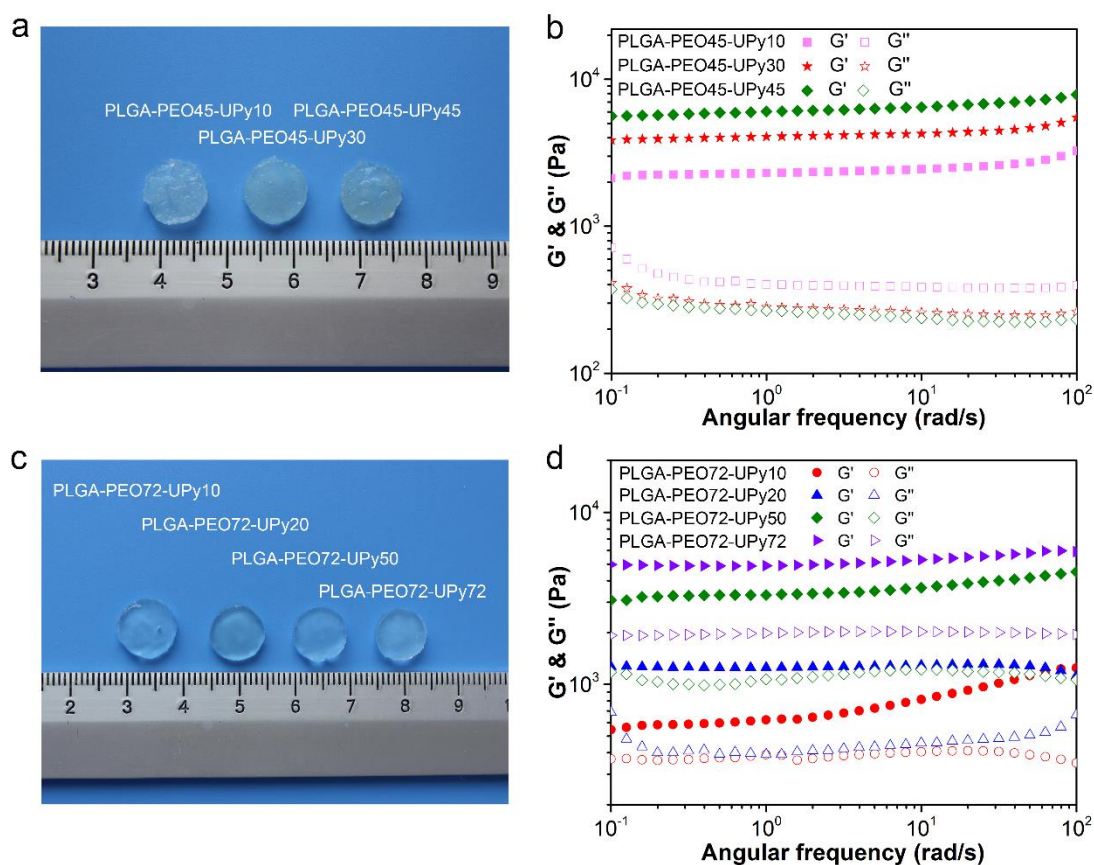


Figure S7. (a) Photographs and (b) Rheology data of hydrogels based on PLGA-PEO45-UPy10, PLGA-PEO45-UPy30 and PLGA-PEO45-UPy45 derived from the pellets cooling from 120 °C. (c) Photographs and (d) Rheology data of hydrogels based on PLGA-PEO72-UPy10, PLGA-PEO72-UPy20, PLGA-PEO72-UPy50 and PLGA-PEO72-UPy72 derived from the pellets cooling from 120 °C.

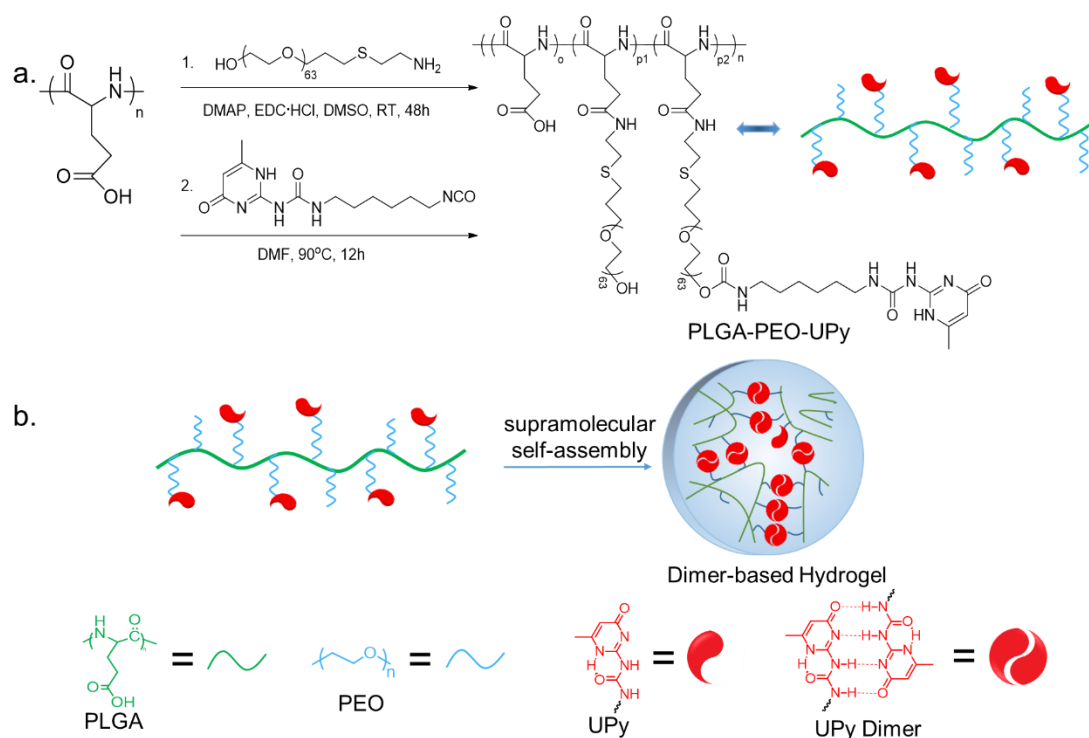


Figure S8. Schematic diagram of the fabrication of the dimer-based hydrogel.

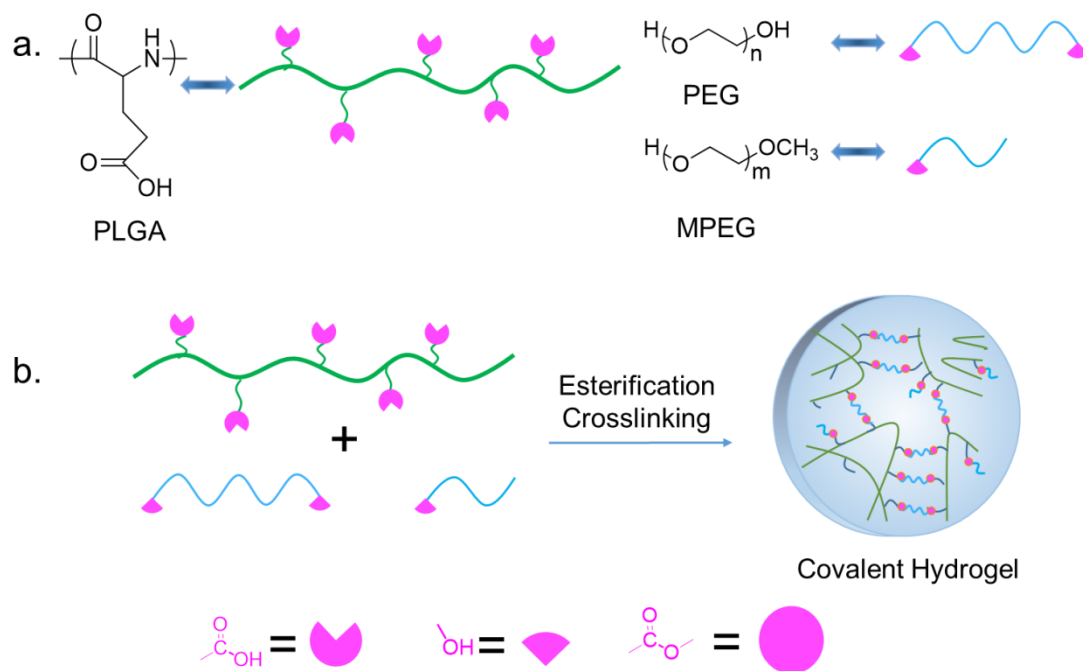


Figure S9. Schematic diagram of the fabrication of the covalent hydrogel.

The chemical structures of the molecules for the supramolecular hydrogels crosslinked by UPy dimers (dimer-based hydrogel) and the traditional hydrogels

crosslinked by ester bonds (covalent hydrogel) were shown in Figure S8 and Figure S9.

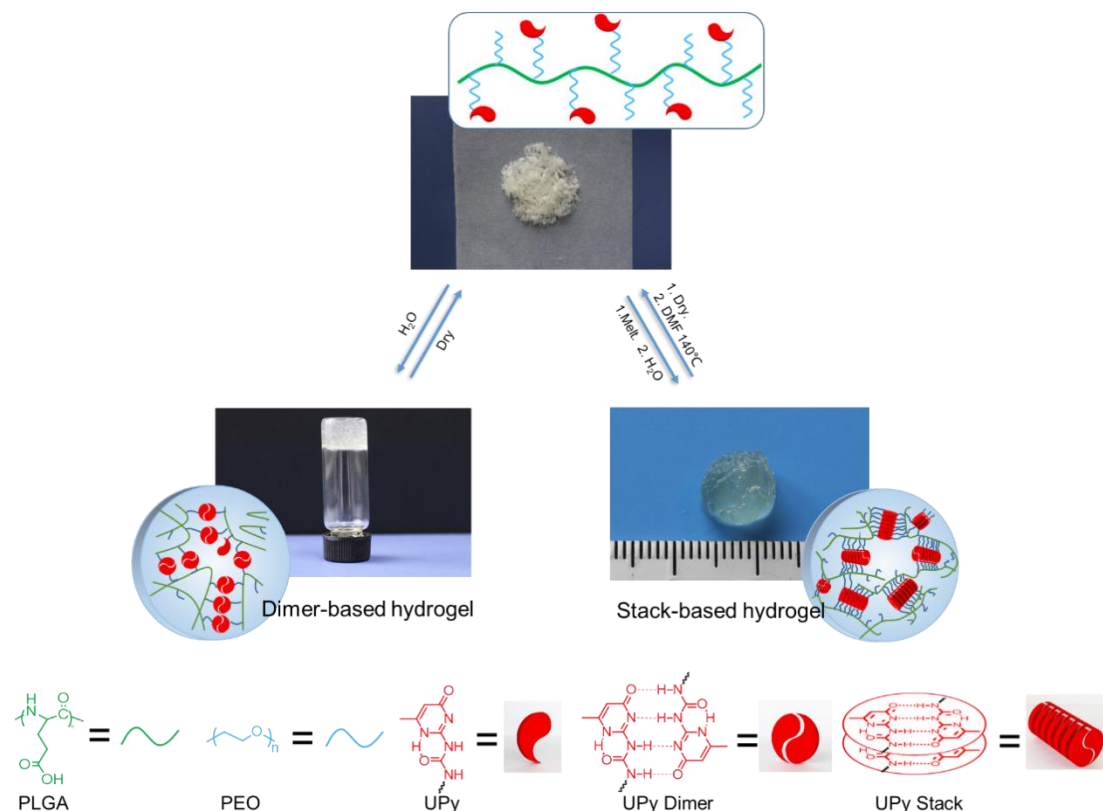


Figure S10. The reversible property of the stack-based hydrogel: the stack-based hydrogel and dimer-based hydrogel transform mutually.

Reversibility of Stack-based Hydrogel: The stack-based mode and dimer mode could transform mutually (Figure S10). The process was stated as followed: the stack-based hydrogels derived from the pellets (polymer PLGA-PEO20-UPy10, 20 mg) which cooling from 140 °C, were dried after lyophilization. The dry gel and dry DMF (3 mL) were added into a flask and were mixed for 4 hours at 140 °C. The mixture was dialyzed in deionized water for 72 hours. White polymer PLGA-PEO20-UPy10 powder was obtained after lyophilization. The powder (0.089 g) and deionized water (1g) were added into a septum capped sample vial. The dimer-based hydrogel was obtained by ultrasound for 3 hours at 25 °C, followed by cooling the solution to 4 °C in a refrigerator overnight.

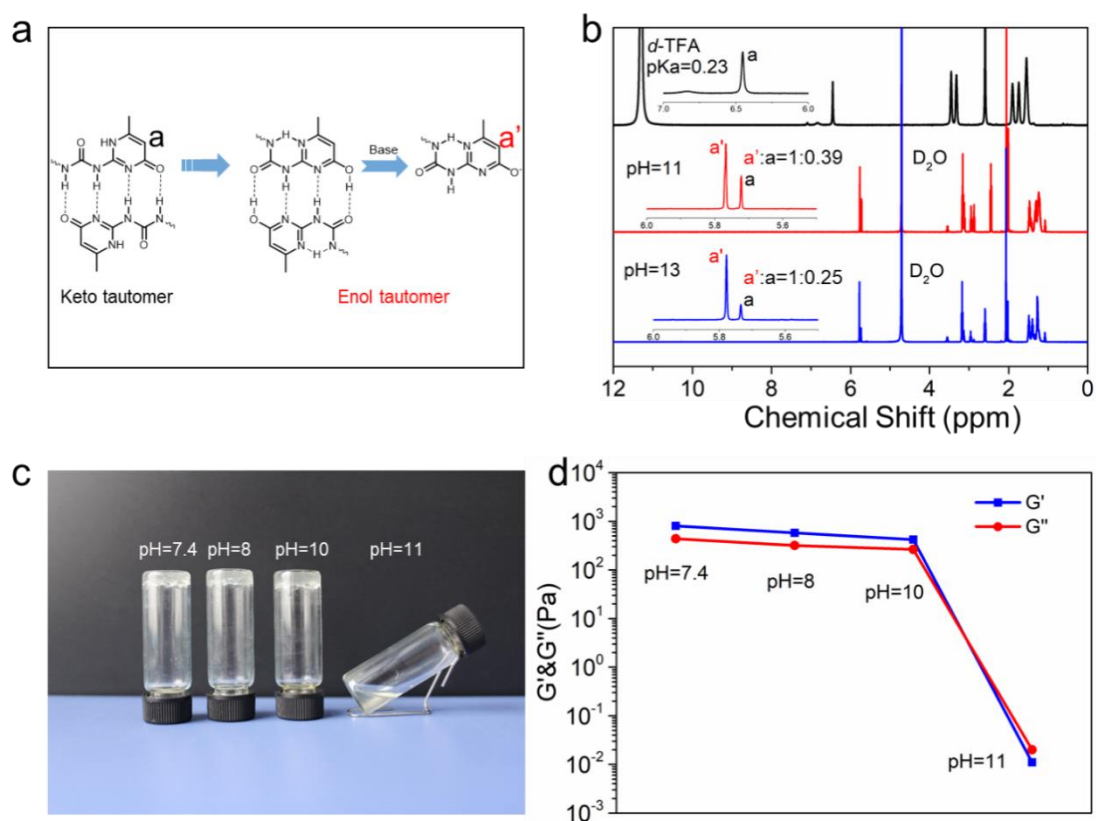


Figure S11. Mechanism of dimer-based hydrogels. (a) UPy tautomeric forms: the keto-tautomer and the enol-tautomer can form homodimers, whereas the enolate formed after deprotonation could not dimerize. (b) ¹H-NMR spectra of UPy in d-TFA and D₂O of different pH (pH=11 and 13) indicating the existence of the enolate at basic conditions. (c) Vial invert test of dimer-based hydrogels at different pH (pH=7.4, 8, 10 and 11). (d) The changes of modulus of dimer-based hydrogels under different pH (pH=7.4, 8, 10 and 11).

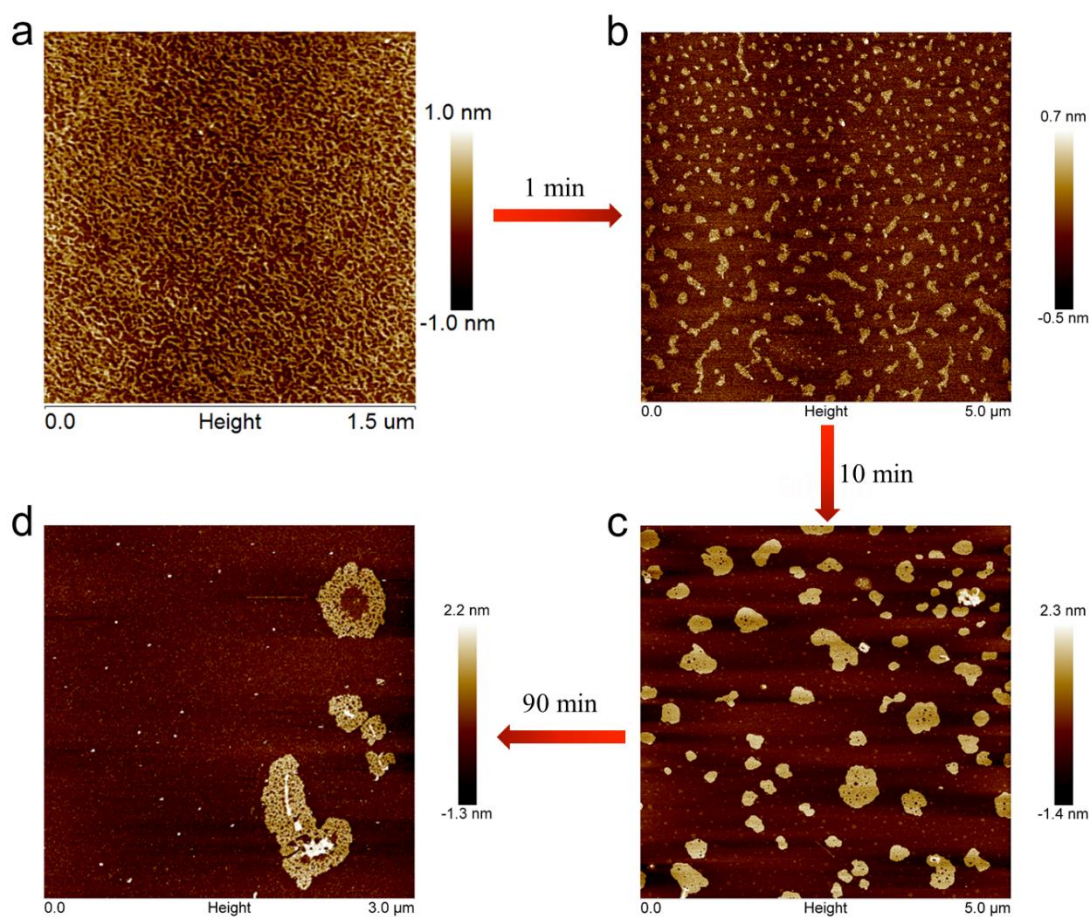


Figure S12. The aggregation process of stacks with different melting time. (a) 0 min, (b) 1 min (c) 10 min and (d) 90 min.

The aggregation process of stacks was tracked by AFM with different melting time (Figure S12). The process of experiment was stated as followed: The same mass of polymers PLGA-PEO20-UPy10 powder were respectively pressed into lidded circular molds. Then, the pellets were heated at 160 °C for 0 min, 1 min, 10 min and 90 min. The annealed pellets were immersed into deionized water, and the soaking liquids were rapidly spin-coated on a freshly cleaved surface of mica, for tracking the self-assembly of polymers PLGA-PEO20-UPy10 using AFM.

In Figure S12a, the legible nanofibers formed due to the phase separation of the PLGA-PEO20-UPy10 polymer in the water, based on the dimerization of the UPy. But when the polymer was heated at 160 °C for 1 min, an aggregate self-assembled morphology began to appear, with the scale of 200 nm (Figure S12b). And the size of aggregation became larger after 10 min (Figure S12c). For the self-assembly of

polymer finished, the pellets were heated for 90 min, and the size of aggregation was largest (about 600 nm) (Figure S12d). The result indicated that the self-assembly of UPy dimers into UPy stacks was given rise to the lateral hydrogen bonding interactions when the melting time went on. The resulting stacks subsequently form a steady and aggregative network in hydrogel, most probably via a secondary nucleation process.²

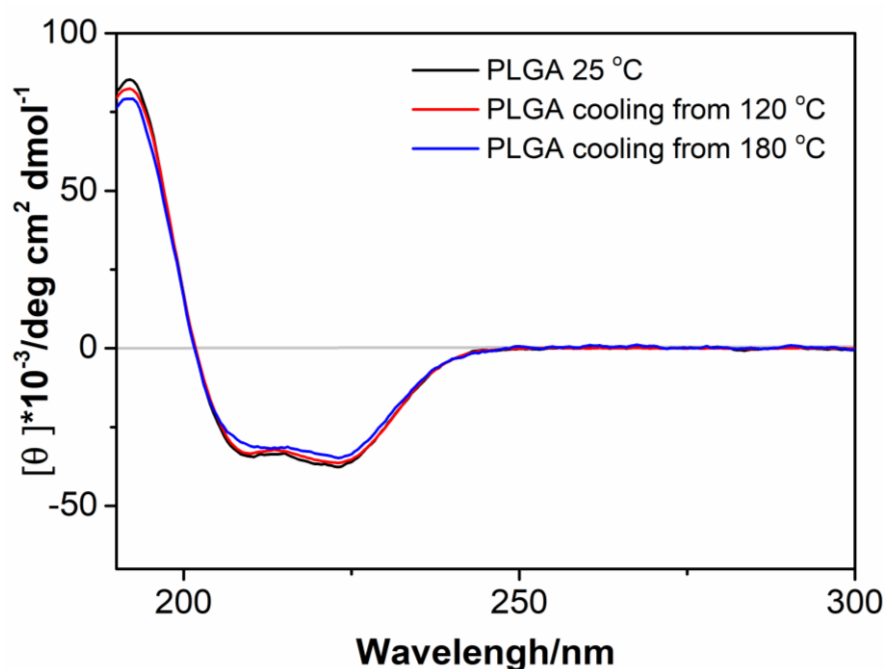


Figure S13. CD spectra of PLGA at room temperature, and annealing from 120 °C and 180 °C.

References:

- (1) Li, G.; Wu, J.; Wang, B.; Yan, S.; Zhang, K.; Ding, J.; Yin, J. Self-Healing Supramolecular Self-Assembled Hydrogels Based on Poly(L-glutamic acid). *Biomacromolecules* **2015**, *16*, 3508-3518.
- (2) Appel, W. P. J.; Portale, G.; Wisse, E.; Dankers, P. Y. W.; Meijer, E. W. Aggregation of Ureido-Pyrimidinone Supramolecular Thermoplastic Elastomers into Nanofibers: A Kinetic Analysis. *Macromolecules* **2011**, *44*, 6776-6784.