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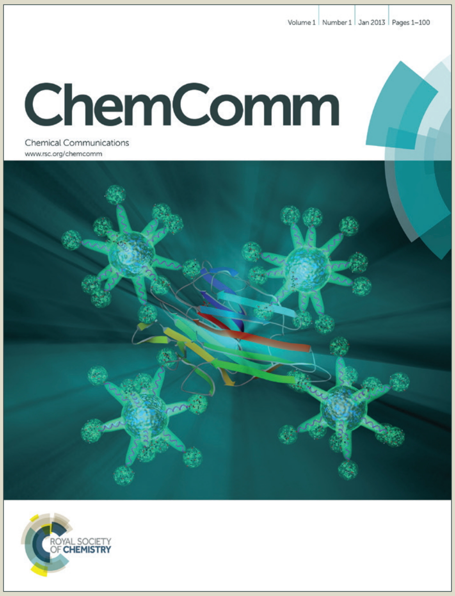

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ARTICLE TYPE

Amino Acid-based Multiresponsive Low-Molecular-Weight Metallo-hydrogels with Load-bearing and Rapid Self-healing Ability

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A multiresponsive metallohydrogel based on amino acid-derived low molecular weight (LMW) ligand and Zn(II) salt was prepared. This hydrogel showed remarkable shape-persistent, self-standing, load-bearing and self-healing properties, which is uncommon in LMW hydrogels.

The ability of autonomic self-healing to restore a damaged function is one of the most fascinating and important properties found in living organisms.[1] Over the past few decades, this feature has inspired researchers to develop self-healable synthetic materials, mostly polymeric materials, to reduce replacement costs while improving their lifetime and safety.[2] In general, these materials are based on either irreversible (e.g., encapsulation of healing agents) or reversible approaches (e.g., dynamic covalent bonds, non-covalent bonds).[2a] Among materials with potential self-healing properties, viscoelastic (soft) materials such as hydrogels are very promising for biomedical applications due to their biocompatibility and similar mechanical properties to those of natural tissues.[2d] The existence of cooperative dynamic interactions in supramolecular hydrogels[3] offers interesting possibilities to promote self-healing mechanisms without an external trigger. Herein, we report a very rare free-standing, moldable, and load-bearing supramolecular metallohydrogels at room temperature from a low-molecular-weight (LMW) amino acid-based ligand in the presence of Zn(II) salts. These hydrogels displayed unique multiresponsive gel-to-sol transitions and autonomic self-healing behavior.

Figure 1 illustrates the instantaneous and spontaneous formation of representative hydrogel (namely ZAVP hydrogel) upon combination of two stock aqueous solutions containing L-valine based molecule (i.e., V = L-3-methyl-2-(pyridine-4-yl-methylamino)-butanoic acid) and sodium perchlorate as ligand systems (VP, respectively), and Zn(II)-based salts (i.e., zinc acetate dihydrate = ZA). The ligands were easily prepared by a slight modification of the procedure reported in the literature (Section S1).[4] Optimization of the concentration of each stock solution (Section S2) allowed the formation of opaque white hydrogels that remained stable upon inversion of the test tube (*vide infra*).

The critical gelation concentration (CGC) for ZAVP hydrogel was established as 84 g L^{-1}, respectively. The hydrogel was found to be thermoreversible and the gel-to-sol transition temperatures (T_{gel}) were established in 61 ± 2 ºC. Complete sol-to-gel transitions occurred within 20 min upon spontaneous cooling the corresponding isotropic solutions. As often observed with other chiral gelators,[5] the enantiomeric purity of the ligand was found to play a key role on the formation of stable gels. The most stable gels were obtained when using enantiomerically pure ligands, although complete gelation could be observed when the enantiomeric excess (ee) was 85% ≤ ee ≤ 100%. In contrast, only partial gelation was achieved in the range 60-80% ee, and no gelation was observed when the ee was < 60% (Section S3 and Figure S1). Moreover, we notice that the bulk gels remained stable during sonication. The use of ligands containing K^+ instead of Na^+ ions provided hydrogels with same properties suggesting a minor role of these ions on the gelation phenomenon (Section S2). Interestingly, the results of a large screening demonstrated that the gelation was specific regarding the presence of Zn(II) salts as coordinating metal. The nature of the counter anion was, however, less critical and similar gels using zinc acetate, zinc perchlorate or zinc nitrate could be obtained. In this contribution we focus on the detailed study of the ZAVP as model system.

Insights into the morphology of the ZAVP hydrogel were obtained by recording SEM/FESEM and ESEM images of the corresponding xerogel (prepared by freeze-drying) and native gel phase, respectively, which revealed a high-aspect ratio fibrilar network as a consequence of a highly anisotropic growth process (Figures 1 and S3). Most of the fibers presented relatively uniform diameters in the range of 20-80 nm and lengths on the micrometer scale.

The Viscoelastic and brittle nature of the hydrogel were confirmed by oscillatory rheological measurements (Figures 2 and S3). Within the linearity limits of deformation, established by dynamic frequency and strain sweep experiments (DFS and DSS, respectively), the average storage modulus ($G' > 10^5$ Pa) was one order of magnitude higher than the loss modulus (G') and constant over the entire range of frequencies (0.1-10 Hz) (Figure 2). Reproducible and relatively constant dissipation factors ($\tan \delta = G''/G' \approx 0.1$) during DFS indicated a good tolerance of the hydrogels to external forces. Further dynamic time sweep (DTS) measurements (ESI) at 0.1% strain and 1 Hz frequency confirmed the stability of the hydrogels at RT within the linear

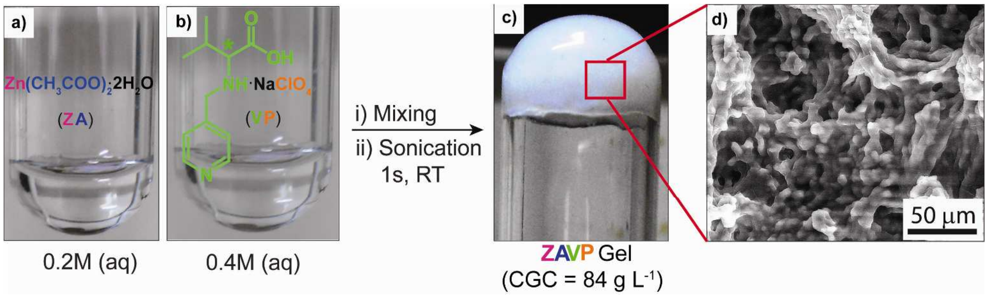

Figure 1. Synthesis of ZAVP (a-c) at the CGC. Total volume of each solution = 0.5 mL . d) SEM-images of the corresponding xerogel.

regime. Remarkably, ZAVP hydrogel displayed also a rapid thixotropic response against the mechanical stress caused by large-amplitude oscillations at room temperature. Figure 2 shows a loop test involving consecutive cycles of low-high strain separated by enough time to guarantee complete gel-to-sol ($G' < G''$) and sol-to-gel ($G' > G''$) transitions while minimizing inertial effects between the steps. These results showed that the original mechanical properties of the gel were fully recovered within 3 ± 1 min after termination of the large stress. This process was repeatable for at least 15 cycles without appreciable reduction in the average magnitude of G' and G'' (Figure 2 and Figure S3).

This thixotropic behavior was also macroscopically observed within ca. 4 min after a shaking-resting cycle applied to the test tube containing the hydrogel (Figure 3). The shear thinning property of the ZAVP hydrogel was observed in microscale and bulk forms. Besides the described response to thermal and mechanical stimuli inducing gel-to-sol transitions, a rapid pH and chemoresponse was also observed (Figure 3). The hydrogel, with an intrinsic pH of ca. 6.5, turned into a clear solution within seconds upon addition of 1 M TFA solution. Restoration of the gel phase was possible by adding an equivalent amount of ammonia to the previous solution. Very interestingly, gel-to-sol transition could be also achieved by adding a 4-fold excess of ammonia (4 M) with respect to the concentration of Zn(II) in the gel phase. In this case, subsequent addition of 4 M TFA solution caused the inverse sol-to-gel process. This particular phenomenon occurs due to the reversible formation of Zn(II)-tetramine complex in the presence of ammonia. Notably enough, hydrogelation with other pyridine-containing gelators at low pH has been previously described as an unfavorable process.[6] Under the same principle of dynamic metal-complexation, the addition of solid crystalline EDTA or Na_2S (equimolar to the amount of Zn(II) present in gel) on top of the gel caused complete dissolution or formation of white precipitate (ZnS), respectively, in quantitative yields within 30 min. Separation of the ZnS and addition of equimolar amounts of ZA to the remaining solutions restored the gel phases within a few minutes. No differences were observed in the properties of the gels obtained through the multiresponsive map depicted in Figure 3. Moreover, we were delighted to observe that macroscopic ZAVP hydrogel was not only multistimuliresponsive in nature but it also exhibited rapid self-healing in air at room temperature without use of any kind of healing agent. Recently, a number of metallogels with self-healing properties have been reported.

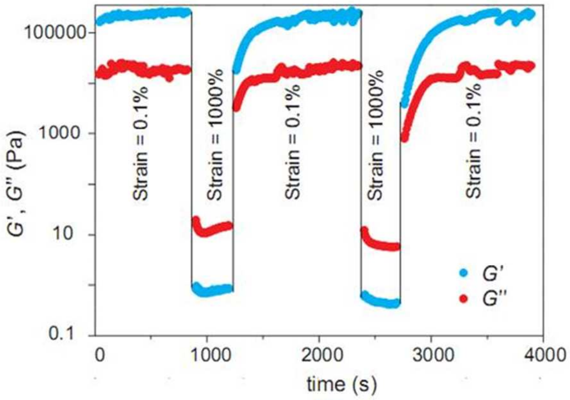

Figure 2. Oscillatory rheology of ZAVP hydrogel prepared at the CGC, Thixotropy-loop test via continuous step-strain measurements at 0.1 Hz.

Nevertheless, most of these examples are either organogels[7] or based on (1) formation of metal coordination polymers, [8] (2) use of ligand-containing polymers for metal complexation,[9] or (3) host-guest polymer interactions.[10] As far as we are aware, this is the second example of low molecular weight metallohydrogel which shows autonomic self-repairing ability.[11] Figure 4 illustrates the self-healing ability of the supramolecular ZAVP hydrogel in a conventional 'gel block fusion' experiment.[7,11] ZAVP hydrogel was first grown inside a hollow glass cylinder, and further cut into smaller pieces (Figures 4a). Remarkably, the gel body was able to support (regardless of time) up to 60-fold its own weight without causing any visible change on its dimensions, shape and consistence (Figures 4b-c). Such high load-bearing strength is a very rare property for LMW gels.[12] When different gel blocks were put in direct contact along the cut surfaces, they were recombined within 3 h at room temperature without the need of any external stimuli (Figures 4d). Thus, we could construct a 30 cm long bridge upon connecting 11 hydrogel blocks, which could be held vertically and horizontally (Figures 4e-f). For clarity, the experiment was made alternating dye-doped (i.e., Rose Bengal) and undoped gel blocks.

The above results together with MALDI-TOF studies of the corresponding xerogels (Section S6) suggested the direct involvement of a reversible Zn(II)-complex in the gelation process, which may undergo successive self-assembly through multiple hydrogen-bonding interactions. Analysis of the obtained spectra showed intense peaks in the LMW region (Figure S4 and S6), which suggested a LMW nature of the gelator instead of a co-ordination polymer structure (co- ordination polymers give

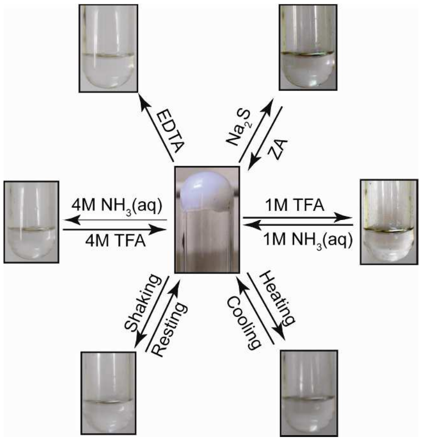

Figure 3. a) Thermal, mechanical, pH, and chemical stimuli-triggered gel–to-sol transitions of ZAVP hydrogel. ZA = Zinc acetate dihydrate

prominent peaks at high molecular weight region). It is worth mentioning that such multiresponsive nature has been observed specially in physical organogels,[13] although it is scarcely found in supramolecular hydrogels.[14]

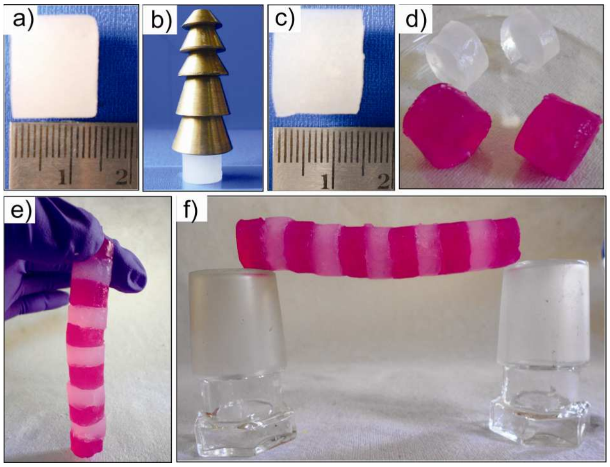

Figure 4. Pictures of a) freshly prepared hydrogel cylinder of 1.4 cm thickness and 1.6 cm diameter; b) 2 g mass bearing a load up to 90 g (total weight of 5 truncated brass cones); and c) maintaining its shape after load is released. d) Moldable and shape-persistent hydrogel blocks cut from a larger cylinder. Pink objects correspond to hydrogel pieces upon doping with Rose Bengal dye. e-f) Bridge constructed by fusing 11 hydrogel blocks together, Light pink coloration of undoped gel blocks is due to the rapid diffusion of the dye through the hydrogel network.

In summary, we have described the facile preparation of new non-polymeric supramolecular metallohydrogels by combining two stock solutions of a amino acid-based ligand (i.e., L-3-methyl-2-(pyridine-4-yl-methylamino)-butanoic acid) and Zn(II) salts. These hydrogels displayed unique multiresponsive gel-to-sol and sol-to-gel transitions, as well as remarkable moldable, load-bearing, and autonomic self-healing behavior at room temperature. Structure-gelation ability relationship studies and testing applications of these materials are currently underway in our laboratories and the results will be reported at due course.

Notes and references

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