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Supramolecular Hydrogels

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Multistimuli-Responsive, Moldable Supramolecular Hydrogels Cross-Linked by Ultrafast Complexation of Metal Ions and Biopolymers**

Zhifang Sun, Fucong Lv, Lujie Cao, Lin Liu, Yi Zhang, and Zhouguang Lu**

Abstract: *A new type of multistimuli-responsive hydrogels cross-linked by metal ions and biopolymers is reported. By mixing the biopolymer chitosan (CS) with a variety of metal ions at the appropriate pH values, we obtained a series of transparent and stable hydrogels within a few seconds through supramolecular complexation. In particular, the CS–Ag hydrogel was chosen as the model and the gelation mechanism was revealed by various measurements. It was found that the facile association of Ag^+ ions with amino and hydroxy groups in CS chains promoted rapid gel-network formation. Interestingly, the CS–Ag hydrogel exhibits sharp phase transitions in response to multiple external stimuli, including pH value, chemical redox reactions, cations, anions, and neutral species. Furthermore, this soft matter showed a remarkable moldability to form shape-persistent, free-standing objects by a fast in situ gelation procedure.*

Stimuli-responsive polymers,[1] such as supramolecular hydrogels,[2] which exhibit responsiveness to external environmental perturbations, have great potential in many fields, such as shape memory devices,[3] sensors,[4] biomedicines,[5] and smart interface materials,[6] among others.[7] Up to now, much attention has been paid to the design and synthesis of these stimuli-responsive supramolecular hydrogels, including synthetic polymers[8] and low-molecular-weight gelators (LMWGs).[9] For example, Tong et al. have reported a dual redox- and light-responsive hydrogel system based on the supramolecular complexation between poly(acrylic acid) and ferric ions in the presence of citric acid.[10] Recently we have showed a similar quadruple stimuli-responsive supramolecular hydrogel based on the LMWG with ferrocenyl groups integrated in the molecular backbones.[11]

However, most of these widely used materials largely depend on the petrochemical industry or organic synthesis and polymerization, which are regarded as unsustainable methods, and the organic synthesis and purification procedures are tedious and expensive.[12] Moreover, the gelation process of these synthetic molecules were always found to be time consuming,[13] thus limiting their practical applications. Biopolymers,[14] a class of renewable natural resources which are abundant in the biosphere, are considered as ideal alternatives to the petroleum-derived polymers. However, utilizing native biopolymers for the design of advanced soft materials still remains a challenge. Thus, it is of great significance to develop multistimuli-responsive, flexible, and processible supramolecular hydrogels based on natural renewable biopolymers.

Herein, we report the first observation of ultrafast hydrogelation via cross-linking by supramolecular complexation between a native biopolymer, chitosan (CS), and transition metal ions, specifically Ag^+, Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pd^{2+} (their corresponding hydrogels are denoted as CS–Ag, CS–Cu, CS–Co, CS–Ni, CS–Zn, CS–Cd, and CS–Pd, respectively). The gelation speed was very fast, occurring mostly within two seconds. Each hydrogel was found to have a high water content, to be stable at room temperature, and could be easily reproduced. As the model material, the CS–Ag hydrogel was further investigated to elucidate the gelation mechanism between CS chains and Ag^+ ions. Interestingly, the CS–Ag hydrogel underwent a reversible gel–sol transition in responsive to multiple external stimuli. The hydrogel also exhibited an excellent moldability to form shape-persistent, free-standing objects using an ultrafast in situ gelation procedure. To our knowledge, no other native biopolymer-based supramolecular hydrogels have been shown to possess all of these features.

Figure 1 shows the fast hydrogelation procedure cross-linked by supramolecular complexation between native CS chains and a variety of metal ions. The gelation procedure was straightforward, requiring simply that the metal-ion solutions be mixed with the CS solution at room temperature at appropriate pH values (Figure 1A).[15] Upon mixing, the metal ions underwent very fast complexation (within 2 s) with the CS chains, leading first to the formation of interwoven networks and finally the formation of hydrogels (Figure 1B,C). The physicochemical properties of these hydrogels are listed in Table S1 in the Supporting Information. Each hydrogel had a high water content, exhibiting a relatively low critical gelation concentration (CGC) with less than 1 wt% of metal–biopolymer system, lower than that of most reported supramolecular hydrogels based on biopolymers. The key factor for the preparation of these hydrogels

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[*] Z. F. Sun, F. C. Lv, L. J. Cao, Prof. Dr. Z. G. Lu
Department of Materials Science and Engineering
South University of Science and Technology of China
Shenzhen 518055 (China)
E-mail: luzg@sustc.edu.cn
Prof. Dr. Y. Zhang
College of Chemistry and Chemical Engineering
Central South University, Changsha 410083 (China)
E-mail: yzhangcsu@csu.edu.cn
Dr. L. Liu
College of Chemistry and Chemical Engineering
Anyang Normal University, Anyang, Henan 455000 (China)

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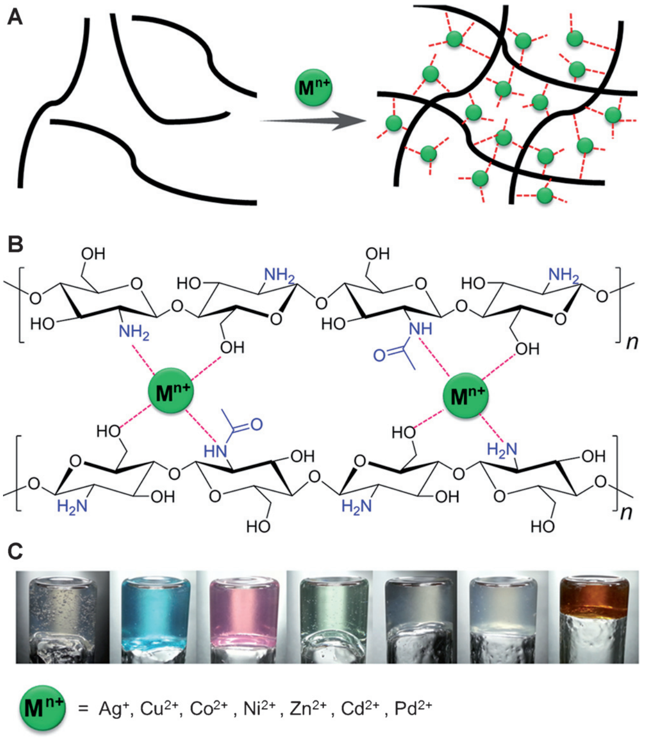

Figure 1. A) Schematic representation of polymer-network hydrogels cross-linked by ultrafast complexation of metal ions and chitosan chains in water. B) Chemical structures of chitosan and their interwoven networks driven by the complexation between metal ions and OH and NH_2 groups in the chitosan chains. C) The complexation in (B) leads to the formation of hydrogels (from left to right: CS–Ag, CS–Cu, CS–Co, CS–Ni, CS–Zn, CS–Cd, and CS–Pd, respectively).

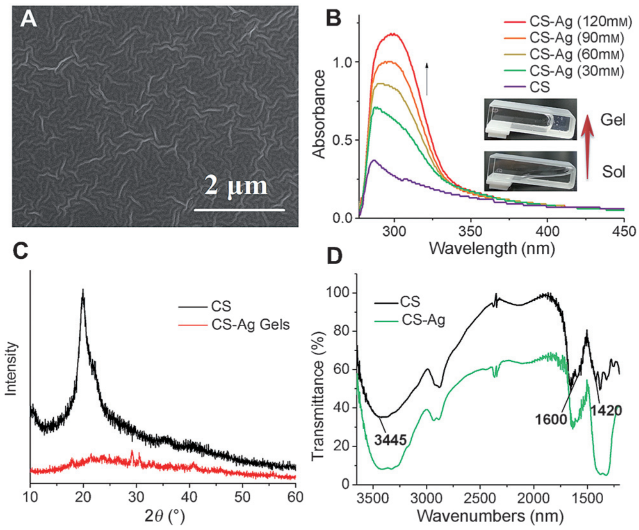

Figure 2. A) SEM image of the CS–Ag hydrogel. B) Concentration-dependent UV/Vis absorption spectra of the CS solution with increasing Ag + ion concentration (indicated by an arrow), showing the transformation of the CS solution from solution to CS–Ag hydrogel. In the legend, numbers in parentheses denote the Ag^+ concentration. C) XRD pattern of the CS powders and CS–Ag xerogels. D) FTIR spectra of CS powders and CS–Ag xerogels.

was the appropriate pH values. Note that the CS solution was prepared by dissolution in acetic acid (1.0 %); a lower pH value would not lead to gelation. Intriguingly, rapid gelation could be observed when the pH value of the CS solution was raised by the addition of NaOH solution (0.2 M; see the Supporting Information for the detailed procedure). The rheological properties of these hydrogels were measured and it was found that, in all hydrogel samples, the G' (storage modulus) was always greater than the G'' (loss modulus), indicating the elastic nature of these hydrogels (Figure S1). Additionally, these hydrogels were stable over a long period, staying intact for up to 6 months at room temperature. Interestingly, unlike other supramolecular hydrogel systems which are vulnerable to high temperature, the CS–metal hydrogels can endure 100 °C without obvious change, indicative of their good thermostability.

To gain insight into the gelation mechanism and the concomitant properties of these hydrogels, CS–Ag was chosen as the model hydrogel for further investigation. This hydrogel was chosen as it had the best gelation properties of the hydrogels prepared herein (Table S1) and it also had excellent stimuli-responsive properties. We first carried out scanning electron microscopy (SEM) to obtain a direct view of the morphology of the CS–Ag hydrogel. As shown in Figure 2 A, the SEM image revealed that the CS–Ag sample was composed of interconnected nanostructures, whereas the CS alone was much smoother (Figure S2 C), indicating that the interwoven networks were cross-linked by Ag^+ ions (Figure S2). The concentration-dependent UV/Vis absorption spectra were then recorded to provide more details of the role of the Ag^+ ions in the complexation with CS chains (Figure 2 B). It was found that with gradual introduction of the Ag^+ solution, the CS solution transformed into a hydrogel. The intensity of the absorbance increased significantly with increasing Ag^+ ion concentration, with the maximum absorption band undergoing a red shift from $\lambda = 287$ nm to 298 nm. This result was attributed to the coordination of the Ag^+ ions, having empty orbitals, to the CS chains, which have plenty of free hydroxy and amino groups with abundant lone-pair electrons.[16] A time-dependent UV/Vis absorption study of the CS–Ag hydrogel was also carried out. As shown in Figure S3, the spectrum of CS–Ag recorded 1 min after mixing with Ag^+ was identical to that after 30 min indicating that the process is not time dependent, which can be ascribed to the extremely fast complexation between the Ag^+ ions and the CS polymer chains. These results were in agreement with the XRD patterns of the CS–Ag xerogels. As shown in Figure 2 C, the intensity of the peak at $2\theta = 20°$ for the crystal form of the pure CS powders decreased significantly and only a much broader, less intense peak at $2\theta = 24°$ was detected for the CS–Ag xerogels. This change in the XRD spectrum is as a result of the complexation between the Ag^+ ions and the CS chains through -OH and -NH_2 binding sites, thus efficiently reducing the hydrogen bonding and destroying the crystal structure of the CS chains.[17] Additionally, the FTIR spectra of the CS powders and the CS–Ag xerogels were recorded to give direct evidence for the complexation. In the spectrum in Figure 2 D, major evidence for the interaction of CS and Ag^+ ions is the shift of the band at 3445 cm^{-1} (attributable to CS ν_{OH} and ν_{NH} absorptions)[16] to 3420 cm^{-1}. Furthermore, from

CS to CS–Ag xerogel the amide II band at 1600 cm^{-1} underwent a blue shift and the C–N band at 1420 cm^{-1} a red shift. These shifts revealed that both -OH and -NH_2 groups in the CS chains took part in the coordination complexation.[17] Therefore, it can be concluded that the fast complexation of Ag^+ ions with -NH_2 and -OH groups in CS chains promoted the rapid gel-network formation.

As the CS chains, the Ag^+ ions, and an appropriate pH value are indispensable for gel formation, once the complexation or the gelation pH range is intentionally changed the gel-to-sol phase transition will take place. After this transition, the gel state can be reformed by restoring the complexation or the pH values, thus showing reversible sol–gel transitions upon external environment changes. Accordingly, we examined the reversible sol–gel transitions in the CS–Ag hydrogel system (Figure 3). As a result of the narrow gelation-suitable pH range for the CS–Ag gel, adding HCl (30 μL of a 0.1 M solution) to the hydrogel (1 mL) caused gel collapse within 10 seconds by shaking. In contrast, when the same amount of NaOH was added into the resulting solution, the gel state could be restored immediately. Additionally, the CS–Ag hydrogel showed reversible responsiveness to metal ions. It was reported that Cu^{2+} ions bind more strongly to CS than other metal ions.[18] When a Cu^{2+} solution (100 μL of a 0.1 M solution) was added into the CS-Ag hydrogel (1 mL), the gel transformed into a sol rapidly (Figure 3). This transition occurred as a result of the strong binding affinity of Cu^{2+} ions for the CS chains, where the Cu^{2+} ions competed and replaced the Ag^+ ions to form a CS–Cu complex. Interestingly, the pH value of the resulting CS–Cu complex was below the minimum gelation pH for the CS–Cu hydrogel; additional NaOH solution would increase the pH values and result in gelation of the CS–Cu material (Figure S4).

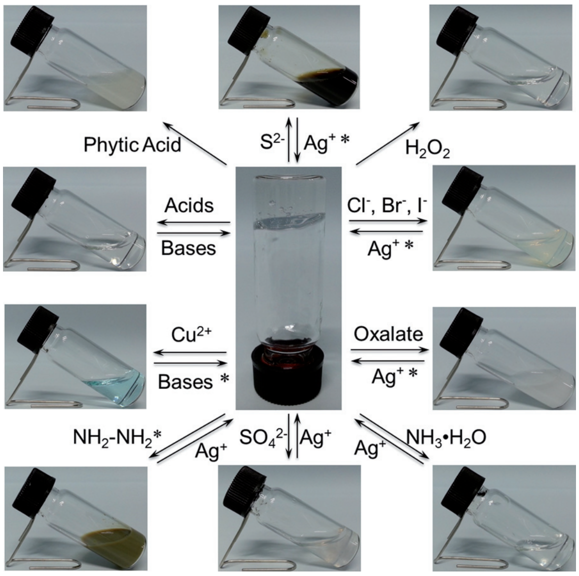

Figure 3. The reversible gel–sol phase transitions of the CS–Ag hydrogel triggered by multiple stimuli. The * symbol indicates that the reformed hydrogels are neither transparent nor colorless. (Gel preparation procedure detailed in the Supporting Information).

As has been established, Ag^+ ions have a remarkable binding affinity for a wide range of anions and molecules, and can be easily reduced by reducing agents. Thus, the reversible gel–sol transition could be tuned simply by adding and removing these anions, molecules, or reducing agents. For example, after an quantity of halide ions (Cl^-, Br^-, I^-), equal to the amount of Ag(I) ions, was added to the CS–Ag hydrogel, it gradually collapsed and to form a milky solution (Figure 3; Figure S5–S7). The SEM images revealed that the solution was composed of nanoparticles, which was ascribed to the formation of AgX (X = Cl, Br, I; Figure S8). The gel state could be restored by adding an excess of Ag^+ ions. Similar reversible gel–sol transitions could be triggered by addition of a small excess of oxalate, S^{2-}, or SO_4^{2-} ions, respectively. These anions can trap Ag^+ ions from the CS–Ag hydrogels leading to the collapse of the gel state which can be subsequently restored by addition of an excess of $AgNO_3$ solution (Figure S9–S12). Interestingly, adding a minimum amount of hydrazine hydrate resulted in the disappearance of the gel state, accompanied by a color change from colorless to brownish grey, and the Ag^+ ions were reduced into Ag nanoparticles (Figure S13). Excessive Ag^+ ions were added for cross-linking the CS chains which remained in the mixture, leading to the recovery of the gel. Furthermore, because of the strong coordination between ammonium hydroxide and Ag^+ ions, adding or removing $NH_3{\cdot}H_2O$ could also trigger the reversible gel–sol transitions.

We have also investigated the effect of other chemical stimuli to realize irreversible sol–gel transitions. For example, when a small excess of phytic acids (PA) was added to the CS–Ag hydrogel, a fast gel-to-sol transformation could be observed instantly, leading to an off-white suspension (Figure 3). The cryo-dried SEM images reveal that the suspension was composed of large bundles, which was ascribed to the strong association between PA and CS chains (Figures S14, S15). This was in good agreement with the previous report by Cui and co-workers,[19] in which the phosphate groups from the PA molecule could tightly bind with the NH_2 groups from the polymer chains. The PA and CS bind together so strongly that we could not restore the gel state by addition of excess Ag^+ ions. Additionally, the CS–Ag hydrogel showed an irreversible response to oxidizing agents. Previously reports indicated that the chitosan could be decomposed slowly in the presence of hydrogen peroxide.[20] With this in mind, a 30 % H_2O_2 solution (30 μL) was added into the CS–Ag hydrogel (1 mL). The gel was found to gradually transform into a clear solution within 5 days (Figure 3). This discovery was very useful to investigate the controlled release of Ag^+ ions (Figure S16), considering that they (and silver nanoparticles[21]) are believed to be broad-spectrum and robust antibacterial agents active against a large variety of pathogenic bacteria.

Compared to preparation processes for most supramolecular hydrogels which rely highly on tedious and time-consuming procedures, such as sonication,[22] repeat heat/cool cycles,[23] or enzyme triggers,[24] our CS–Ag hydrogel can be readily prepared by simply mixing the $AgNO_3$ solution and chitosan solution at room temperature (Figure 4 A). The silver ions then cross-link chitosan chains to form, in situ,

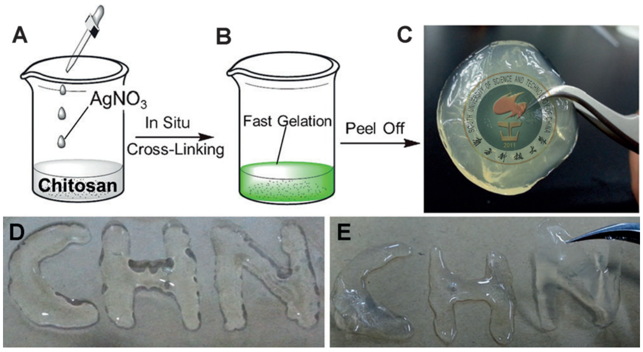

Figure 4. Hydrogels are rapidly formed upon A) addition of silver nitrate solution (0.3 M) into the chitosan solution (4.0 wt%). B) Complexation between CS and Ag$^+$ took place rapidly in situ within a few minutes and C) the cross-linking of chitosan and silver ions resulted in formation of the elastic hydrogels. D, E) Photographs of the shape-persistent, free-standing hydrogel characters "CHN" in D) the sol state before and E) the gel state after being immersed into the AgNO$_3$ solution for 1 min.

polymer networks, thus leading to gelation within a very short timeframe (Figure 4B). This procedure is relatively simple, although the gelation time is depended on the concentration of the chitosan solution. For example, keeping the AgNO$_3$ concentration the same (0.3 M), the gelation occurred within 2 seconds (with shaking) when the concentration of CS was 0.4 wt%, whereas it occurred within 1 min when the CS was at 4.0 wt%. To our surprise, when the hydrogel (CS at 4.0 wt%) was peeled away from the beaker, a shape-persistent, free-standing gel object was obtained (Figure 4C). A rheological study was performed to investigate the mechanical strength of this gel object. As shown in Figure S17, a G' value of circa 4400 Pa is achieved, which is much larger than that of the G'' value, indicating that the as-prepared gels are both elastic and relatively tough.

The good mechanical properties, as well as the facile preparation procedures, inspired us to examine the moldabilities of our hydrogels. As shown in Figure 4D, a CS solution (4.0 wt%) was intentionally dropcast by syringe onto the bottom surface of a petri dish in the letter shape of "CHN". Subsequently, silver nitrate solution (0.3 M) was added into the petri dish and complexation between the CS polymer chains and Ag$^+$ ions instantly occurred. Finally, free-standing gel objects were formed and removed from the petri dish. Interestingly, we found that the gel objects perfectly inherited the "CHN" shape which was identical to the original shape of the precursor CS solution (Figure 4E). These excellent moldable properties may find application in the design of moldable, shape-specific objects.

In summary, we have demonstrated that ultrafast complexation between biopolymer chitosan and a variety of metal ions can be used to fabricate a series of supramolecular hydrogels with relatively high water content. These hydrogels are facile to prepare and the gelation time is very short, almost instantaneous upon mixing the CS and metal-ion solutions, making this one of the most facile reported hydrogelation procedures. As a model of these metal–chitosan gel systems, we have shown that the CS–Ag hydrogel exhibited versatile and multifunctional properties. For example, the hydrogel was shown to be responsiveness to a variety of external stimuli and was also moldable, such that shape-persistent, free-standing objects could be formed. We believe these remarkable features make such biopolymers very useful natural resources for the design of advanced soft materials, and the gel systems in this paper may find practical usages in fields such as smart devices, logic gates, sensors, and in antibacterial gel membranes.

Keywords: biopolymers · hydrogels · sol–gel processes · supramolecular chemistry · transition metals

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