



Synthesis and characterization of a novel double cross-linked hydrogel based on Diels-Alder click reaction and coordination bonding



Shubin Li, Lu Wang*, Xuemei Yu, Chengli Wang, Zhenyu Wang

Harbin Institute of Technology, 73 Huanghe Road, Nangang District, Harbin 150090, PR China

ARTICLE INFO

Keywords:

Hydrogel
Self-healing
Double cross-linked network
Diels-Alder click chemistry
Coordination bond

ABSTRACT

Hydrogels, promising biological materials, need to have both strong mechanical properties and also inherent self-healing properties. In this work a double cross-linked network (DN) hydrogel was designed and prepared by combining a Diels-Alder click reaction and coordination effects. This DN hydrogel had good thermodynamic properties, anti-EDTA performance and self-healing properties. In addition, the mechanical properties, swelling properties and surface morphology of DN hydrogels can be controlled by adjusting the ratio of Fe^{3+} -catechol. The adjustment of pH value can change the color, crosslinking mode and mechanical properties of the DN hydrogel. This smart hydrogel created from DA click chemistry and coordination effects has significance for guiding the design of new hydrogels with good mechanical properties, self-healing properties and controlled cross-link density.

1. Introduction

Hydrogels are three-dimensional networks formed of hydrophilic polymer chains [1–9]. Recently, hydrogels have been widely used as drug-delivery systems, cell carriers, wound dressings and scaffolds [10–23]. The most common way to form hydrogels is to form covalent bonds between the polymer chains [24–26]. Since covalent bonds are relatively stable, most covalent hydrogels exhibit excellent stability and excellent mechanical properties. Therein, the Diels-Alder (DA) bond is considered to be the most promising covalent bond for cross-linked hydrogels [27–29] because the DA reaction is not only fast and effective but is also selective. Moreover, the DA reaction in aqueous environment leads to no byproducts, high yields, and can operate under mild conditions without adding any catalyst [30–32]. Recent literature has shown that cross-linked polyester networks based on DA click chemistry have excellent mechanical properties compared to traditional hydrogels, and the synthetic hydrogels also have shape memory ability [33,34]. Owen et al. synthesized hydrogels via reacting furan-modified hyaluronic acid with bis-maleimide-poly (ethylene glycol) in a Diels-Alder coupling reaction [35]. The hydrogel achieved the best mechanical properties by controlling the hydrogel concentration and furan substitution. This means that the introduction of DA bonds can play an important role in enhancing mechanical properties of hydrogels.

However, due to irreversible, permanent covalent bond breaking, once the covalent hydrogel was damaged, it was very difficult to be repaired or recovered. These deficiencies greatly limit the application of covalent hydrogels. To surmount this shortcoming, supramolecular interactions have been introduced into hydrogel systems [36–42]. Because of their reversibility, supramolecular interactions have a variety of advantages. For instance, they can respond quickly to pH change [43], external forces [44] and temperature [45–50], and the hydrogels cross-linked by supramolecular interactions have excellent self-healing capacity [51–55]. In the past decades, supramolecular interactions such as host-guest interactions [56–58], hydrogen bonds [59–63] and electrostatic interactions [64,65] have been used for supramolecular hydrogel formation.

Generally, because of the reversible association of the supramolecular interactions, all the supramolecular hydrogels should have good self-healing ability. However, achieving rapid and efficient self-healing remains a daunting challenge [66]. A hydrogel system based on host-guest interactions achieved complete recovery of mechanical properties [67]. However, the healing process usually takes a long time.

Some studies have found that mussel-inspired Fe^{3+} -catechol complexes can quickly and efficiently recombine after cleavage of the coordination bonds [68]. Recently, some of the mussel-inspired chemical materials have been synthesized [69]. The general process involves

Abbreviations: DA, Diels-Alder; retro-DA, retro-Diels-Alder; SN, single cross-linked network; DN, double cross-linked network; Mal-PEG-Mal, dimaleimide poly (ethylene glycol); DSC, differential scanning calorimetry; TGA, thermogravimetric analysis; Tmax, maximum weight loss temperature; SEM, scanning electron microscopy; DI water, distilled water; G' , storage modulus; G'' , loss modulus

* Corresponding author at: School of Chemical Engineering and Chemistry, Harbin Institute of Technology, 73 Huanghe Road, Nangang District, Harbin 150090, PR China.
E-mail address: hitwanglu@hit.edu.cn (L. Wang).

<http://dx.doi.org/10.1016/j.msec.2017.08.031>

Received 21 May 2017; Received in revised form 9 August 2017; Accepted 10 August 2017

Available online 12 August 2017

0928-4931/ © 2017 Published by Elsevier B.V.

grafting catechol groups onto the macromolecule polymer and allowing the polymer to be cross-linked by the coordination of Fe^{3+} -catechol, imitating the natural process for byssal thread assembly. Based on this particular structure, the mussel attachment lines of the cuticle of mussel byssal threads demonstrate excellent self-healing performance [70]. Nevertheless, due to the low stability of the supramolecular interactions, the mechanical properties of synthetic hydrogels are lower than those of covalent hydrogels.

Therefore, to solve the above problems, in this contribution, a double cross-linked hydrogel was designed based on coordination effects and a DA click reaction. We estimate that DA click chemistry can enhance the mechanical properties of hydrogels and maintain the stability of hydrogel structures, while the coordination between Fe^{3+} and catechol will give the hydrogel self-healing properties and achieve the controllability of cross-linking density. In addition, based on the detailed study on the effects of the pH and the ratio of Fe^{3+} -catechol on the hydrogels, we obtained the new cross-linking mechanism of DA reaction bond and coordination bond. This type of smart hydrogel based on DA click chemistry and coordination effects has important significance for guiding the design of new hydrogels with good mechanical properties, self-healing properties and controlled cross-link density. This investigation opens the door of DN hydrogel for potential applications in biomedical fields, such as tissue engineering.

2. Materials and methods

2.1. Materials

Chitosan (CS) (average molecular weight [MW] of approximately 100,000) and dimaleimide poly (ethylene glycol) (Mal-PEG-Mal) (Mw = 2000) were purchased from Aldrich Chemical Company (St Louis, MO, USA). All other reagents used in the experiments were purchased from Sigma Aldrich unless otherwise indicated.

2.2. Synthesis of *N*-(furfural) chitosan (FC)

N-(furfural) chitosan (FC) was prepared by covalent attachment of the free amino groups of chitosan (CS) and the aldehyde groups of furan formaldehyde. Briefly, 1 g of chitosan (5.59 mmol $-\text{NH}_2$) was dissolved in 200 mL of 2% aqueous acetic acid. Subsequently, 643 μL of furan formaldehyde (5.59 mmol $-\text{CHO}$) was added dropwise with a pipet, after which the solution was stirred at room temperature for 2 h. Then, a freshly prepared aqueous of NaH_3BCN (10 mL, 10 mM) was gradually added to the reaction mixture, which was then stirred at room temperature for another 5 h. Some small bubbles were observed during this process. FC was precipitated by the addition of NH_4OH (150 mL, 12 M) and then washed with H_2O , $\text{H}_2\text{O}:\text{C}_2\text{H}_5\text{OH}$ 75:25 (v/v), $\text{H}_2\text{O}:\text{C}_2\text{H}_5\text{OH}$ 50:50 (v/v), $\text{H}_2\text{O}:\text{C}_2\text{H}_5\text{OH}$ 25:75 (v/v) and $\text{C}_2\text{H}_5\text{OH}$. The product was dried under vacuum at room temperature for 3 h. After drying, the product was Soxhlet-extracted with ethyl ether for 48 h. Finally, the purified FC (0.91 g; 91% yield) was dried under vacuum at room temperature for 5 h.

2.3. Synthesis of catechol-modified *N*-(furfural) chitosan (CFC)

Catechol-modified *N*-(furfural) chitosan (CFC) was prepared by covalent attachment of free amino groups of FC and aldehyde groups of 3,4-dihydroxy benzaldehyde. Briefly, 1 g of FC was dissolved in 100 mL of 2% aqueous acetic acid. 3,4-Dihydroxy benzaldehyde (0.77 g, 5.59 mmol $-\text{CHO}$) was dissolved in 5 mL of DMF and then added to the reaction mixture. The mixture solution was stirred at room temperature for 6.5 h. After that, freshly prepared aqueous NaH_3BCN (10 mL, 10 mM) was gradually added to the reaction mixture and stirred at room temperature for another 6.5 h. CFC was precipitated with 300 mL of $\text{C}_2\text{H}_5\text{OH}$ and then successively washed several times with H_2O and $\text{C}_2\text{H}_5\text{OH}$. The purified CFC (0.94 g; 94% yield) was dried in vacuum at

room temperature for 3 h and stored under nitrogen at -20°C .

2.4. Preparation of SN and DN hydrogels

The prepared CFC was used for all gel experiments. Stock solutions of FeCl_3 (119 mM, 60 mM, 40 mM) and CFC (58 mM) were prepared in 2% acetic acid (v/v). The stock solutions were used to fabricate single cross-linked network (SN) hydrogels and double cross-linked network (DN) hydrogels. The SN hydrogels were formed by mixing 65 μL of the FeCl_3 solution (40 mM) and 0.5 mL of the CFC solution (58 mM), which sets a Fe^{3+} -catechol ratio of 1:3. The hydrogel was cross-linked by interactions between Fe^{3+} and catechol over several minutes. To prepare DN hydrogels, 14.9 mg of Mal-PEG-Mal was added to the mixture solution of the appropriate CFC and FeCl_3 mixture solution. Specifically, 65 μL of a FeCl_3 solution (119 mM, 60 mM, 40 mM) was added to 0.5 mL of the CFC solution (58 mM) to set the Fe^{3+} -catechol ratios as 1:1, 1:2, and 1:3, respectively. Thus, the DN hydrogels were cross-linked by both between Fe^{3+} -catechol coordination and Diels-Alder click chemistry interactions. In addition, the solution needed to be thoroughly mixed to establish a homogenous color and a stable physical state. The hydrogel formation was determined by the inversion method.

2.5. Characterization of synthetic substances

2.5.1. Fourier transform infrared spectroscopy (FT-IR)

Infrared spectra were recorded on an FT-IR spectrometer (PerkinElmer, USA) in pellet form with KBr, and the test range was $500\text{--}4000\text{ cm}^{-1}$.

2.5.2. Nuclear magnetic resonance (^1H NMR)

^1H NMR spectra of CFC were recorded with a ^1H NMR spectrophotometer (Bruker Avance III 400, USA). The sample was solubilized in $\text{DCl}/\text{D}_2\text{O}$ solution (0.5 N) and tested at 25°C . The degree of substitution was calculated using the following formula:

$$\begin{aligned} \text{Substitution rate of furan} \\ = \frac{\frac{1}{3} \times [\text{Area}(6.52\text{ppm}) + \text{Area}(6.64\text{ppm}) + \text{Area}(7.62\text{ppm})]}{\text{Area}(3.1\text{ppm})} \times 100\% \end{aligned} \quad (1)$$

$$\text{Substitution rate of catechol} = \frac{\frac{1}{3} \times \text{Area}(6.8\text{ppm}\text{--}7.0\text{ppm})}{\text{Area}(3.1\text{ppm})} \times 100\% \quad (2)$$

2.5.3. X-ray diffraction (XRD)

X-ray diffraction (XRD) was performed with an X'Pert X-ray diffractometer (PANalytical B.V., Netherlands) at room temperature. The operating voltage and current were 40 kV and 200 mA, respectively. The scan angular speed was $5^\circ/\text{min}$ from 5° to 90° .

2.6. Thermodynamic properties of the hydrogels

2.6.1. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed with a DSC 200 F3 (Netzsch, Germany) under nitrogen atmosphere. The heating rate was $10^\circ\text{C}/\text{min}$.

2.6.2. Thermogravimetric analysis (TGA)

Thermogravimetric analysis (TGA) was performed on a TG/DTA 6300 (Hitachi, Japan) with a heating rate of $10^\circ\text{C}/\text{min}$ in nitrogen.

2.7. Study of hydrogel cross-linking mode

2.7.1. UV-Vis spectroscopy

The interactions between Fe^{3+} -catechol were monitored on a U-

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