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Knoevenagel Condensation Reaction-Empowered Hydrogels with pH-Tunable Dynamic Properties

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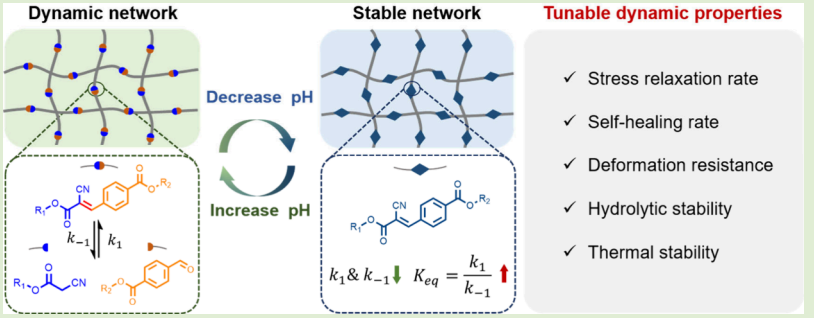

ABSTRACT: Dynamic hydrogels have found extensive applications in various biomedical fields owing to their remarkable dynamic properties, such as fast stress relaxation and self-healing capabilities. In this work, we report the development of a hydrogel empowered by the reversible Knoevenagel condensation (KC) reaction featuring pH-tunable dynamic properties. By adjusting the pH, the exchange rates and quantities of the dynamic C═C bonds formed via the KC reaction can be regulated through modulation of the association rate constant (k_1), dissociation rate constant (k_{-1}), and equilibrium constant (K_{eq}) of the reversible KC reaction. Specifically, pH reduction decelerated both k_1 and k_{-1} of the KC reaction while elevating the K_{eq}. As a result, when the pH decreased from 10 to 1, the KC reaction-formed dynamic hydrogels exhibited a progressive increase in relaxation time ($\tau_{1/2}$) from 100 to over 1,000 s, accompanied by enhanced structural stability and improved mechanical performance. This study provides a new strategy to design the dynamic hydrogels with tunable dynamic properties through the pH-responsive KC reaction.

Dynamic hydrogels are widely used in cell transplantation, wound healing and drug delivery due to their unique dynamic properties granted by dynamic cross-links, such as injectability, reprocessability, and time-dependent viscoelastic properties, including creep, stress relaxation, and self-healing.[1−12] It has been found that precise control of exchange rates and quantities of the dynamic cross-links—comprising the association and dissociation rate constants (k_1 and k_{-1}) as well as the equilibrium constants (K_{eq})—is crucial for modulating the dynamic properties of hydrogels.[13−19] For example, Tibbitt et al. correlated the dissociation rate constants (k_{-1}) with the dynamic properties of borate cross-linked hydrogels through manipulating the pH of the medium, providing insight into the relationship between exchange rates of cross-links and hydrogel viscoelasticity.[20] Similarly, Baker et al. employed imine bonds to construct dynamic networks with tunable binding kinetics (k_1 and k_{-1}) and equilibrium constants (K_{eq}), enabling accurate predictions of hydrogel viscoelastic behavior.[13] Furthermore, Xia et al. introduced dynamic hydrazone bonds for dynamically cross-linked hydrogels, allowing for independent regulation of binding kinetics (k_1 and k_{-1}) without altering the equilibrium constants (K_{eq}), contributing to a comprehensive analysis of the relationship between binding kinetics (k_1 and k_{-1}) and dynamic properties of hydrogels.[21] These studies highlight the critical role of precisely regulating the dynamic exchange rates and quantities of dynamic cross-links in modulating the dynamic properties of hydrogels.

The dynamic C═C double bonds formed by the Knoevenagel condensation (KC) reaction, as a novel type of dynamic covalent bond, have garnered increasing attention in recent years.[22−25] In the previous work of our group, we demonstrated the dynamic KC reaction that can occur under aqueous conditions.[25,26] The activated methylene group is deprotonated to form a carbon anion, which acts as a nucleophile to attack the carbonyl group of the aldehyde, followed by an intramolecular rearrangement to form a C═C bond.[27] The resulting dynamic C═C bonds are dissociative, as they can revert back to the precursor methylene group-containing compounds and aldehyde group-containing com-

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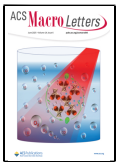

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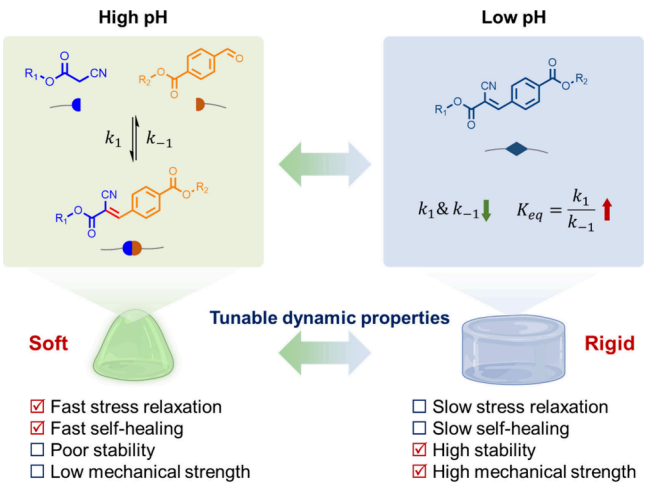
pounds upon the addition of H_2O, involving nucleophilic attack of hydroxide anion, subsequent intramolecular proton transfer and C−C bond cleavage (Figure S1). Additionally, these bonds are found to be thermosensitive and have been successfully utilized to construct dynamic hydrogels, which have further been applied in cell transplantation and wound healing.[26,28] Recently, we successfully utilized this dynamic KC reaction to develop other dynamic materials, such as recyclable and self-healable elastomers, further demonstrating its broad versatility.[29,30] However, our understanding and development of dynamic KC reaction are still in their early stages, and further exploration is needed.

In this study, we report the facile preparation of a dynamic hydrogel with pH-tunable dynamic properties. Adjusting the pH value of the medium can significantly tune the dynamic exchange rates and quantities of the formed C=C bonds by altering the binding kinetics (k_1 and k_{-1}) and equilibrium constants (K_{eq}) of the reversible KC reaction, thereby regulating the macroscopic dynamic properties of the obtained hydrogels (Scheme 1). Specifically, when the pH was reduced

Scheme 1. Schematic Illustration of the pH-Tunable Dynamic Properties of the Dynamic Hydrogel through Regulating the Binding Kinetics and Equilibrium Constants of the Reversible KC Reaction



from 10 to 1, both the k_1 and k_{-1} of reversible KC reaction decreased by 2 orders of magnitude, while the K_{eq} simultaneously increased. Consequently, at high pH, the dynamic hydrogel exhibited soft mechanical properties characterized by rapid stress relaxation, accelerated self-healing kinetics, yet compromised stability, and reduced mechanical strength. In contrast, under low pH conditions, the hydrogel transitioned to a rigid state with prolonged stress relaxation and delayed self-healing dynamics, accompanied by enhanced stability and elevated mechanical strength.

The reversibility of the KC reaction between benzaldehyde group and cyanoacetate group in aqueous environment has been previously demonstrated in our earlier work.[25,26,28] Herein, we present a novel demonstration of the pH-responsiveness of the reversible KC reaction, wherein both the binding kinetics (k_1 and k_{-1}) and equilibrium constants (K_{eq}) vary as a function of pH (Figure 1A). To prove it, we synthesized three model compounds: cyanoacetic acid-terminated polyethylene glycol (mPEG-CA) (cyanoacetic acid is a classical compound for providing the active methylene group to form the KC reaction), 4-formylbenzoic acid-terminated polyethylene glycol (mPEG-FA), and the product of the KC reaction between mPEG-CA and mPEG-FA, referred to as mPEG-CF-mPEG. The structures of three model compounds were confirmed through ^{1}H NMR, ^{13}C NMR, and MALDI-TOF-MS (Figures S2−S10).

To study the impact of pH on the association rate constants (k_1), we prepared 1 wt % solutions (weight/volume percentages, w/v, %) of mPEG-CA and mPEG-FA at various pH values. Equal molar ratios of mPEG-CA and mPEG-FA were mixed in solutions at the same pH, and the time-dependent association process was monitored using a UV−vis spectrometer. The absorption peak at 256 nm (A_1), corresponding to the benzaldehyde group of mPEG-FA, gradually decreased, while the absorption peak at 303 nm (A_2), representing mPEG-CF-mPEG, simultaneously increased (Figure 1B−D and Figure S11). The ratio of A_2/A_1 correlates with the formation rate of mPEG-CF-mPEG, which progressively decreased as the pH value decreased (Figure 1E). These findings demonstrate that the association rates can be significantly modulated by the pH value of the solution. Further, the association rate constants (k_1) were calculated (Figure 1J) from the curves in Figure 1E. Since minimal mPEG-CF-mPEG formation occurred within 60 min at pH 1, k_1 values are only shown for pH 4, 7, and 10. Compared to the k_1 values at pH 10 and pH 7 (8.93×10^{-3} and 6.08×10^{-3} $mM^{-1}s^{-1}$, respectively), the k_1 values at pH 4 decreased to 3.71×10^{-4} mM^{-1} s^{-1}. These findings suggest that reducing the medium's pH significantly inhibits the association rates (k_1), presumably due to the increased hydrogen ion concentration in the solution, which hinders the deprotonation of methylene groups adjacent to the cyano group of mPEG-CA into carbanions, thus markedly decreasing the k_1 values.[27]

Next, to study the impact of pH on the dissociation rate constants (k_{-1}) of the KC reaction, we monitored the dissociation process of mPEG-CF-mPEG at various pH values via UV−vis spectrometer. With increasing incubation time of mPEG-CF-mPEG in different pH solutions, the absorption peak at 256 nm (A_1) gradually increased, while the absorption peak at 303 nm (A_2) simultaneously decreased, indicating the dissociation of mPEG-CF-mPEG (Figure 1F−H and Figure S12). Additionally, the dissociation rates exhibited a gradual decline with a decreasing pH (Figure 1I), suggesting that pH significantly affects the dissociation rates. And the dissociation rate constants (k_{-1}) are calculated (Figure 1K) from the curves in Figure 1I. Since minimal deformation of mPEG-CF-mPEG occurred within 120 min at pH 1, the k_{-1} values are only shown for pH 4, 7, and 10. Compared to the k_{-1} values at pH 10 and pH 7 (2.56×10^{-4} and 1.36×10^{-4} s^{-1}, respectively), the k_1 values at pH 4 decreased to 4.75×10^{-6} s^{-1}. These results indicate that decreasing the pH significantly inhibits both association and dissociation rates of the reversible KC reaction.

In addition to the influence on binding kinetics, pH also modulates the equilibrium constant (K_{eq}) of the KC reaction. We characterized the equilibrium states of mPEG-CF-mPEG at different pH values using UV−vis spectroscopy. The absorption peaks at 303 nm corresponding to mPEG-CF-mPEG increased progressively as the pH decreased, suggesting that lower pH values enhance the K_{eq} of the reversible KC reaction (Figure S13). This observation is consistent with the results (Figure 1L), which were derived from Figure 1J,K by the equation $K_{eq} = k_1/k_{-1}$ at different pHs. These findings

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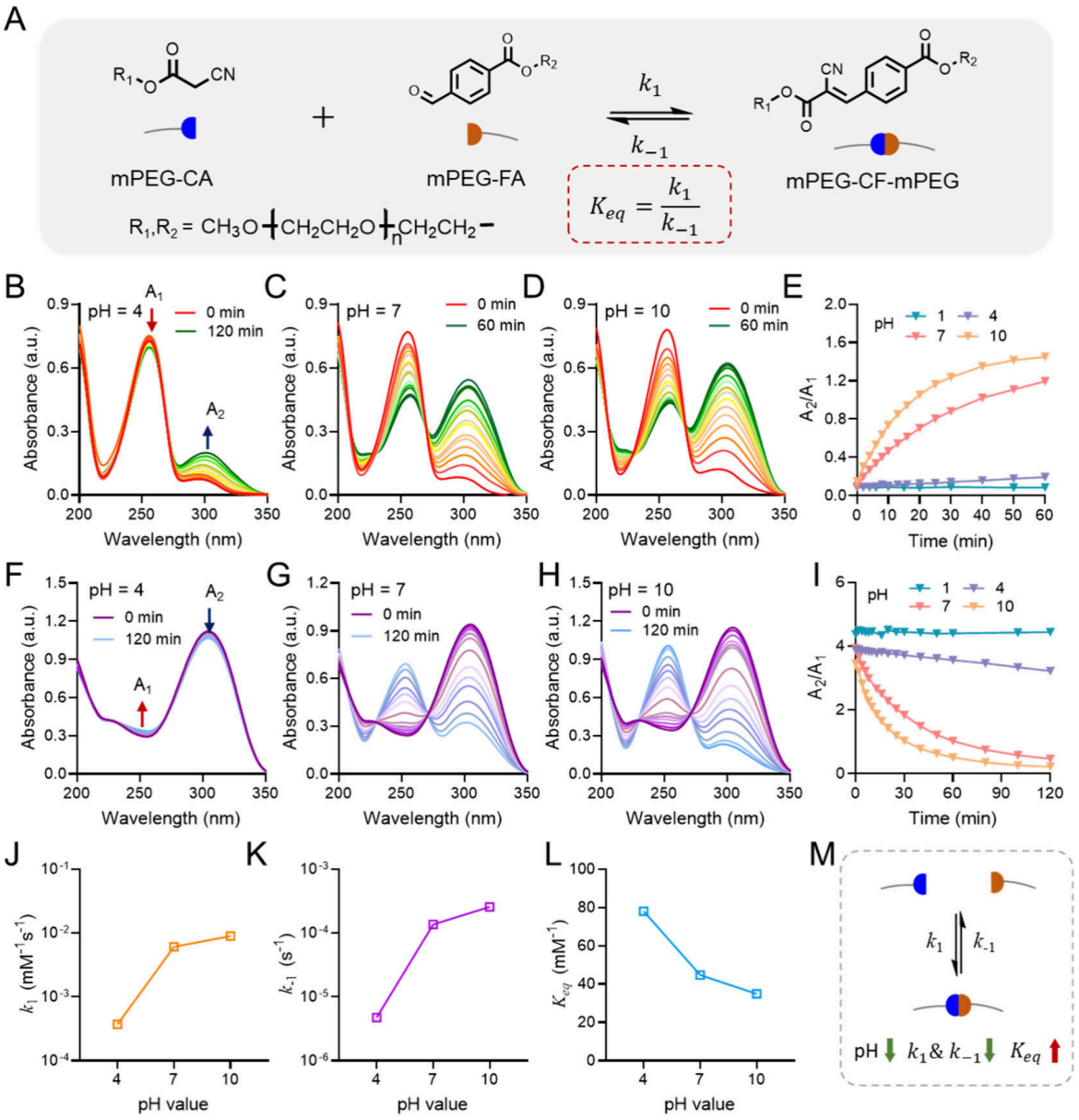

Figure 1. pH responsiveness of the KC reaction. (A) Illustration of the reversible KC reaction between the model compounds mPEG-CA and mPEG-FA, and their product mPEG-CF-mPEG. Time-dependent UV−vis absorbance spectra of 1 wt % mixed mPEG-CA and mPEG-FA solutions at medium pH values of (B) 4, (C) 7 and (D) 10. Time-dependent UV−vis absorbance spectra of mPEG-CF-mPEG solutions at medium pH values of (E) 4, (F) 7 and (G) 10. (H) Changes in the absorption ratio of peak A_2 against peak A_1 in panels (B), (C), and (D) and Figure S11 over time. (I) Changes in the absorption ratio of peak A_2 against peak A_1 in panels (E), (F), and (G) and Figure S12 over time. (J) The association rate constants (k_1) were obtained from panel (E). (K) The dissociation rate constants (k_{-1}) were obtained from panel (I). (L) The K_{eq} was obtained from panels (J) and (K) by the equation $K_{eq} = k_1/k_{-1}$. (M) Illustration showing how pH affects k_1, k_{-1} and K_{eq}.

indicate that pH can effectively modulate both the binding kinetics (k_1, k_{-1}) and equilibrium constant (K_{eq}) of the reversible KC reaction, thereby altering the dynamic exchange rates and quantities of the formed C═C bonds (Figure 1M). This may provide a novel approach for preparing KC reaction-empowered hydrogels with pH-tunable dynamic properties.

To prepare the hydrogel with pH-tunable dynamic properties via the reversible KC reaction, we selected 4-arm poly(ethylene glycol) to construct polymer networks with high homogeneity and no chain entanglements (Figure 2A).[17,31] We first synthesized four-arm polyethylene glycol terminated with cyanoacetic acid (4-arm PEG-CA) and 4-formylbenzoic acid (4-arm PEG-FA) as model systems. The products were confirmed via ^{1}H NMR and ^{13}C NMR spectra (Figures S14 to S17). Subsequently, we prepared dynamic hydrogels (4-arm PEG-Gel) with concentrations of 8, 10, and 15 wt % by mixing the two polymers. The gelation times were found to be 17, 10, and 5 min for the hydrogels with concentrations of 8, 10, and 15 wt %, respectively. The oscillatory frequency sweep (Figure 2B) revealed that all hydrogels conformed to the canonical Maxwell model,[20] exhibiting a consistent relaxation behaviors ($\tau_R \sim 120$ s), calculated as $\tau_R = 1/\omega_c$. These findings were consistent with the relaxation time ($\tau_{1/2} \sim 100$ s), quantified by the time at which the stress relaxed to half of its original value, obtained by stress relaxation tests (Figure 2C,D), demonstrating that the relaxation behavior of dynamic hydrogels was independent of the polymer concentration.

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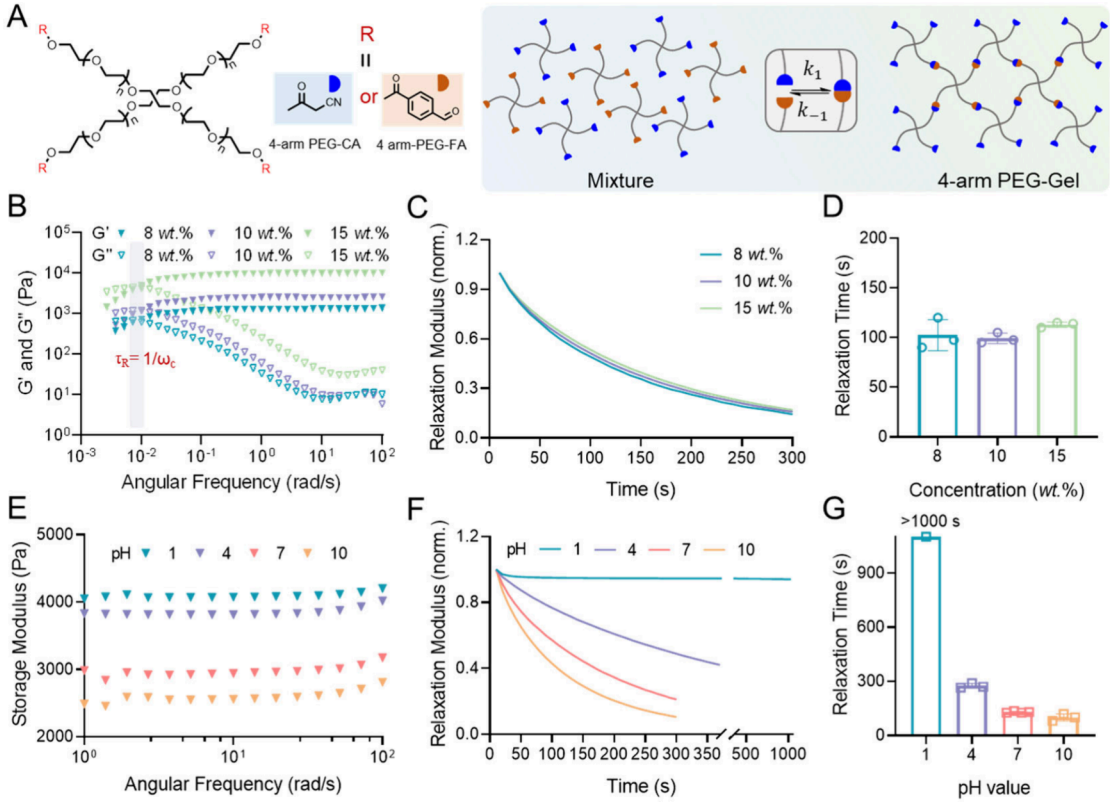

Figure 2. Rheological characterization of pH-modulated dynamic hydrogels cross-linked by the KC reaction. (A) The dynamic hydrogels were prepared by mixing 4-arm PEG-CA and 4-arm PEG-FA solutions in equal mass fractions. (B) Oscillatory frequency sweep of dynamic hydrogels at concentration of 8, 10, and 15 wt %. (C) Relaxation behaviors of dynamic hydrogels under 1% strain. (D) Relaxation time ($\tau_{1/2}$) of dynamic hydrogels obtained from panel (C). (E) Oscillatory frequency sweep of 10 wt % dynamic hydrogels with different medium pH values (pH = 10, 7, 4 and 1). (F) Normalized relaxation behaviors of dynamic hydrogels at different medium pH values (pH = 10, 7, 4 and 1) under the 1% strain. (G) Relaxation time ($\tau_{1/2}$) of dynamic hydrogels obtained from panel (F). All of the measurements were performed at 25 °C.

Furthermore, the results (Figure 2B) also indicated that hydrogels cross-linked via the KC reaction adhered to classical rubber elasticity principles, wherein the plateau modulus (G') of dynamic hydrogels was influenced by variations in cross-linking density induced by polymer concentration.[20] Additionally, the k_{-1} also have an influence on G', so we hypothesized that pH could modulate the G' of KC reaction-cross-linked dynamic hydrogels by altering the K_{eq} and k_{-1} of the KC reaction. To test this, we adjusted the medium pH of the prepared 10 wt % 4-arm PEG-Gel to 10, 7, 4, and 1, and measured their G'. The frequency sweep results (Figure 2E) confirmed our speculation, showing that the G' increased from 2600 to over 4000 Pa as the pH decreased from 10 to 1. Compared with high pH, the hydrogels at low pH exhibit higher G' because the increasing K_{eq} enhances the cross-linking density and the decreasing k_{-1} promotes the cross-links to stay formed. These findings demonstrate that pH can tune the mechanical properties of dynamic hydrogels by regulating the K_{eq} and k_{-1} of the KC reaction.

To quantitatively elucidate the modulation of the dynamic properties of KC reaction cross-linked hydrogels through pH variation, we initially characterized the stress relaxation behaviors of 4-arm PEG-Gel (10 wt %) at various pH levels under a 1% strain. The experimental results (Figure 2F,G) revealed that the stress relaxation rates decreased significantly with a reduction in medium pH from 10 to 1 with the relaxation time increasing progressively from approximately 100 to over 1,000 s. These findings indicate that lowering pH can effectively reduce the exchange rates of dynamic C═C bonds by decreasing the association and dissociation rate constants (k_1 and k_{-1}), thereby reducing the energy dissipation capacity of 4-arm PEG-Gel. This provides an effective method for regulating the stress relaxation behavior of KC reaction cross-linked dynamic hydrogels.

The pH-induced reduction in the association and dissociation rate constants (k_1 and k_{-1}) and equilibrium constants (K_{eq}) is expected to alter the dynamic and mechanical properties of the KC reaction cross-linked dynamic hydrogels, including the stiffness and strength.[17] A decrease in k_1 and k_{-1} would likely reduce the exchange rates of dynamic cross-links, thereby slowing the rearrangement rates of cross-links. Consequently, this would lead to a diminished energy dissipation capacity. In conjunction with the increased cross-linking density due to enhanced equilibrium constants (K_{eq}), this could ultimately enhance the stiffness and strength of dynamic hydrogels. This enhancement is expected to improve the hydrogels' resistance to deformation under external forces. To demonstrate this, we performed loading−unloading compression tests on 4-arm PEG-Gel at various pH values. Both the stiffness and the strength of dynamic hydrogels exhibited a significant increase as the pH changed from 10 to 1 (Figure 3A). The compression modulus calculated from Figure 3A increased from 5.13 to 22.20 kPa as the pH decreased from 10 to 1 (Figure S18). Furthermore, by measuring the hydrogel

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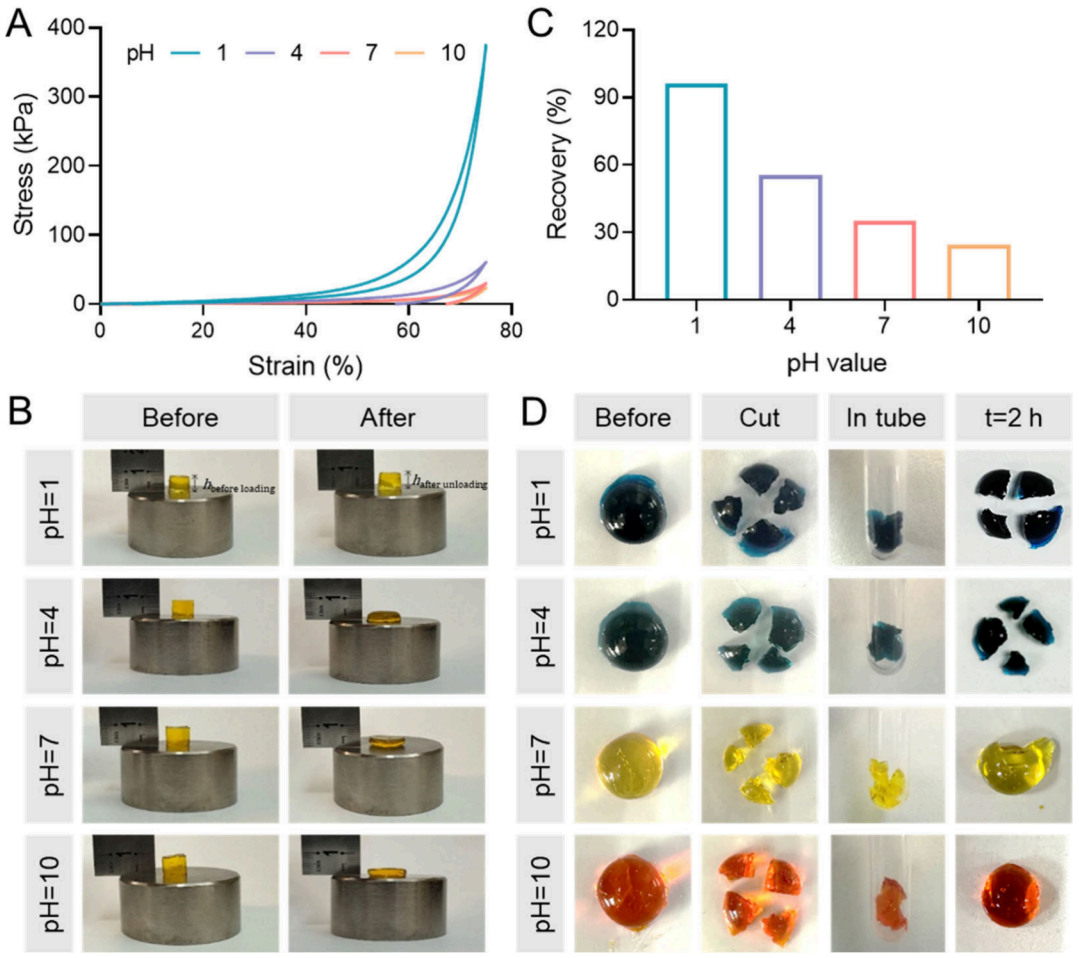

Figure 3. Compression and self-healing behaviors of pH modulated KC reaction cross-linked dynamic hydrogels. (A) Stress−strain curves of dynamic hydrogels with different medium pH values during compression process. (B) Images of dynamic hydrogels with different medium pH values before and after compression (initial height = 9 mm, compression rate = 2 mm/min, compression shift = 7 mm). (C) Recovery of dynamic hydrogels after deformation was obtained from panel (B), the ratios of $h_{\text{before loading}}$ against $h_{\text{after unloading}}$. (D) Self-healing behaviors of the dynamic hydrogels under different pH conditions.

heights (h) before loading and after unloading, we calculated recovery ratios by $h_{\text{before loading}}$ against $h_{\text{after unloading}}$ (Figure 3B). The recovery ratios (Figure 3C) were markedly higher at pH 4 and 1 (55.6% and 96.1%, respectively) compared to those at pH 7 and 10 (35.3% and 24.4%, respectively). These findings provide compelling evidence that pH-induced changes in binding kinetics (k_1 and k_{-1}) and equilibrium constants (K_{eq}) effectively modulate the dynamic and mechanical properties of the KC reaction cross-linked dynamic hydrogels.

The self-healing property of dynamic hydrogels, an essential dynamic property stemming from bond rearrangement, exhibits a positive correlation with association and dissociation rate constants (k_1 and k_{-1}).[20] As k_1 and k_{-1} decrease with lowering pH, the rates of dynamic bond rearrangement diminish, potentially resulting in a loss of self-healing capability in dynamic hydrogels. To evaluate the effect of pH on self-healing behavior, 4-arm PEG-Gel prepared at different values was cut into four small fragments and incubated at 37 °C in centrifuge tubes for 2 h. As shown in Figure 3D, the fragments at pH 7 and 10 successfully re-formed into intact hydrogels with the self-healing efficiency over 90% (Figure S19). However, those at pH 4 and 1 remained fragmented and failed to heal. These findings suggest that the pH-induced reduction in association and dissociation rate constants (k_1 and k_{-1}) inhibits the rearrangement of hydrogel networks via a decrease in the exchange rates of dynamic cross-links, thereby modulating the macroscopic self-healing behavior of dynamic hydrogels.

Furthermore, owing to the rapid exchange rates of dynamic cross-links, the majority of dynamic hydrogels display elevated degradation rates. To explore how medium pH influences the degradation rates of KC reaction cross-linked dynamic hydrogels, we immersed 4-arm PEG-Gel in solutions with varying pH values and monitored their degradation behaviors. The dynamic hydrogels in pH 7 and pH 10 solutions degraded significantly faster than those in pH 4 and 1 solutions (Figure 4A). Further to quantitatively assess the degradation process, dynamic hydrogels (300 μL) were immersed in 1 mL of different pH solutions, and their weights were recorded over time. The hydrogels in pH 7 and 10 solutions degraded completely (Figure 4B and Figure S20) within 12 and 8 h, respectively, while those in pH 4 and 1 solutions exhibited prolonged stability and were observed to degrade after 18 and 31 days, respectively. The results demonstrate that acid-induced reduction of binding kinetics (k_1 and k_{-1}) and increase of K_{eq} could significantly enhance the macroscopic retention time of KC reaction cross-linked dynamic hydrogels. This is achieved by slowing the exchange rates of the dynamic cross-

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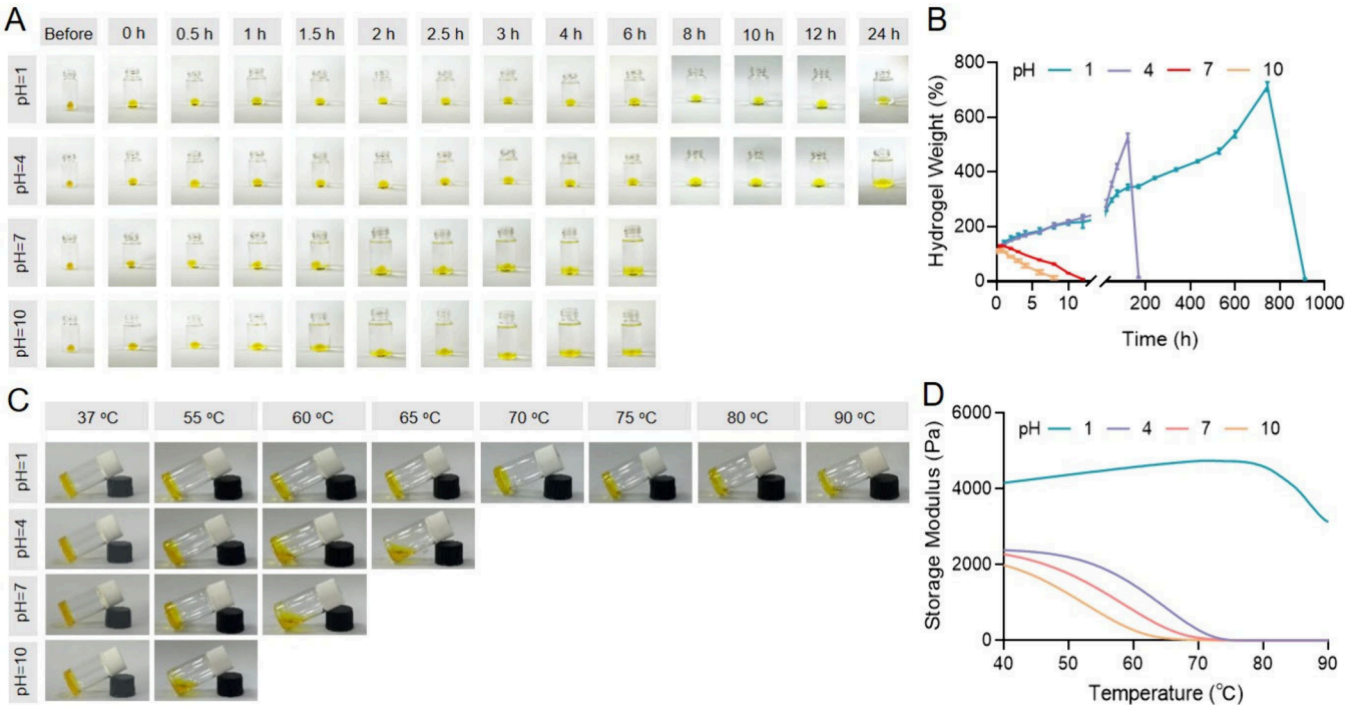

Figure 4. Degradation behaviors and thermosensitive properties of pH modulated dynamic hydrogels. (A) Degradation images of dynamic hydrogels cross-linked via the KC reaction under different pH conditions (10 wt %, 300 μL hydrogel in 5 mL ultrapure water, 25 °C). (B) Degradation curves of dynamic hydrogels cross-linked via the KC reaction under different pH conditions (10 wt %, 300 μL hydrogel in 1 mL ultrapure water, 25 °C). (C) Images of pH modulated dynamic hydrogels under different temperature for 5 min. (D) Rheological characterization of pH modulated dynamic hydrogels to obtain the change of storage modulus as the temperature increased (heating rate = 5 °C/min, f = 1 Hz, γ = 1%).

links and increasing the cross-linking density. In contrast to other dynamic covalent bonds with acid-responsive dissociation properties, such as imine and boronic ester bonds, a contrasting behavior was observed for the dynamic C═C bonds formed via the KC reaction.

Previous studies have demonstrated that the KC reaction is thermosensitive, enabling a gel-to-sol transition upon temperature elevation.[25] We hypothesized that pH-regulated binding kinetics and equilibrium constants would enhance the quantities and stability of cross-links, thereby improving the thermostability of KC reaction cross-linked dynamic hydrogels. To prove that, 4-arm PEG-Gel with different pHs were subjected to gradually increasing temperature until they transformed into sol. The transition temperature increased from 55 to over 90 °C as the pH decreased from 10 to 1 (Figure 4C). Rheological temperature scanning further confirmed this trend (Figure 4D). These results indicate that pH-modulation can effectively enhance quantities and the stability of cross-links, thereby modulating the macroscopic thermosensitive properties of KC reaction cross-linked dynamic hydrogels. In a word, the way of pH-modulated binding kinetics (k_1 and k_{-1}) and equilibrium constants (K_{eq}) to tune the exchange rates of dynamic cross-links could significantly tune the dynamic properties of dynamic hydrogels, including their hydrolytic and thermal stability.

In summary, we reported the successful preparation of a dynamic hydrogel with pH-tunable dynamic and mechanical properties through a pH-regulated KC reaction. By changing the pH from 10 to 1, the binding kinetics (k_1 and k_{-1}) decreased by 2 orders of magnitude and the equilibrium constant (K_{eq}) increased, leading to the decline of dynamic exchange rates of the C═C bonds and increasing of the cross-linking density of dynamic hydrogels. As a result, the dynamic hydrogels demonstrate high stress relaxation rates and degradation rates under basic and neutral pH conditions while exhibiting high stability and mechanical strength under acidic pH conditions. These findings provide a deeper understanding of the correlation between microscopic parameters (k_1, k_{-1} and K_{eq}) of the reversible KC reaction and macroscopic dynamic properties of hydrogels, which may shed a new light on the development of dynamic hydrogels for various biomedical applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.5c00218.

Materials and methods, synthesis and characterization of model compounds and polymers, including ^{1}H NMR spectra, ^{13}C NMR spectra, UV−vis spectra and MALDI-TOF-MS, and characterization of the self-healing and degradation behaviors of hydrogels (PDF)

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Notes

The authors declare no competing financial interest.

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