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Multi-stimuli responsive self-healing metallo-hydrogels: tuning of the gel recovery property†‡

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A series of amphiphilic tyrosine based self-healable, multi-stimuli responsive metallo-hydrogels have been discovered. Formation of these hydrogels is highly selective to Ni^{2+} ions. The self-healing property and the stiffness of these metallo-hydrogels can be tuned by varying the chain length of the corresponding gelator amphiphile.

Peptide/amino acid based supramolecular gels[1] composed of low-molecular weight gelators are an important field of current research. These gelator molecules are self-assembled using various non-covalent interactions such as hydrogen bonding, π–π interaction, hydrophobic interaction and others to form a fibrillar network structure that is occupied by solvent molecules to form gels under suitable conditions. These non-covalent interactions are weak in nature and they can be broken and reformed in response to the various external stimuli[2] such as heat, pH of the medium, external chemicals, sonication, mechanical force and irradiation by light. Stimuli responsiveness of these soft gel materials with a highly permeable network structure offers potential applicability[1,3] in drug delivery, regenerative medicine, nanoparticle and nanoclusters synthesis and other fields. It is well known that peptides or amino acids form complexes with various transition metals.[4] The side chain of tyrosine plays a crucial role in the stability of the metal complex. This is due to the possibility of coordination of the hydroxyl group at the 4-position of the aromatic ring in addition to the carboxylate and amino group. The hydrophobic surface of the phenyl ring also shields the attack of water molecules in aqueous medium.[5] Sometimes metal ions triggered the self-assembly of peptides and amino acid derivatives to form supramolecular metallo-gels.[6] Metallo-gelators belong to a special class of gelators due to their quick response to various stimuli. Diverse kinds of molecules are found to form metallo-gels including cholesterol derivatives, pyridine complexes and various metal organic frameworks (MOFs). Moreover, self-healable supramolecular soft materials[7] are one of the emerging field in advanced materials research. Self-healing gels are able to partially or completely repair the damage imposed on them and the original structure can be restored. There are several examples of self-healing gels based on clay-composite, polymer and nano-composite and others. The modulation of the self-healing property in gels always remains to be a challenging task. However, none of the above-mentioned examples corresponds to multi-stimuli responsive metallo-hydrogels with self-healing property. So, there is a genuine need for the discovery of a common structural motif which shows multi-stimuli responsive metallo-gel formation with a self-healing property and tuning of the self-repairing property by variation of the gelator structure keeping the basic nature of the gelator molecules the same.

In this report, a series of tyrosine based amphiphiles[8] **P_1–P_3** (Fig. 1a) have been found to form hydrogels in aqueous phosphate

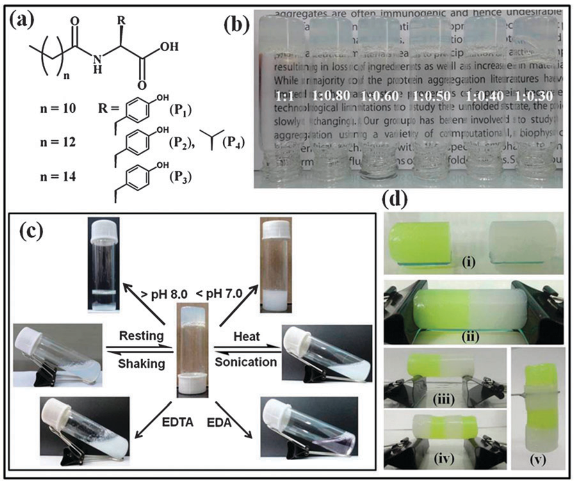

Fig. 1 (a) Chemical structures of various amphiphiles (**P_1–P_4**). (b) Pictures of glass vials containing metallo-hydrogels obtained from different proportions of the **P_3** and nickel salt ($NiCl_2$). (c) Multi-stimuli responsiveness shown by the hydrogel obtained from **P_3**. (d) Illustration of self-healing behavior (i–v) shown by the metallo-hydrogel obtained from **P_3**.

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buffer solutions (pH 7.0 to 8.0) in the presence of Ni^{2+} ions. These metallo-hydrogels exhibit remarkable self-healing property. The self-healing property of these hydrogels can be nicely tuned by varying the chain length of these amphiphiles. These metallo-hydrogels exhibit multi-stimuli responsiveness towards various stimuli including pH of the medium, temperature, mechanical forces and external chemicals.

Amphiphiles $\mathbf{P_1}$–$\mathbf{P_3}$ are self-assembled in aqueous phosphate buffer solutions of pH ranging from 7.0 to 8.0 in the presence of Ni^{2+} ions to form a translucent hydrogel. These amphiphiles were first dissolved in phosphate buffer solution by heating; then $NiCl_2$ was added concomitantly to this solution. It turned into a white coloured suspension upon the addition of $NiCl_2$. These mixtures were then sonicated for a few minutes to produce a clear solution and kept at room temperature without any disturbance to form hydrogels. The amphiphile $\mathbf{P_3}$ forms a gel within a few minutes. However, amphiphiles $\mathbf{P_2}$ and $\mathbf{P_1}$ form a gel after 3 h and 18 h of standing respectively. These metallo-hydrogels are stable over several months. Without Ni^{2+} ions, upon standing or sonication all these amphiphiles were precipitated from the solution. To investigate the effective ratio of the gelator and Ni^{2+} ions for gelation, the Ni^{2+} ion concentration was systematically decreased keeping the concentration (10 mM) of the gelator $\mathbf{P_3}$ fixed (Fig. 1b). By varying the gelator : Ni^{2+} ion ratio it was observed that the gelation took place from 1 : 1 to 1 : 0.3 ratio of gelator : Ni^{2+} ions. The opacity of the metallo-gels increases upon increasing the Ni^{2+} ion concentration. An increase in gelator : Ni^{2+} ion ratio above 1 : 1 causes precipitation, while a decrease of this ratio below 1 : 0.3 results in a viscous solution with no gel formation. Two other gelators ($\mathbf{P_1}$ and $\mathbf{P_2}$) have also shown similar behaviour (not shown here). In order to examine further structural effect (regarding the substitution of the amino acid) on gelation, $\mathbf{P_4}$ (Fig. 1a) was synthesized and tested for gelation. However, $\mathbf{P_4}$ was unable to form any type of gel under similar conditions. All amphiphiles are unable to form any kind of hydrogel in the presence of other metal ions such as Zn^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+}, Fe^{2+} and Hg^{2+}. The gelation of these amphiphiles has also been studied by using $NiSO_4$ and $Ni(ClO_4)_2$ separately. However, no significant change in gel formation has been noticed. This precludes the possibility of anion effect in gelation. So, it can be stated that metallo-hydrogelation is very much selective and specific not only to the tyrosine based amphiphiles but also to the presence of Ni^{2+}. The minimum gelation concentrations (MGC) of the metallo-hydrogels were found to be 10 mM, 9 mM and 7 mM at 1 : 0.5 ratio for $\mathbf{P_1}$, $\mathbf{P_2}$ and $\mathbf{P_3}$ respectively.

The morphological features of these metallo-hydrogels were investigated by TEM studies. TEM images (Fig. S13, ESI‡) vividly indicate that these metallo-hydrogels form thick tape like nanofibrillar network structures with different widths for different hydrogels. Widths of these nanofibers range from 60–80 nm, 60–70 nm and 120–150 nm for $\mathbf{P_1}$, $\mathbf{P_2}$ and $\mathbf{P_3}$ gels respectively.

These hydrogels are highly sensitive to pH and stable within the pH range 7.0 to 8.0. Above pH 8.0 these gelators form solutions and after 3–4 h they are precipitated and below pH 7.0 these gelators form suspensions (Fig. 1c). The thermal behavior of these metallo-gels has been studied by measuring the gel melting temperature (T_{gel}) at different ratios of gelators to Ni^{2+} ions (Fig. S14, ESI‡). Above the T_{gel}, all these gels turn into solution and the nickel hydroxide is precipitated out. Due to the low solubility of nickel hydroxide in water, the whole solution is turned into a white colored suspension (Fig. 1c). This suspension is transformed into a metallo-hydrogel upon cooling it to room temperature (25 °C) followed by sonication. However, below room temperature the gel phase remains intact (up to 5 °C was studied). T_{gel} of these metallo-hydrogels increase with an increase in the concentration of Ni^{2+} ions up to a certain value, then it decreases upon further increase in the Ni^{2+} ion concentration keeping the pH (7.46) constant. It is observed that the T_{gel} reaches the maximum value at the ratio 1 : 0.5 of gelator : Ni^{2+} ions. These metallo-hydrogels are sensitive to suitable metal chelating agents like ethylene diamine (EDA) or EDTA. Gel to sol transformation occurs in the presence of EDA while gel to precipitate occurs in the presence of EDTA (Fig. 1c), indicating the chemical responsiveness of these metallo-hydrogels.

The gel–sol transformation can also be achieved by the application of mechanical force (Fig. 1c). These hydrogels are transformed into solution upon the application of mechanical forces such as vigorous shaking but regained by the complete withdrawal of the mechanical force and keeping the solution at room temperature without any disturbance. Interestingly, these metallo-hydrogels have shown significant self-healing property. These hydrogels can be recovered from any damage imposed on them. The time needed to recover the gel state is highly dependent on the chain length of the corresponding gelator amphiphiles. Thus the self-healing property can be nicely tuned by changing the chain length of these amphiphiles. It was noticed that the hydrogel obtained from $\mathbf{P_3}$ reformed immediately (within 1 min) after it was broken. The other two amphiphiles $\mathbf{P_1}$ and $\mathbf{P_2}$ reformed within 8 min and 5 min respectively. The self-healing property was explored (Fig. 1d) by cutting the gel into two round-shaped pieces with a razor and then these pieces were put together with a moderate press. It was found that after 25–30 min these parts merged into a continuous block for all hydrogels. This fused block could then be suspended in air (Fig. 1d, iii–v) or can be stretched by pulling the two ends as shown in Fig. S15, ESI.‡ Similarly, the self-healing property of two other gels obtained from gelators $\mathbf{P_1}$ and $\mathbf{P_2}$ is illustrated in Fig. S16, ESI.‡

Fig. S17a (ESI‡) shows the variations of G' and G'' against angular frequency (ω) of each gelator (10 mM). G' and G'' do not vary significantly with the range of applied angular frequency (ω) and do not cross each other ($G' > G''$) throughout the experimental region. This indicates the presence of a stable and rigid gel phase material. Interestingly, the stiffness of these metallo-gels is increased upon increasing the alkyl chain length of gelator molecules. It is evident from the rheological experiments (Fig. S17a, ESI‡) that the rigidity of the metallo-gel is as follows: $\mathbf{P_1} < \mathbf{P_2} < \mathbf{P_3}$. There are only a few reports on the control of stiffness of gels by incorporating carbon based nanomaterial(s)[7] into the native gels. However, controlling the gel stiffness by simply varying the alkyl chain length of amphiphiles has not yet been reported.

A simple step strain experiment[9] was performed for all these metallo-gels (10 mM) in several steps (Fig. 2 and Fig. S17, ESI‡). At first gels were subjected to a constant strain of 0.1% (step 1). Then the strain was increased from 0.1% to 20% and was kept for a few minutes at 20% strain to break gels completely (step 2).

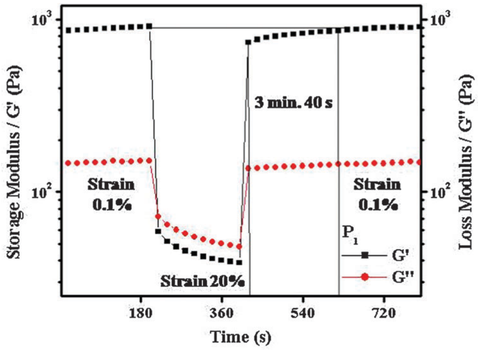

Fig. 2 The step strain experimental data obtained from the $\mathbf{P_1}$ metallo-hydrogel. The concentration was maintained at 10 mM in 1 : 0.5 gelator and Ni^{2+} ratio respectively.

Then the strain was decreased from 20% to 0.1% again and kept for a few minutes at 0.1% to observe the gel restoration kinetics (step 3). The angular frequency was kept constant at 1 rad s^{-1} throughout the three steps of the entire experiment. It was observed that the loss modulus values (G'') were greater than the storage modulus (G') values when the constant strain was 20%, indicating the sol-like nature of these gels during the second interval of the experiment. Immediately after removing the 20% strain, $\mathbf{P_1}$, $\mathbf{P_2}$ and $\mathbf{P_3}$ gels recovered 80%, 80% and 83% of their original stiffness respectively (Fig. 2 and Fig. S17, ESI‡). Interestingly, the complete recovery time was estimated to be 3 min 40 s for the $\mathbf{P_1}$ hydrogel, while that for the other two metallo-gels obtained from $\mathbf{P_2}$ and $\mathbf{P_3}$ were 4 min 40 s and 6 min respectively. The recovery time was calculated from the point of withdrawal of 20% strain after the complete breakage of the gel up to the point the gel phase was repaired again and restores its 100% strength in the third interval of the step strain experiment.

Fourier transform infrared (FT-IR) spectra in the non-gel state (without Ni^{2+} ions) and in the gel state (in the presence of Ni^{2+} ions) were almost identical except for the –OH stretching frequency of the side chain tyrosine moiety (Table S1, ESI‡). The –OH stretching frequency of the tyrosine moiety of $\mathbf{P_3}$ was observed at 3440 cm^{-1} in the non-gel state. However, in the gel state this peak was shifted to around 3400 cm^{-1} (Fig. S18, ESI‡). The –OH stretching frequency for other two gelators $\mathbf{P_1}$ and $\mathbf{P_2}$ was observed at 3425 cm^{-1} and 3415 cm^{-1} respectively. These values indicate that the tyrosine –OH is involved in the hydrogen bond formation in the gel network.

Small angle X-ray scattering (SAXS) was performed to examine the molecular assembly in the gel state. In SAXS (Fig. S19a, ESI‡) peaks were observed at $2\theta = 4.35°$, 3.9° and 3.4° with the corresponding d spacing values of 20.15 Å, 22.5 Å and 25.8 Å for gelators $\mathbf{P_1}$, $\mathbf{P_2}$ and $\mathbf{P_3}$ respectively. These values match well with the calculated molecular length of these individual gelator molecules. In the wide angle region (Fig. S19b, ESI‡) many sharp peaks were observed for all these gelators and each of these peaks matched well with the pure nickel hydroxide X-ray diffraction pattern.[10] Thus, it is evident from the XRD data that nickel hydroxide was formed in phosphate buffer medium (pH 7.46).

Results of XRD studies of all these amphiphiles ($\mathbf{P_1}$–$\mathbf{P_3}$) indicate that the nickel hydroxide is formed after the addition of $NiCl_2$ salt into the buffer solution of these amphiphiles. FT-IR studies indicate that the tyrosine –OH is hydrogen bonded to the nickel complex in the gel state as it is evident from the significant red shift of the tyrosine –OH peak and in the non-gel state that this phenolic –OH of the tyrosine residue remains unaffected. Other peaks of these gelator molecules remain unchanged in the presence of Ni^{2+} ions. This study clearly suggests that the carboxylate oxygen and amide –NH of these gelators do not interact with Ni^{2+} ions and it is the tyrosine –OH that interacts with the hydrated nickel complex. A schematic representation of the self-assembly of these metallo-hydrogels is shown in Fig. S20, ESI,‡ illustrating the stepwise assembly of the gelator molecules to form a tape-like network structure.

In conclusion, a series of tyrosine based multi-stimuli responsive self-healing metallo-hydrogels have been discovered. These hydrogels have shown stimuli responsiveness towards heat, mechanical shaking, pH of the medium and external chemicals. Remarkably, these metallo-hydrogels exhibit self-healing property and the self-healing property has been successfully tuned by varying the alkyl chain length of these gelator molecules. In this study, we have not only identified the specific motif (tyrosine based amphiphiles with varied alkyl chain lengths) for metallo-hydrogelation but also modulated the self-healing property of these gels by changing the alkyl chain length of these gelators. These multi-stimuli responsive self-healable nickel containing hydrogels hold promise to make stimuli responsive self-healable smart materials in future.

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