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Cite this: DOI: 10.1039/c0xx00000x

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COMMUNICATION

A Cu²⁺ specific metallohydrogel: preparation, multi-responsiveness and pillar[5]arene-induced morphology transformation†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/c0xx00000x

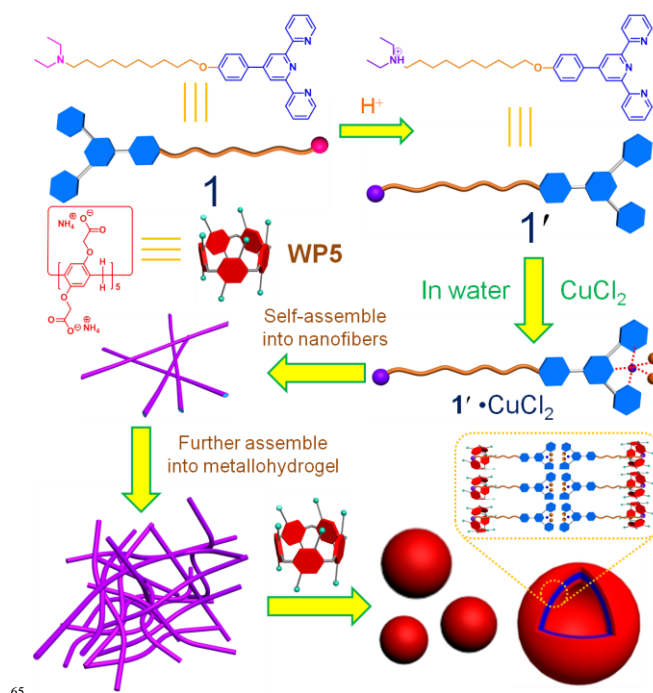
A Cu²⁺ specific metallohydrogel was constructed from a terpyridine-based low molecular weight ligand. The metallohydrogel showed multi-responsive gel-to-sol transitions and pillar[5]arene-induced nanofiber-to-vesicle transformation at the nanoscale.

Self-assembly of small molecules has been extensively utilized as an efficient strategy to construct and modulate nanostructures in the past few decades.¹ Among all the self-assembly behaviours of small molecules, gelation has in particular been applied in many fields such as organic–inorganic hybrid materials,² optoelectronics³ and medicines.⁴ One of the most urgent and desirable features of these gels is the dynamic nature of the assemblies which allows structural modulations at the molecular level. Plenty of such functional materials have been reported in recent literature where it was possible to modify the physical properties by applying external stimuli such as pH,⁵ light⁶ and chemical agents.⁷ This has also encouraged the application of such responsive supramolecular assemblies as potential indicator systems for changes in the immediate environment. Among various stimuli applied to modify gel behaviour, metal ions have been some of the most common regulators. On several occasions, introduction of metal ions into the gelator media was shown to have triggered long range self-assemblies which ultimately resulted in the formation of a 3D-gel network.⁸

Pillar[*n*]arenes as a brand new class of supramolecular hosts next to crown ethers,⁹ cyclodextrins,¹⁰ calixarenes¹¹ and cucurbiturils,¹² have been a rising star in supramolecular chemistry since 2008.¹³ Their repeating units are connected by methylene bridges at the *para*-positions, forming a unique rigid pillar architecture that differs from the basket-shaped structure of *meta*-bridged calixarenes. Among all chemically-modified pillararenes, anionic water-soluble pillararenes whose two rims are modified with carboxylate groups, have been widely used in constructing supramolecular amphiphiles, *etc.*¹⁴

Terpyridines are some of the most extensively utilized ligands to complex transition metal ions and have often been utilized as building blocks to fabricate supramolecular gel systems.¹⁵ The easy tunability of their physical properties by varying the metal ions made them a very promising prospect for such assemblies. However, the terpyridines lack the binding specificity towards any particular metal ion due to the universal coordination ability, leading to a situation that the gelation process is not metal ion

specific. Beyond above, copper can indeed be considered as the most versatile metal ions and the most largely analysed elements among the eight biologically essential metals (Ca, Mg, Mn, Fe, Cu, Zn, Co and Mo). It plays a key role in several physiological processes, such as electron transfer reactions, oxygen transport and enzyme catalysis. Furthermore, copper deficiency can cause dangerous effects, for example, anemia.¹⁶ Thus, developing a Cu²⁺ specific metallohydrogel may have potential applications in biologically relevant fields. Herein, we reported a terpyridine-based low molecular weight ligand **1** (Scheme 1) which can form hydrogel under slightly acidic conditions (**1** turned to **1'**) only in the presence of divalent copper ions (and chloride). The metallohydrogel showed multi-responsiveness including thixotropy, *etc.* More interestingly, water-soluble pillar[5]arene **WP5** can form a stable host–guest complex with **1'** and further induce the gel-to-sol transition and morphology transformation in the nanoscale dimension.



Scheme 1 Chemical structures of ligands **1** and **1'** and anionic water-soluble pillar[5]arene **WP5** and cartoon representations of the gelation process and **WP5**-induced morphology transformation.

Ligand **1** was synthesized by two simple steps (Scheme S1, ESI†). Before gelation, 2.00 mmol of ligand **1** was firstly solubilized in an aqueous solution (10.0 mL) of 0.200 M HCl, obtaining a 0.200 M solution of **1'**. As confirmed by UV-Vis experiments (Fig. S8, ESI†), the diethylamine group was protonated while the terpyridine group remained its original state at this pH, indicating that **1'** was amphiphilic and still able to coordinate with metal ions. Then transmission electron microscopy (TEM) and scanning electron microscopy (SEM) experiments were carried out to investigate the self-assembly behaviour of **1'**. Both of the microscopy images showed that **1'** just self-assembled into brick-like assemblies due to hydrophilic/hydrophobic interactions and π - π stacking interactions (Fig. S9, ESI†). However, the coordination of **1'** to metal ions was perceived to cause significant charge polarization in complexes, leading to stronger intermolecular interactions and morphology transformation of self-assembly. Based on this, several divalent metal ions were tested and disappointingly most of them only induced the color change of the solution or just precipitated out of the solution. Intriguingly, the phenomenon of gelation happened immediately when equal equiv. copper chloride was added to an aqueous solution of **1'** (Fig. 1).

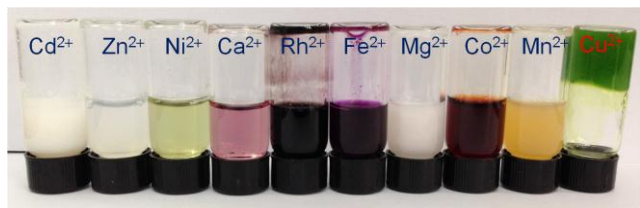


Fig. 1 Photographs of **1'** in the presence of divalent metal ions (from left to right: 2 mM of (chloride salt of) Cd^{2+} , Zn^{2+} , Ni^{2+} , Ca^{2+} , Rh^{2+} , Fe^{2+} , Mg^{2+} , Co^{2+} , Mn^{2+} , Cu^{2+} in 2 mM of **1'**).

The formation of the gel was found to be hampered in the presence of other divalent metal ions in combination with Cu^{2+} (Fig. S10, ESI†). Though the reasons for this unusual selectivity are not perfectly understood, it can be assumed that the large size and the coordination mode of the divalent copper cation play a vital role. As reported by Griffith *et al.*, hexa-coordinated transition metal complexes of terpyridine analogues are not suitable for extended networks/ structures due to geometrical constraints.¹⁷ A possible mechanism was proposed to explain the gelation: CuCl_2 forms penta-coordinated N_3Cl_2 terpyridine complexes (**1'•CuCl₂**) owing to its larger size and coordination mode, which may facilitate stronger π - π stacking interactions between the central pyridine ring of the terpyridine domain and the benzene ring of the adjacent complex,¹⁸ thus forming nanofibers. Those nanofibers then further twist together to form a 3D-network due to the van der Waals interactions of the alkyl chains.

To better understand the gelation mechanism and the morphological properties of the gel in the nanoscale dimension, the morphology of the xerogel was elucidated by SEM and TEM images. Different from the brick-like structure self-assembled from **1'**, the TEM image revealed that the structure of the gel matrix consists of a uniform and dense network of very thin nanofibers about 10 nm in diameter and several micrometers in length (Fig. 2a), which confirms the proposal of the gelation

mechanism. Moreover, a 3D-network was also observed by an SEM image (Fig. 2b), consistent with the result obtained from TEM.

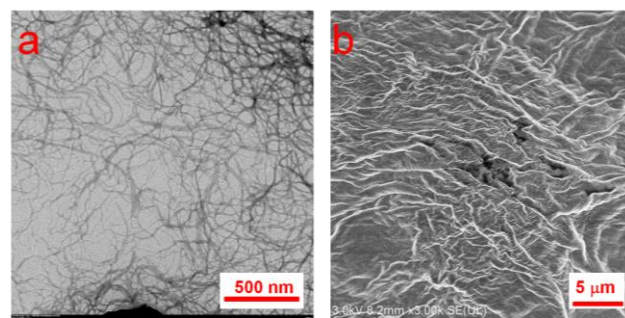


Fig. 2 (a) TEM and (b) SEM images of the metallohydrogel of **1'•CuCl₂** (2.00 mM) in water.

The metallohydrogel formed solely in the presence of Cu^{2+} (and chloride anions) showed multi-responsiveness including physical and chemical responsivenesses (Fig. 3). Upon heating for 1 minute at 60 °C, the transition of gel-to-sol was successfully achieved. After standing for 5 minutes at ambient temperature, the sol turned to the gel again, indicating that the gel-to-sol transition of this metallohydrogel was totally reversible upon heating or cooling, respectively. Moreover, the metallohydrogel transformed into a viscous sol upon shaking, which altered into a robust gel again upon resting, indicating a thixotropic behavior. Interestingly, the addition of a little excess of sodium *L*-ascorbate under Ar atmosphere led to precipitation from the gel state, presumably because of the reduction of Cu^{2+} to Cu^+ under this condition. The reversible gel formation was realized when the precipitate was kept under an oxygen environment for 1 day, which again oxidized Cu^+ to Cu^{2+} . Furthermore, the hydrogel could also be disrupted progressively when a few drops of TBAOH solution were added onto the top of the preformed gel of **1'•CuCl₂** because the formed $\text{Cu}(\text{OH})_2$ precipitated out from the solution.

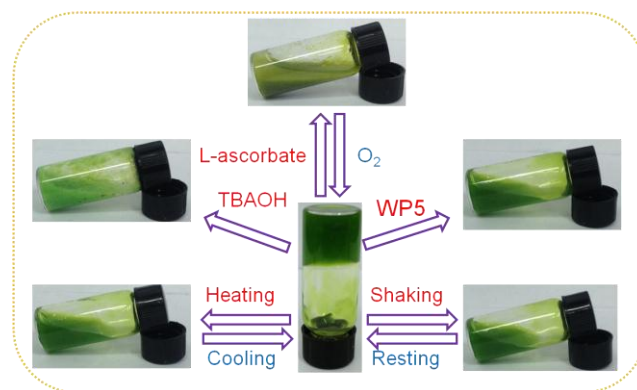


Fig. 3 Photographs of the gel-to-sol transitions of the metallohydrogel triggered by different stimuli.

Moreover, we wondered whether the ammonium salt group on **1'** could be threaded through the cavity of water-soluble pillararene **WP5** to form a host-guest complex, which may also affect the morphology change of the gel in both the micro and macro scale. In order to testify that, model compound **M1** (Fig.

4a) was utilized to investigate host–guest interactions between **WP5** and the diethylammonium salt group. The proton NMR spectrum of an equimolar aqueous solution of **WP5** and **M1H** (**M1** protonated with 1 equiv. HCl) showed that the complexation is in fast exchange on the proton NMR time scale (Fig. 4b, 4c and 4d). Protons H_a, H_b, H_c, H_d, H_e and H_f on **M1H** shifted upfield after complexation while protons H₁ and H₂ on **WP5** shifted downfield. 2D NOESY NMR spectroscopy was then performed to study the relative positions of the components in the host–guest complex. Nuclear overhauser effect (NOE) correlations were observed between the signals related to protons H_d, H_e and H_f on **M1H** and protons H₃ on **WP5**, while no NOE was observed between protons H_a, H_b and H_c on **M1H** and protons on **WP5**, suggesting that protons H_d, H_e and H_f were located in the cavity of **WP5** (Fig. S12). These phenomena suggested that linear model compound **M1H** was threaded through the cavity of cyclic host **WP5** to form a [2]pseudorotaxane with the positive ammonium salt head close to the negative carboxylate groups of **WP5**. Isothermal titration calorimetry (ITC) experiments were performed to provide thermodynamic insight into the inclusion complexation between **WP5** and **M1H**. The K_a value of **WP5**⊃**M1H** was determined to be $(1.58 \pm 0.25) \times 10^6 \text{ M}^{-1}$ in 1:1 complexation as shown in Fig. S12. Besides, model compound **M2** (Scheme S2, ESI†) with two tertiary amine groups at both ends of alkyl chains was also synthesized to investigate host–guest interactions between **WP5** and the diethylammonium salt group. The results obtained further confirmed that the diethylammonium salt group could be threaded through the cavity of **WP5** (Fig. S14 and S15, ESI†).

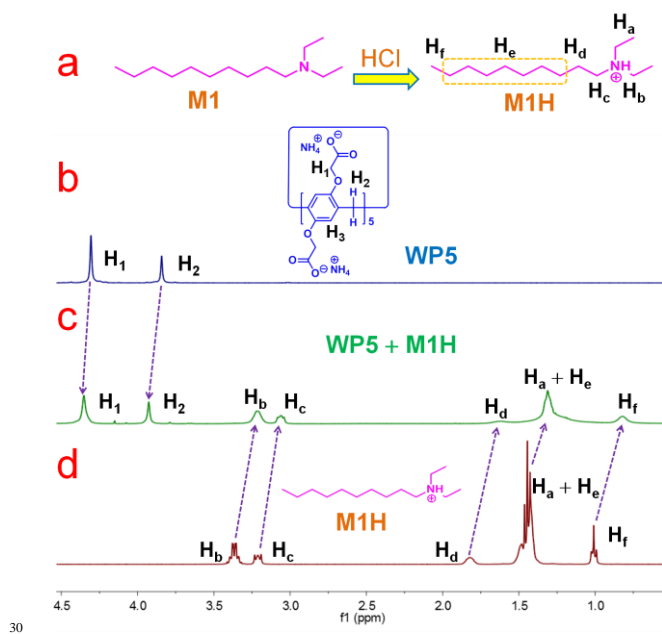


Fig. 4 (a) Chemical structures of **M1** and **M1H**. Partial ¹H NMR spectra (400 MHz, D₂O, room temperature): (b) **WP5** (2.00 mM); (c) **WP5** (2.00 mM) and **M1H** (2.00 mM); (d) **M1H** (2.00 mM).

Since **1'** could form a stable host–guest complex with **WP5**, we wondered whether the gel would be disrupted upon the addition of **WP5**. As expected, the metallohydrogel collapsed to sol after adding equal equiv. **WP5** (Fig. 3). Then TEM and SEM

experiments were conducted to investigate its morphology in nanoscale dimension. Surprisingly, vesicular aggregates about 300 nm in diameter were observed by both images. This may be due to the introduction of the rigid pillar[5]arene structure which will hinder the gelation. Moreover, the formed **WP5**⊃**1'**•CuCl₂ acted as a supra-amphiphile and self-assembled into bilayer vesicles due to the steric hindrance and the electrostatic repulsion generated from the insertion of **WP5**. Both the gel-to-sol and the nanofiber-to-vesicle transitions indicate that the tertiary amine group plays the same important role as the terpyridine group in the gelation process.

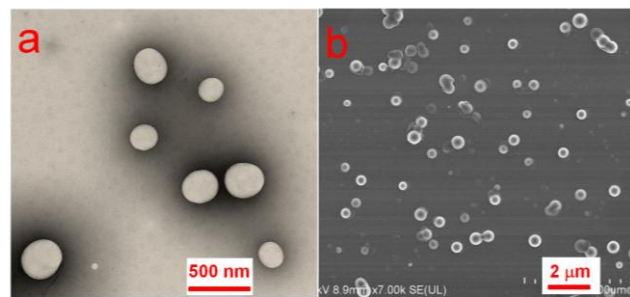


Fig. 5 (a) TEM and (b) SEM images of the metallohydrogel after adding **WP5**.

In conclusion, we have developed a terpyridine-based low molecular weight ligand **1** which can form hydrogel under slightly acidic conditions only in the presence of divalent copper ions (and chloride). However, other divalent metal ions could not induce the gelation. The microscopy investigations revealed that the gel structure consists of a thin fibrous (about 10 nm in diameter) network. The metallohydrogel exhibited multiple responsivenesses towards gel-to-sol transitions including thixotropy, temperature, and addition of alkali or sodium L-ascorbate. More interestingly, **WP5** could form a stable host–guest complex with **1'**, resulting in the gel-to-sol transition in macroscopic dimension and leading to the nanofiber-to-vesicle transformation at the nanoscale. These findings may have potential applications in biologically relevant fields and contribute to the investigations in rationalizing the course of aggregation.

This work was supported by Fundamental Research Funds for the Central Universities.

Notes and references

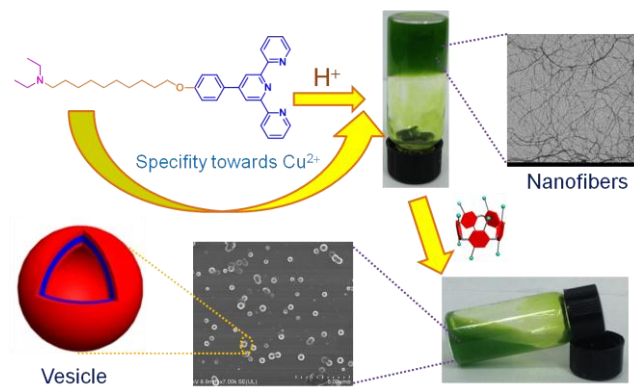
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† Electronic Supplementary Information (ESI) available: Synthetic procedures and other characterizations, See DOI: 10.1039/c0xx00000x.

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Colour Graphic:



A Cu²⁺ specific metallohydrogel was constructed by a terpyridine-based low molecular weight ligand. The metallohydrogel showed multi-
85 responsiveness and its morphology could be transformed by pillararene-based host-guest interaction.