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Stimuli-responsive hydrogels prepared by simultaneous “Click Chemistry” and metal-ligand coordination

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Abstract: A novel strategy to synthesize stimuli-responsive metal-coordinated polymeric gels (MCPGs) via one-pot CuAAC and non-covalent metal coordination chemistry was demonstrated. 4'-((4-prop-2-ynoxyphenyl)-2,2':6',2''-terpyridine (Terpy- ϕ -CH₂C \equiv CH) and α,ω -diazido/hydroxyl PEG (PEG₄₅(N₃)₂) were used as precursors to yield linear terpyridine-terminated PEG derivatives with 1,2,3-triazole rings and terpyridine ligands in their main chains to serve as ligands for chelating a range of transition and/or lanthanide metal ions. It was found that the bridging metal complexes could not only act as branching or crosslinking sites within the three-dimensional polymer networks but could also bestow special properties to the final gels, such as stimuli-responsive and thixotropic features, thereby allowing facile and efficient design and synthesis of promising intelligent materials.

Keywords: copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC); metal coordination; reversible cross-linking; stimuli-responsive hydrogels; one-pot reaction

1. Introduction

Polymeric gels, a kind of three-dimensional polymeric networks swollen by a significant amount of water or organic solvent, have found a lot of applications in the fields of great social impacts like biomedicine or functional materials science.¹⁻⁴ Traditional polymeric gels are usually classified as chemical and physical gels, depending on the types of cross-links (chemical cross-linking or physical interactions) within polymeric backbones.^{5, 6} Usually, chemically cross-linked gels are achieved through permanent and strong covalent bonds, and they cannot be redissolved as they are thermally irreversible.^{7, 8} Gels formed by weak and transient non-covalent interactions (physical entanglements) are observed to display fascinating reversible and triggered self-healing properties compared to those by covalent bonding.^{9, 10} The common non-covalent interactions include hydrogen bonding, π - π stacking, metal-ligand interactions, van der Waals interactions, solvophobic forces, donor-acceptor interactions, ionic interaction and so on.^{7, 9-23} The gels based on physical interactions are considered as stimuli-sensitive matrices for controlled release, sensing, and other advanced functional materials.²⁴

Among the multiple weak non-covalent interactions, metal-ligand coordination is particularly attractive as the coordinative bond is relatively strong,^{25, 26} highly directional,²⁷ dynamic and reversible. Most importantly, metal-ligand bonds are easily tuned from weak to nearly covalent in nature by varying the binding metal ions, counterions, and ligand structures.²⁸⁻³¹ As perspectives, incorporating coordination complexes into polymeric architectures opens up the possibility of imparting new chemical and physical properties to metal-coordinated polymeric gels (MCPGs) under different situations.³² The stimuli sensitive MCPGs undergo sol-gel phase transition when the coordination number or the redox state of the metal center changes.¹⁰ Therefore, metal-containing gels could respond to a broad range of chemical and physical stimuli, providing a unique promising platform for environmental and physiological applications. Of particular interest here is the kinetically labile feature of metal-ligand interactions within such gels.³³ Intrinsic self-healing property as well as comparable mechanical strength to those of covalent cross-linked gels could thus

be expected on them.³⁴ Briefly, such stimulus-sensitive and readily tunable “smart” gels could be applied as intelligent soft materials in catalytic, light-emitting, optical, magnetic, and electrical fields.^{7, 35-39}

“Click chemistry”, especially copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC),⁴⁰⁻⁴⁴ has been addressed with a considerable amount of attentions, and has been used to synthesize a range of functional and complex polymer materials due to its superior specificity, fast reaction rates, high yields and insensitivity toward various functional groups.⁴⁵⁻⁵⁰ Meudtner et al.⁵¹ synthesized poly[(1,2,3-triazol-4-yl-1,3-pyridine)-*alt*-(1,2,3-triazol-1-yl-1,3-phenylene)]s via step-growth polymerization using CuAAC. The resultant polymers having 2,6-bis(1,2,3-triazolyl) pyridine units in their main chains were capable of chelating to a range of metals, thus inducing efficient gelation of the polymer solutions utilizing metal-ligand binding as a driving force.

As a further exploration, we aimed to synthesize linear terpyridine-functionalized PEG derivatives with 1,2,3-triazole ligands via CuAAC in order to prepare gels cross-linked by copper ions via coordination chemistry. Terpyridine (Terpy) functionalized in the 4th position is of great interest in coordination and macromolecular chemistry due to the fact that Terpys are versatile ligands for metal complexes with large stability association constants.^{17, 52} In the work, one-pot simultaneous metal-ligand coordination chemistry and CuAAC reactions were investigated by a mixture of 4'-(4-prop-2-ynyloxyphenyl)-2,2':6',2''-terpyridine (Terpy- ϕ -CH₂C \equiv CH) and α,ω -diazido/hydroxyl PEG (PEG₄₅(N₃)₂), where Terpy- ϕ -CH₂C \equiv CH took dual roles both as a reactant and as a ligand for anchoring CuAAC catalyst to promote the formation of 1,2,3-triazole linkages as new coordination points. Thus, well-defined macromolecules and MCPGs via one-pot non-covalent metal coordination chemistry and CuAAC were demonstrated. Interestingly, the switch from Cu⁺-MCPGs to the oxidized state, Cu²⁺-MCPGs, through a slow oxidation process (oxidation from Cu⁺ to Cu²⁺ occurs through simple exposure to ambient oxygen) was demonstrated. Comparison of their corresponding emission and absorption properties, and mechanical properties was also carried out.

To the best of our knowledge, this is the first report to date that describes the preparation of MCPGs using one-pot simultaneous coordination chemistry and CuAAC.

2. Experimental Section

2.1 Materials

Poly (ethylene glycol) (PEG, $M_n = 2000$, Alfa Aesar) was dried at 120 °C under high vacuum for at least 4 h before use. Epichlorohydrin (99%) and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine (PMDETA, 99%) were purchased from Aldrich Chemical Co. and used without further purification. Copper(I) bromide (CuBr, 98%), sodium azide (NaN₃, 99%), sodium hydride (NaH, 60%) and ammonium chloride (NH₄Cl) were purchased from Shanghai Chemical Reagent Plant. CuBr was washed consecutively with glacial acetic acid and methanol, to remove the impurities and dried in a vacuum oven. Propargyl bromide (80%), 2-acetylpyridine (98%) and 4-hydroxybenzaldehyde (98%) were purchased from J&K Chemical Co. and were used without further purification. Tetrahydrofuran (THF) was dried over sodium wire/benzophenone and distilled before use. An aqueous EDTA-disodium salt solution (16 g /L), adjusted to a pH of 8-9, was used to remove copper ions in aqueous extraction steps. All other reagents were of analytical grade from Shanghai Chemical Reagent Plant and were used as-received. Synthesis of TPOM-PEG hydrogel from Tetrakis(2-propynyloxymethyl)methane (TPOM) and α,ω -diazido/hydroxyl PEG₄₅ was carried out as described by a previous study.⁵³ Di-alkynyl terminated PEG ($M_n = 2000$) was obtained as described in a previous report.⁵⁴

2.2 Chemical Synthesis

2.2.1 Synthesis of 4'-(4-prop-2-ynyloxyphenyl)-2,2':6',2''-terpyridine (Terpy- ϕ -CH₂C \equiv CH)

2-Acetylpyridine (10.0 g, 82.5 mmol) was added to a suspension of crushed NaOH pellets (3.3 g, 82.5 mmol) in poly(ethylene glycol) (PEG 300) (100 mL) and the above mixture was stirred for 30 min at 0 °C. 4-(Prop-2-ynyloxy)benzaldehyde (6.59g, 41.2 mmol) was further added into the above mixture and the suspension was kept at 0 °C for 4 h. The suspension was stirred adequately with a magnetic stirrer. After that, excessive NH₄OAc (20 g) was added and the reaction mixture was heated to 110 °C,

followed by vigorous stirring for another 2 h. During this process, the color of the mixture changed from red to dark green with the formation of a fine precipitate. Doubly-distilled water (150 mL) was added into the above mixture. The solid after being collected by filtration was washed with 100 mL of water twice and cold ethanol thrice (20 mL each). Recrystallization from CHCl_3 -MeOH afforded nattierblue crystalline solid which was further dried under vacuum.

2.2.2 Synthesis of PEG-based copper-cross-linked MCPGs via one-pot simultaneous CuAAC and metal coordination chemistry

PEG₄₅(N₃)₂ (0.2 g, 0.1 mmol), Terpy- ϕ -CH₂C \equiv CH (0.0726 g, 0.2 mmol) and DMF-CHCl₃ mixture (2 mL, V/V = 2:1) were added into a small sample vial with a gas-tight lid. The vial was put under ultrasonic agitation in order to make a homogeneous reaction mixture. After the solution was turned to transparent, 28.7 mg (0.2 mmol) of CuBr was added into the vial which was then degassed with N₂ for about 5 min. After that, 5 μ L of PMDETA was added into the vial via a syringe. The vial was then put under ultrasonic agitation at room temperature. Gelation of the polymer networks was achieved within several minutes. In addition, the reaction was further allowed to react at room temperature without sonication for three days to consolidate into a denser and stronger gel phase.

2.2.3 Synthesis of linear Terpy-functionalized (Terpy-terminated) PEG derivative

In a two-necked flask equipped with a nitrogen inlet, PEG₄₅(N₃)₂ (1 g, 0.5 mmol) and Terpy- ϕ -CH₂C \equiv CH (0.36 g, 1 mmol) were dissolved in 20 mL of CHCl₃. The solution was degassed for 20 min with N₂. CuBr (1 mmol) was added with stirring to the solution in the counterflow of N₂. After that, 0.1 mL of PMDETA was added via a syringe, whereupon the solution turned dark green. The mixture was stirred under N₂ at room temperature for 72 h. The reaction was then diluted with CH₂Cl₂, further transferred into a separation funnel, washed successively with aqueous Na₂-EDTA solution thrice and brine, and dried over Na₂SO₄. The solvent was removed in vacuum,

and the resulting concentrated polymer solution was slowly added to an excess amount of cold diethyl ether, whereupon a yellow green precipitate formed. The precipitate was filtered off, washed with cold diethyl ether, and dried under vacuum overnight.

2.3 Characterization

Chemical structures of PEG derivatives and alkynyl-functionalized terpyridine were characterized by ^1H NMR and Fourier Transform Infrared Spectra (FT-IR). ^1H NMR spectroscopy was recorded on a Bruker ARX 300 MHz spectrometer using CDCl_3 as a solvent in 1000 scans and a relaxation time of 2 s using tetramethylsilane (TMS) as an internal reference. FT-IR was measured on a Bruker Vector 22 IR spectrometer in the solid state (KBr cell of 0.2 mm length). All measurements were performed at room temperature and within the range of $400\text{-}4000\text{ cm}^{-1}$. Number-average molecular weights (M_n) were measured by Gel Permeation Chromatography (GPC) using a Waters 1515 system equipped with two PL Mixed-C columns using THF as an eluent at a flow rate of 1.0 mL/min at $40\text{ }^\circ\text{C}$ against commercial polystyrene standards (Waters ShodexVR). The MCPGs were dried in a LGJ-10C freeze-dryer. Differential Scanning Calorimetry (DSC) measurements were performed under a nitrogen atmosphere on a TA Instrument DSC Q-10 calorimeter. All samples were pre-heated from room temperature to $120\text{ }^\circ\text{C}$ at a rate of $10\text{ }^\circ\text{C}/\text{min}$ and held for 2 min to erase the thermal history. Samples were then cooled to $-50\text{ }^\circ\text{C}$ at a rate of $10\text{ }^\circ\text{C}/\text{min}$, held for another 2 min, and finally heated to $120\text{ }^\circ\text{C}$ again at a rate of $10\text{ }^\circ\text{C}/\text{min}$. All prepared PEG network samples were tested in crimped aluminum pans. Thermal stability of the PEG-based MCPG network was determined on a Thermogravimetric Analyzer (TA SDT Q-600) at a temperature ranging from $50\text{ }^\circ\text{C}$ to $600\text{ }^\circ\text{C}$ with a heat rate of $10\text{ }^\circ\text{C}/\text{min}$ in the presence of a nitrogen flow. UV-visible absorption spectra were recorded on UV-1750 UV-vis spectrophotometer (Shimadzu) using quartz cuvettes (1 cm path length) and the scanning range was from 200 to 800 nm. The thickness of the gel used was 0.1 cm. Absorbance of gels was measured by holding a film of the gel between two cover slips and placing them directly in the light

path of the spectrophotometer. Air was used as a reference to blank the data.

Fluorescence emission spectra were measured on a Shimadzu RF-5031 fluorescence spectrophotometer, with an excitation wavelength at 283 nm.

Ionic conductivity data were obtained by a four-probe AC impedance method to investigate the bulk membrane conduction with a linear probe head (ST2253 Jingge electronic Co., LTD, China) at an ambient temperature. Circular pieces (diameter: 1 cm, thickness: 0.1 cm) of PEG-based MCPGs membranes were loaded into a glass conductivity cell attached with four platinum wire current collectors. Current was supplied through the outer wires, while the potential difference was measured between the inner wires. To avoid any possible interference from any residue solution on the gel surface, the MCPGs were carefully tapped dry before each measurement. The four-probe technique offers many advantages over the two-probe technique, including measuring the bulk property of the membrane instead of the surface property and minimizing the error stemming from contact resistance and electrode resistance.⁵⁵

Morphological characteristics of PEG-based MCPGs were observed with Scanning Electron Microscopy (SEM) on a XL30 microscope. The samples were dried by a vacuum pump for 3-5 h before the analyses. The specimens were placed on aluminum stumps for SEM observation and were coated with gold prior to loading into the SEM chamber. The accelerating voltage of SEM was 25 kV and the emission current was 10 μ A.

Rheological behaviors of PEG-based MCPGs were characterized by dynamic shear oscillation measurements, and oscillatory frequency sweeps were carried under strain or stress control by recording the evolution of storage moduli under decreasing frequency. The rheological characterization of PEG-based MCPGs was performed on a rheometer with parallel plate geometry (25 mm diameter rotating top plate) (MCR102 Modular Compact Rheometer Anton Paar). A series of PEG-based MCPGs

were formed into gel disks (25 mm diameter, 10 mm thickness) and then dried for 24 h at room temperature before measurement. All samples were subjected to an oscillatory preshear of 500% strain (applied at 5 Hz) for 30 s, and subsequently allowed to equilibrate for 90 min prior to measurements. In particular, the dynamic storage modulus as a function of frequency was determined ranging from 0.1 to 150 Hz at a strain of 5%. All measurements were conducted at ambient temperature.

3. Results and Discussion

3.1 One-pot organometallic coordination chemistry and CuAAC reaction

Schematic illustration for the synthesis procedures and molecular structures of a typical one-pot reaction via simultaneous “click chemistry” and coordination chemistry was shown in Scheme 1. Briefly, the synthetic strategy involved three main steps. Initially, a polymer with epoxy groups reacted with sodium azide to yield the corresponding PEG₄₅(N₃)₂ (see Supporting Information).⁵⁶ After that, preparation of 4'-(4-prop-2-ynyloxyphenyl)-2,2':6',2''-terpyridine (Terpy-φ-CH₂C≡CH) was allowed through the improved Kröhnke reaction between 2-acetylpyridine and 4-(prop-2-ynyloxy)benzaldehyde at a molar ratio of 2 : 1.⁵⁷

One-pot coordination chemistry and CuAAC reaction was conducted by a mixture of Terpy-φ-CH₂C≡CH and PEG₄₅(N₃)₂ in the presence of Cu(I) as the catalyst with a molar ratio of [Terpy-φ-CH₂C≡CH] : [PEG₄₅(N₃)₂] : [CuBr] at 2 : 1 : 2 in DMF-CHCl₃ solution (Scheme 1). Terpy-φ-CH₂C≡CH acted not only as a reactant, but also as a ligand for CuAAC organometallic catalyst. The chemical structure of polymer extracted from the reaction mixture after removal of the Cu⁺ was ascertained by ¹H NMR analysis (Figure 1a). The presence of chemical shifts at about 7.48 ppm (peak f), 2.90 ppm (peak l) and 2.56 ppm (peak m), corresponding to the protons of triazole rings, -CH₂-N₃ protons and -C≡CH protons, respectively, suggested that the resulting polymers were the mixture of Terpy-φ-CH₂C≡CH, PEG₄₅(N₃)₂ and linear Terpy-terminated PEG derivative. Figure 2A displayed FT-IR spectrum of the polymer extract after removal of the Cu⁺. It was suggested that “click chemistry” was taken place, but not entirely completed based on the reduction of a characteristic absorbance peak at 2098 cm⁻¹ which was assigned to azido groups. Since the FT-IR results were consistent with those of ¹H NMR (Figure 1a), it was indicated that one-pot reaction of Terpy-φ-CH₂C≡CH could allow the partial formation of triazole groups as new coordination points. Among the reaction mixture, Terpy-φ-CH₂C≡CH first acted as a ligand to give rise to the mono-(Terpy-φ-CH₂C≡CH)-Cu(I) and/or di-(Terpy-φ-CH₂C≡CH)-Cu(I) complexes which then self-catalyzed CuAAC of

Terpy- ϕ -CH₂C≡CH and/or (Terpy- ϕ -CH₂C≡CH)-Cu(I) complexes with PEG₄₅(N₃)₂. The reaction allowed the formation of Cu(I) macro-organometallic complex with the progress of CuAAC. At the same time, triazole groups formed within the macromolecules could also serve as ligands to coordinate Cu(I), which provided new multiple coordination points to Cu(I) macro-organometallic complex to immobilize the Cu(I)/complex catalysts. The decrease in mobility of the Cu(I) macro-organometallic complex restricted the completeness of CuAAC reaction.

To promote the one-pot CuAAC and coordination chemistry reaction, additional ligands were added to enhance the catalytic performance of Cu(I). PMDETA (0.1 equiv relative to CuBr) was added into the above mixture (Scheme 1). Interestingly, gel was obtained in 5 min and it was referred to as Gel-1. The gelation was probably due to participation of as-synthesized 1,2,3-triazole to the coordination with copper ions, which led to the formation of cross-linking points within the reaction system.⁵¹ According to ATR-FTIR measurement of the dried Gel-1, the characteristic absorbance peaks of azido groups ($\nu = 2098 \text{ cm}^{-1}$) and alkynyl moieties ($\nu = 2110 \text{ cm}^{-1}$) were absent (Figure 2B). It could then be indicated that “click chemistry” was approximately completed and the azido and alkynyl moieties were quantitatively transformed into 1,2,3-triazole rings via CuAAC. In this reaction system, Terpy- ϕ -CH₂C≡CH and PMDETA both acted as ligands to give rise to the (Terpy- ϕ -CH₂C≡CH)-Cu(I) and PMDETA-Cu(I) complexes which then catalyzed CuAAC of Terpy- ϕ -CH₂C≡CH and/or (Terpy- ϕ -CH₂C≡CH)-Cu(I) complexes with PEG₄₅(N₃)₂. Cu(I) macro-organometallic complex and 1,2,3-triazole linkages as new coordination points to coordinate Cu(I) were formed with the progress of CuAAC. Although the Cu(I) macro-organometallic complex catalyst was fixed, the PMDETA-Cu(I) complex could move freely to take its full duty in catalysis in the reaction medium to result in the accomplishment of CuAAC reaction.⁵⁸ It was reported that the concentration of Cu(I) catalyst played an important role in gelation and it was significant to maintain a sufficient concentration of the catalytically active complexes throughout the whole reaction process.^{53, 59} The completion of CuAAC

consequently allowed the complete formation of MCPG in the reaction system. In summary, based on the above results, it was suggested that here copper(I) bromide not only served as a catalyst for “click chemistry”, but also acted as a coordinative cross-linker for efficient gelation.

At a high precursor concentration, the Terpy-terminated PEG derivative was cross-linked with copper ions, leading to the formation of MCPG. At a low precursor concentration, the Terpy-terminated PEG derivative was also coordinated with copper ions, but it was a highly branched polymer dissolved in the solvent. By washing with aqueous Na₂-EDTA solution to remove the copper ions, the coordination interaction between copper ions, Terpy and 1,2,3-triazole was disconnected, and the linear Terpy-terminated PEG derivative was obtained. The successful removal of copper ions was ascertained by GPC. The linear Terpy-terminated PEG derivative had a M_n of 2.8×10^3 g/mol and PDI of 1.2 (Figure S5B). The M_n and PDI of the linear Terpy-terminated PEG derivative were close to that of PEG₄₅(N₃)₂, indicating that no chain extension or cross-linking was taken place. As shown in the FT-IR spectrum of the linear Terpy-terminated PEG derivative (Figure 2C), the absorbance peaks of azido moieties of PEG₄₅(N₃)₂ and alkynyl groups of Terpy- ϕ -CH₂C \equiv CH were absent. In the ¹H NMR spectrum of the linear Terpy-terminated PEG derivative (Figure 1b), the proton signals in the aromatic region of 7.1 ~ 8.8 ppm (peak a ~ e, g, h) could be attributable to the protons of pyridine rings. It was indicated from the presence of a new peak at about 7.48 ppm (peak f), assigned to the protons of triazole rings, that click coupling reaction was occurred and the Terpy moieties were successfully attached onto the PEG chains.

The obtained metal-free Terpy-terminated PEG derivative was then utilized to study the coordination interaction with Cu²⁺. After dissolving CuBr₂ and Terpy-terminated PEG derivative (molar ratio: [Cu²⁺] : [Terpy-terminated PEG derivative] = 2 : 1) in DMF-H₂O mixture at room temperature, a gel was formed, suggesting that a three-dimensional network structure was formed by the connection

between ligands and Cu^{2+} . Therefore, it was the added Cu^{2+} that presumably connected the polymer chains at various points, leading to a rather efficient macromolecular crosslinking process that was primarily based on coordinative bonds.⁵¹ The resulting gel was referred to as Gel-2.

The storage modulus (G') curve of Gel-2 was approximately the same as that of Gel-1 after being exposed to the atmospheric oxygen (Figure S6). It was suggested that the cross-linking densities and rheological properties of Gel-1 after being exposed to the atmospheric oxygen were comparable to those of Gel-2. Although PMDETA nearly had no side effects on the performance of Gel-1, it was employed to enhance the reaction rate of CuAAC as a free catalyst. In addition, Gel-3 was formed in the same manner as that for Gel-2, except an increased molar ratio of $[\text{Cu}^{2+}]$: [Terpy-terminated PEG derivative] = 2.2 : 1. However, the increase in the amount of Cu^{2+} did not change the gel rheological properties obviously (Figure S6). Thus, the molar ratio of $[\text{Cu}^{2+}]/[\text{Terpy-terminated PEG derivative}]$ was fixed at 2 : 1 for the following studies.

The nature of cross-links in MCPGs that relies on the combination of polymeric ligands and metal ions is of great interest. Hence, to further explore special properties of the current PEG-based MCPGs prepared from the one-pot process, it is necessary to understand the cross-linking mechanism. Some models of polymer networks were thus proposed in order to prove the synergetic effect of 1,2,3-triazole rings and terpyridine moieties in coordination with metal ions (Scheme 2A and B). These different model reactions were challenged by several control experiments under similar reaction conditions. Schubert et al.⁶⁰ synthesized a bis-terpyridine-poly(ethylene glycol) polymer which could coordinate with ruthenium(II) ions to form a chain extended metal-containing coordination polymer with an average molecular weight of 1.4×10^5 g/mol determined by GPC. The metal-containing coordination polymer contained about 15 repeat units of bis-terpyridine-poly(ethylene glycol) polymer. Di-alkynyl terminated PEG₄₅ and

PEG₄₅(N₃)₂ could also form a linear chain extended polymer (Figure S5C, $M_n = 1.4 \times 10^4$ g/mol, PDI = 1.3) with 1,2,3-triazole rings through CuAAC. These two control experiments revealed that either 1,2,3-triazole rings or terpyridine moieties could not form PEG-based MCPGs in the presence of metal ions. Therefore, synergistic coordination of 1,2,3-triazole rings and terpyridine moieties with copper ions played an important role in the formation of PEG-based MCPGs as shown in Scheme 2C.

3.2 Multiple stimuli-responsive properties of PEG-based MCPGs

Decomposition and dramatic changes in the physical state of gel, could be triggered by a wide range of environmental stimuli. The responsiveness of PEG-based MCPGs to multiple external stimuli, such as temperature, pH, sonication and EDTA, was demonstrated as shown in Figure 3. Due to the weak nature of non-covalent interaction, PEG-based MCPGs collapsed in response to the above mentioned factors. However, they could undergo a reversible sol-gel phase transition upon the removal of these external stimuli. For example, the addition of a small amount of aqueous Na₂-EDTA solution into a preformed gel would lead to the decomposition of the gel into a sol instantaneously, due to ligand exchange and chelation between EDTA and copper ions. The above gel to sol process could be reversed by adding excess amount of copper salts. Similar reversible phenomena could be observed when the gel was heated (thermal stimulus), or treated with acids as well as sonication (Figure 3). The thermal cleavage of the gel was due to its acceleration effect on the ligand exchange. Acids would lead to the protonation of pyridine groups by forming pyridine hydrochloride. Hence, a decrease in the degree of polymerization and subsequent increase in dangling ends (more free ligands) resulted in the disruption of complexation and subsequent collapse of the gel structure. It is noted that addition of acids also altered the pH and ionic strength of the system, which could significantly affect the stability of the gels in which electrostatic interactions presumably existed.³³ The gel also exhibited a pronounced thixotropic behavior by its responsiveness to sonication, suggesting a rigid rather than flexible network structure. Notably, kinetic lability of MCPGs' metal coordinated cross-linked networks that could result in

“dynamic” polymers whose binding equilibrium is sensitive to environmental factors, is indicative of their highly stimuli-responsive nature.^{61, 62} Precisely, as illustrated in Scheme 2C, the stability of the MCPGs was related to the rates of ligand exchange reactions of different Terpy complexes. Stimuli could either accelerate the ligand exchange or break the coordination interaction, resulting in a gel-to-sol transition of the MCPGs.^{24, 63, 64}

The above oxidation process could be occurred via exposure of the prepared PEG-based Cu^+ -MCPG (Gel-1a) to the moist air (a slow oxidation process: oxidation from Cu^+ to Cu^{2+} occurs through simple exposure to the atmospheric oxygen). The oxidized state, Cu^{2+} -MCPG, was obtained after being exposed to air for a week (Gel-1b) and one month (Gel-1c), respectively.

3.3 Morphology of the MCPGs

In order to obtain visual insights into the aggregation mode in the gel phase, freeze-dried samples of MCPGs were prepared for SEM observation. The cross-sectional images of the freeze-dried Gel-1a network and Gel-1c network were shown in Figure 4A (A_1 , A_2) and B (B_1 , B_2), respectively. Gel-1a network had a typical microporous structure with pore sizes of several micrometers (Figure 4A₁ and A₂). It is possible that the porous structure of a gel is originated from the macroscopic molecular defects of the polymer networks. However, Gel-1c network had a dense morphology (Figure 4B₁ and B₂). It seemed that upon ageing for several weeks in air, the cross-sectional morphology of the gel altered significantly (Figure 4A₁ versus Figure 4B₁). Microcrystalline copper cutting structures were observed (Figure 4B₁ and B₂), indicating an uncompleted crystallization process as proposed by Menger on physical gelation.^{65, 66} Gel-1c was obviously rearranging their structure over time when being exposed to moist air.

3.4 Rheological behavior

Rheological behavior is one of the most important physical properties of gels.

Representative profiles of the storage modulus of Gel-1a, Gel-1b and Gel-1c were shown in Figure 5 to investigate the influence of oxidation degree of copper ions on the mechano-responsive behaviors of gels. For all these samples, the respective storage modulus, G' , exhibited a frequency-independent plateau at low frequencies (0-40 1/s), enabling us to determine the elasticity of the MCPGs. As demonstrated in Figure 5, the storage modulus of Gel-1a was smaller than those of the other two gels at each tested frequency. All storage moduli of three samples exhibited strong dependence on frequencies higher than 40 1/s, indicating a relatively more elastic response of their networks. This behavior is typical of colloidal gels as higher deformation frequencies would elicit an elastic response from local structures, which can relax at lower frequencies.⁶⁷

3.5 Optical properties

The optical properties of as-prepared PEG-based MCPGs were investigated by UV-visible absorption and fluorescence spectroscopy. The absorption spectra of linear Terpy-functionalized PEG derivative, Gel-1a, Gel-1b and Gel-1c were shown in Figure 6a and 6b, respectively. The UV-Vis absorption spectrum of linear Terpy-functionalized PEG derivative in acetonitrile consisted of three peaks centered at 227 nm, 253 nm and 283 nm, which were all associated with π - π^* transitions of the heteroaromatic backbone (Figure 6a A). The characteristic absorption bands of Gel-1a appeared at 283 nm and 344 nm, typical π - π^* electronic transitions of the backbone conjugated linkages between the terminal terpyridine units (Figure 6a B). On the other hand, the π - π^* absorption bands of Gel-1c exhibited slightly blue shifts to 268 nm and 335 nm (Figure 6a D), and the intensity of the absorption increased substantially compared to that of Gel-1a (Figure 6a B).

Furthermore, compared to linear Terpy-terminated PEG derivative, Gel-1c also exhibited a typical broad peak at about 635 nm after the addition of copper ions (Figure 6b A). This was most likely associated with the metal-to-ligand charge-transfer (MLCT) transition as well as a bathochromic shift of the π - π^* band in

the copper complex. The absorption spectrum of Gel-1b network exhibited a very weak absorption maximum at about 648 nm (Figure 6b C), and the intensity of the π - π^* absorption bands (278 nm and 335 nm) increased slightly (Figure 6a C) compared to Gel-1a (Figure 6a B). Furthermore, the absorbance at MLCT band increased with the increase in Cu^{2+} concentration and then saturated.

The fluorescent emission spectra of Gel-1a, Gel-1b and Gel-1c under an excitation wavelength at 283 nm were shown in Figure 7. The fluorescence of Gel-1a was represented by a strong vibronic band at about 547 nm and a secondary band at about 416 nm. Gel-1c had a major emission peak centred around 539 nm with a slight blue-shift in emission and the intensity of its emission band increased dramatically in comparison to Gel-1a. Gel-1b also exhibited similar emission maximal peaks at 406 and 559 nm comparable to those of Gel-1a, albeit the intensity of the emission maximum at 406 nm became much stronger than that at 559 nm. Metal coordination and π - π interactions in MCPGs would usually result in the reduction in π - π^* transition energy, and the shift from fluorescent emission peaks to visible regions was most likely associated with ligand-to-metal charge-transfer (LMCT) transitions.⁶⁸ It seemed that the fluorescent emission intensity of the MCPG enhanced with the increase in the oxidation degree of copper ions.

4. Conclusions

A simple strategy was developed to prepare well-defined macromolecules and PEG-based MCPGs via one-pot simultaneous CuAAC and coordination chemistry from a reaction mixture of Terpy- ϕ -CH₂C \equiv CH and PEG₄₅(N₃)₂ utilizing metal-ligand binding as a driving force. The as-prepared MCPGs exhibited peculiar and tunable physical and chemical properties. The synthesis method of simultaneous “click chemistry” and coordination chemistry could provide a versatile and feasible platform to prepare well-defined and tailor-made MCPGs of fascinating functionalities. As a perspective, such easy-to-synthesize and multiple stimuli-sensitive MCPGs could find potential applications at frontiers among biomedicine, coordination chemistry, supramolecular chemistry and materials science as smart devices or matrices.

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Notes and references

Electronic Supplementary Information (ESI) available: Details of experiments and analyses. NMR and FT-IR spectrums. GPC, TGA, DSC, rheological and ionic conductivity curves.

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Legends for Schemes and Figures

Scheme 1. General approach of the different routes for one-pot organometallic coordination chemistry and CuAAC reaction between synthesized PEG₄₅(N₃)₂ and Terpy- ϕ -CH₂C \equiv CH.

Scheme 2. Schematic illustration for forming the linear chain extended polymer networks (A) and (B), and for the proposed possible coordination structure and reversible cross-links of PEG-based MCPGs networks (C).

Figure 1. ¹H NMR spectra of product of one-pot reaction between PEG₄₅(N₃)₂ and Terpy- ϕ -CH₂C \equiv CH via simultaneous coordination chemistry and CuAAC after Cu⁺ removal (a) and product of one-pot reaction between PEG₄₅(N₃)₂ and Terpy- ϕ -CH₂C \equiv CH via simultaneous coordination chemistry and CuAAC with addition of PMDETA as additional ligands after Cu⁺ removal (linear Terpy-terminated PEG derivative) (b) in CDCl₃-*d*.

Figure 2. FT-IR spectra of product of one-pot reaction between PEG₄₅(N₃)₂ and Terpy- ϕ -CH₂C \equiv CH via simultaneous coordination chemistry and CuAAC after Cu⁺ removal (A), product of one-pot reaction between PEG₄₅(N₃)₂ and Terpy- ϕ -CH₂C \equiv CH via simultaneous coordination chemistry and CuAAC with addition of PMDETA as additional ligands (Gel-1) (B) and product of one-pot reaction between PEG₄₅(N₃)₂ and Terpy- ϕ -CH₂C \equiv CH via simultaneous coordination chemistry and CuAAC with addition of PMDETA as additional ligands after Cu⁺ removal (linear Terpy-terminated PEG derivative) (C).

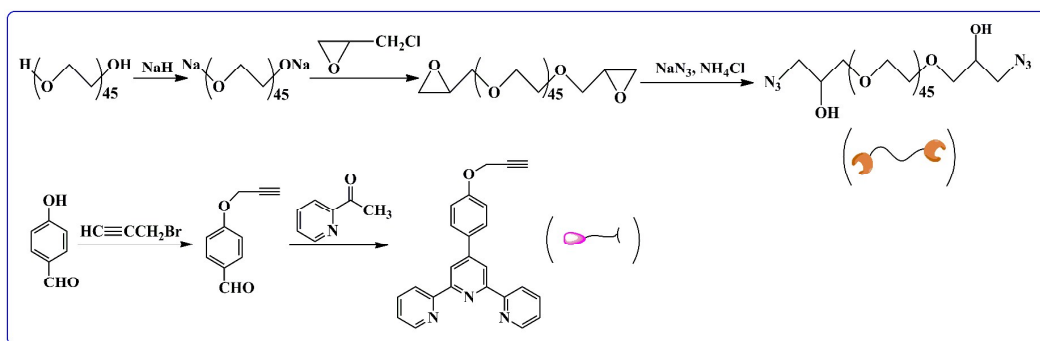
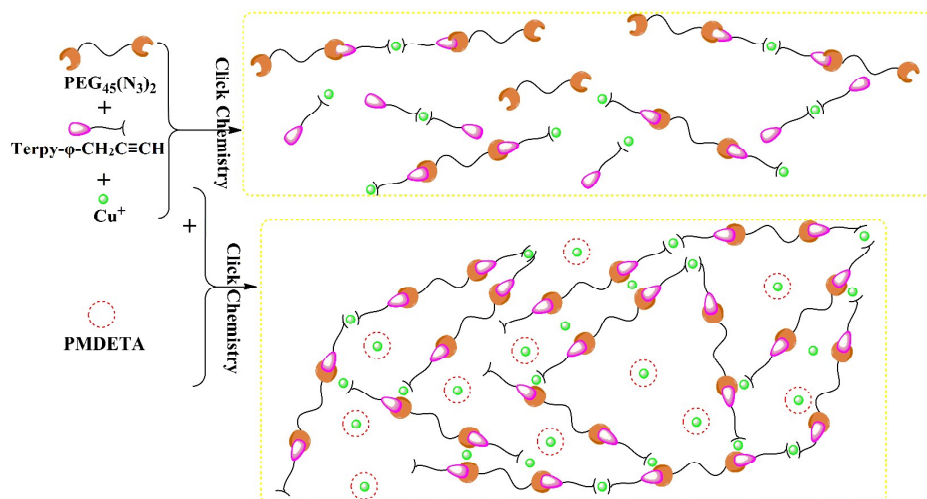
Figure 3. Reversible sol-gel phase transition of PEG-based MCPGs in response to external stimuli.

Figure 4. Scanning electron microscopy observation of cross-sectional views of the freeze-dried Gel-1a network (A₁ and A₂) and Gel-1c network (B₁ and B₂).

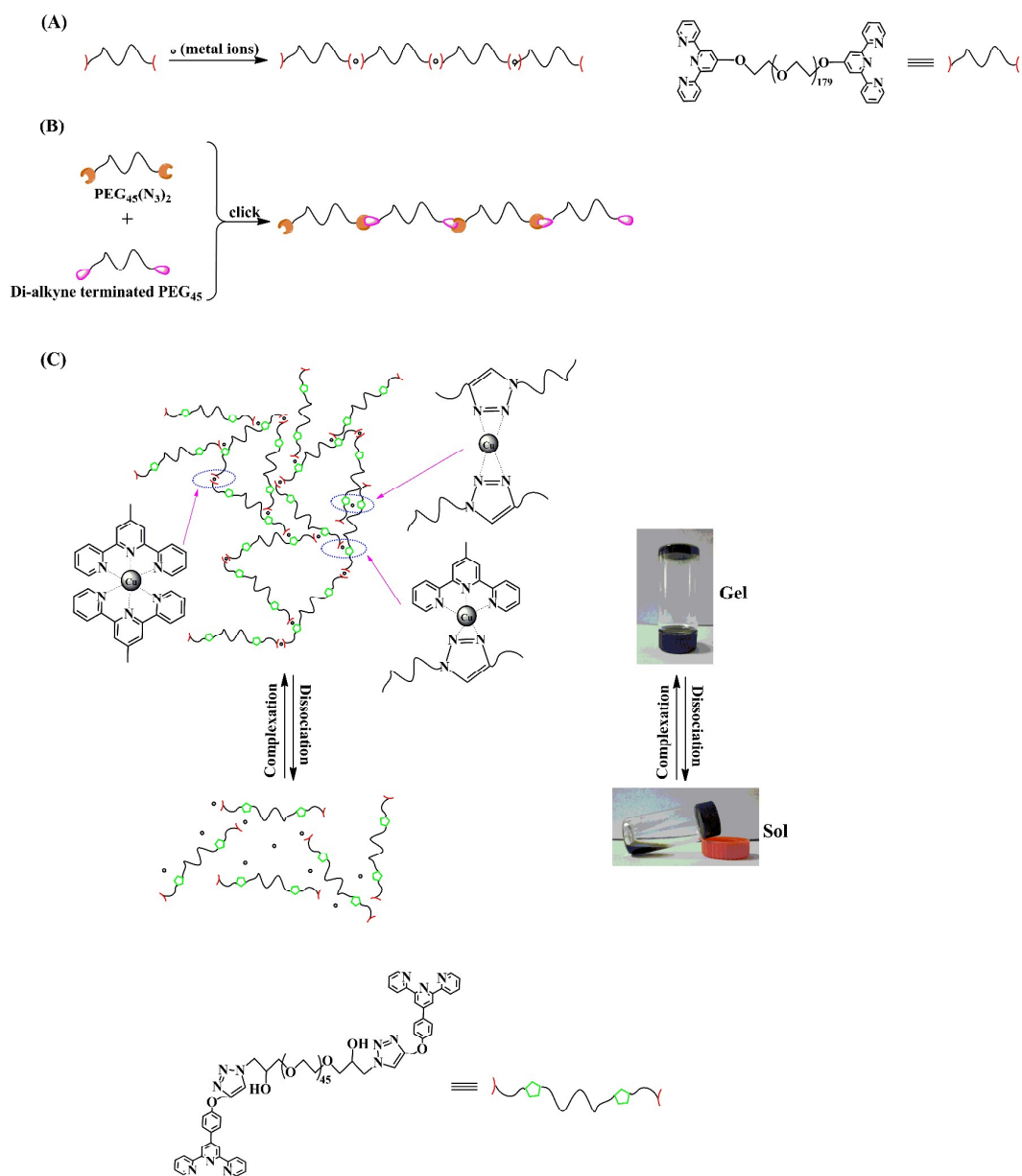
Figure 5. Storage modulus as a function of frequency (Hz) at a strain of 5% for Gel-1a (A), Gel-1b (B), and Gel-1c (C), respectively. (The reported results are the average of 3 repeat experiments and 9 samples)

Figure 6. UV-visible absorption spectra (a) and (b) in the ultraviolet and visible regions of linear Terpy-terminated PEG derivative (A), Gel-1a (B), Gel-1b (C), and Gel-1c (D). (The reported results are the average of 3 repeat experiments and 9 samples)

Figure 7. Fluorescence emission spectra of Gel-1a (A), Gel-1b (B), and Gel-1c (C) at an excitation wavelength at 283 nm.



Scheme 1



Scheme 2

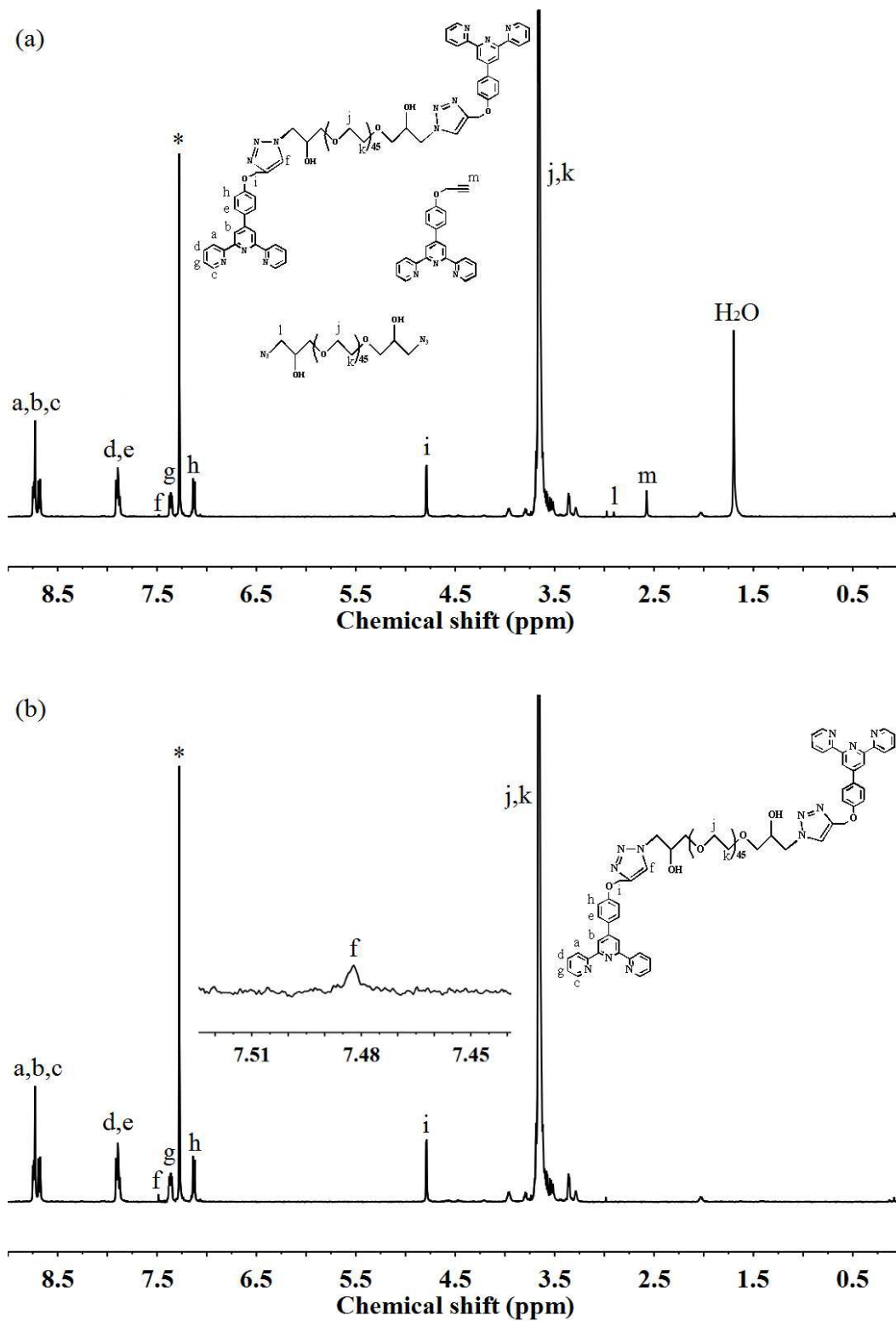


Figure 1

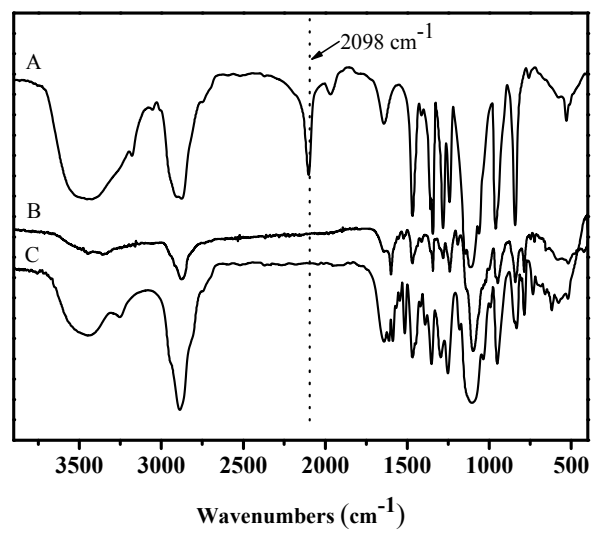


Figure 2

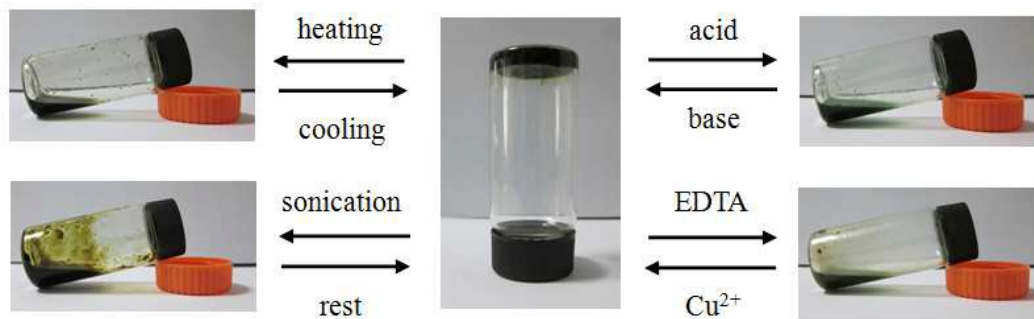


Figure 3

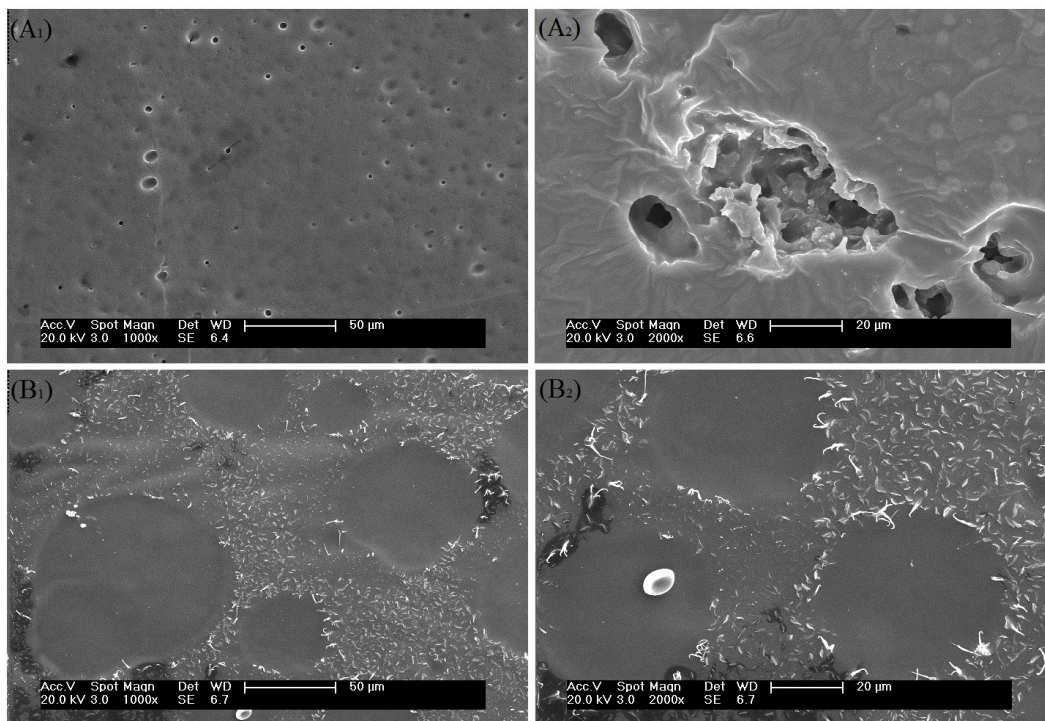


Figure 4

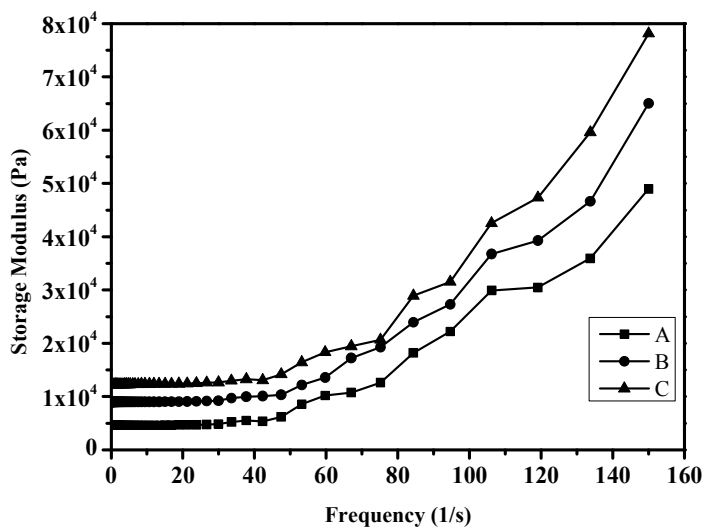


Figure 5

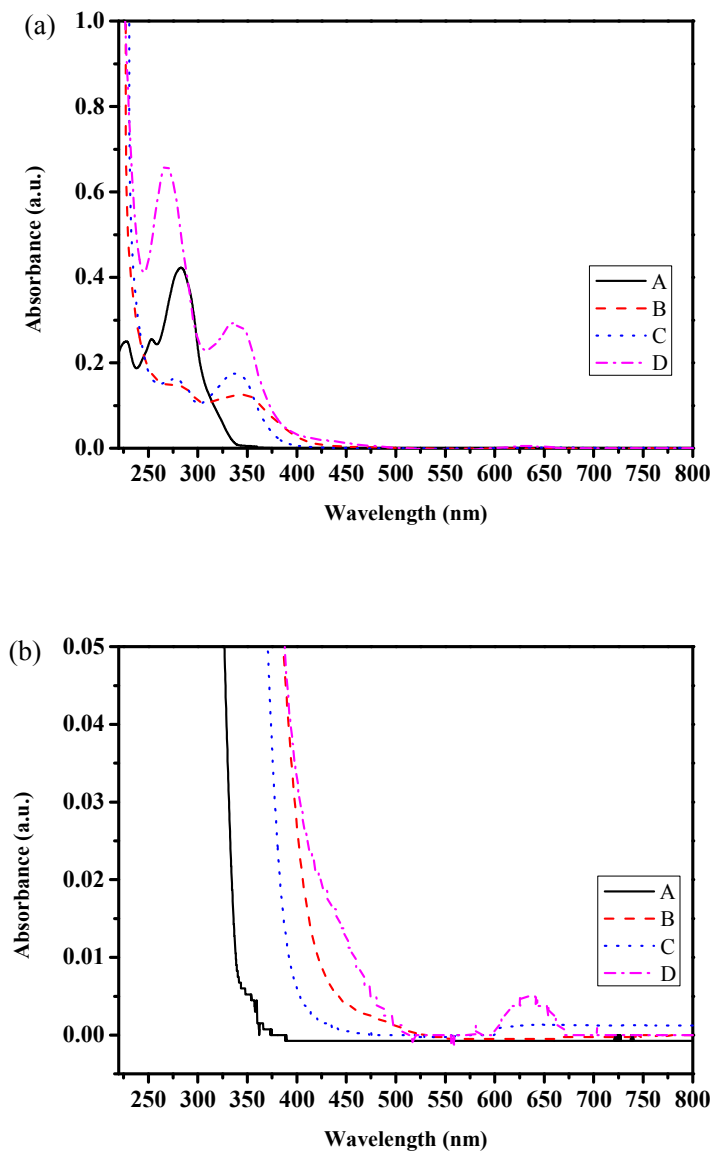


Figure 6

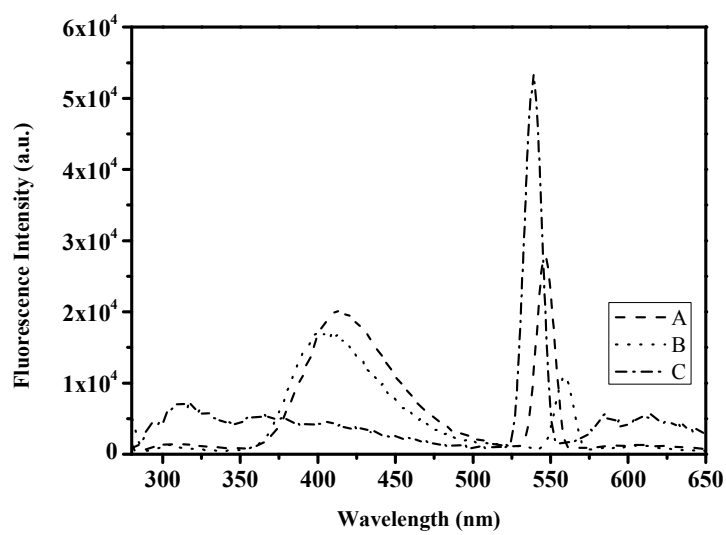


Figure 7

Graphic TOC

Title: Stimuli-responsive hydrogels prepared by simultaneous “Click Chemistry” and metal-ligand coordination

Authors: Yang Li, Chao Zhou, Liqun Xu, Fang Yao, Lian Cen*, Guo Dong Fu*

