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# Fabrication of thermo-responsive hydrogels from star-shaped copolymer with a biocompatible β-cyclodextrin core

Huijuan Zhang [a], Qiang Yan [a], Yan Kang [a], Lilin Zhou [a], Hang Zhou [a], Jinying Yuan [a,*], Sizhu Wu [b,*]

[a] Key Laboratory of Organic Optoelectronics and Molecular Engineering of Ministry of Education, Department of Chemistry, Tsinghua University, Beijing 100084, PR China
[b] State Key Laboratory of Organic-Inorganic Composites, Beijing University of Chemical Technology, Beijing 100029, PR China

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ABSTRACT

A thermally reversible hydrogel composed of a three-arm star copolymer with a specific host β-cyclodextrin (β-CD) center has been developed. The synthesis of this star copolymer initiates with β-CD core, from which sequential polymerization of a temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAM) block and a hydrophilic poly(*N*,*N*-dimethylacrylamide) (PDMA) block as asymmetric arms (named β-CD-*g*-(PNIPAM-*b*-PDMA)$_3$) is performed *via* RAFT protocol. Below the *lower critical solution temperature* (LCST) of PNIPAM segment, the polymer is of good water-solubility and exhibits a sol state. Upon thermal stimulus, free-standing hydrogels can be formed rapidly at sufficiently high concentrations. By comparing the sol–gel transition of the star polymer with that of its linear counterpart without this feature, we concluded that the special star-shape topology and the thermal-collapsed PNIPAM chains were responsible for this gelation behavior. The rheology measurements indicate the mechanical properties of the polymer hydrogels and the thermal reversibility of the sol–gel transition. Using Rhodamine B as a molecule to model a typical drug, we realize the favorable encapsulation and releasing process from the hydrogel, demonstrating that this star polymer has the potential to function as an injectable hydrogel for drug delivery and gene transport.



## 1. Introduction

Stimuli-sensitive hydrogels have attracted significant attention due to their potential applications in drug delivery and tissue engineering [1–9]. Generally, the network of this type of hydrogel is formed by chemical cross-linking or physical entanglement, which is able to respond to external stimuli, i.e., temperature, pH or ionic strength [10–16]. Among these stimuli, temperature-responsiveness is convenient to manipulate and the stimulation mode is adaptive to physiological conditions [17–20]. To this end, thermosensitive hydrogels have achieved great progress and received much attention in recent years [21–33].

Arms and coworkers [27] reported thermo-responsive gelator on the basis of ABA triblock copolymers comprising of poly(*N*-isopropylacrylamide) (PNIPAM) and poly(2-methacryloyloxyethylphosphorylcholine) (PMPC) blocks, which are water-soluble in dilute aqueous solution at 20 °C whereas form free-standing gels at 37 °C. McCormick's group [28] exploited an ordered physical gel from ABA triblock copolymers, in which the outer A blocks are poly(*N*,*N*-dimethylacrylamide) (PDMA) and the central B block is PNIPAM. Quite recently, Liu and coworkers [34,35] reported the thermo-induced aggregation behaviors of $(AB)_n$ multiblock copolymers, *m*-PDMA$_P$-PNIPAM$_q$, in dilute solutions and their gelation behaviors at high concentrations. It was found that only *m*-PDMA$_p$-PNIPAM$_q$ multiblock copolymers with PDMA and PNIPAM sequence lengths located within a specific range can form physical gels at elevated temperatures. Up to now, the majority of work focused on thermo-responsive hydrogels fabricated by the linear block copolymers.

Star polymers, as one of the branched macromolecules, are of great interest to polymer chemists due to their multi-arm topological architecture, lower hydrodynamic size, ideal rheological behaviors, and particular bulk and solution properties compared with their linear counterparts [36–42]. Dendrimer-like star-branched polymers are a special type of hyperbranched polymer, which have received much attention in recent years. Liu et al. reported that dendrimer-like star-branched PNIPAM [43] was synthesized *via* the combination of click chemistry and atom transfer radical polymerization (ATRP) by employing the arm-first approach. The unique thermal phase transition behavior of this dendrimer-like star-branched polymer in aqueous solutions was

* Corresponding authors. Tel.: +86 10 62783668; fax: +86 10 62771149.
*E-mail addresses:* yuanjy@mail.tsinghua.edu.cn (J. Yuan), wusz@mail.buct.edu.cn (S. Wu).

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further investigated by turbidimetry. Zhu et al. [44] prepared an asymmetric block copolymer of polyether dendrimer and PNIPAM by atom transfer radical polymerization methods. The self-assembly behaviors of this asymmetric copolymers in aqueous solution was also investigated. However, the attempts to use star-shaped polymer to construct the thermosensitive hydrogels are seldom made [45,46].

β-CD is widely used in the pharmaceutical field because of its high biocompatibility, easy availability, and its capability to form inclusion complexes [47]. Based on the host-guest inclusion complexation, β-CD and its derivatives have been used as building blocks for a wide variety of polymeric networks and assemblies in recent years [48–62]. More importantly, β-CD is one of the excellent candidates as the core scaffold for the synthesis of star polymers [63–68]. Gou et al. [69] synthesized the amphiphilic drug-conjugated $A_{14}B_7$ miktoarm copolymer based on poly(ε-caprolactone) (PCL) and poly(ethylene glycol) (PEG). These amphiphilic star copolymers could self-assemble into multimorphological aggregates in aqueous solution. Li and coworkers [70] reported the synthesis of star-shaped PNIPAM with a β-CD core and investigated their self-assembly and thermosensitive micellization with bis(adamantyl)-terminated poly-(propylene glycol) (PPG-$(Ad)_2$).

While the aforementioned work mainly focused on the synthesis and self-assembly of star polymers as nano-scale assemblies, stimuli-responsive macroscopic hydrogel networks based on β-CD-core star polymers were rarely reported. In this paper, we have reported a temperature-responsive hydrogel based on a biocompatible β-CD-core star copolymer. By employing β-CD-xanthate as a chain transfer agent (CTA), star-shaped β-CD-*g*-(PNIPAM-*b*-PDMA)$_3$ copolymer was synthesized with sequential RAFT method. There are two parts in the arms of this star-shaped copolymer: the hydrophilic PDMA blocks and the temperature-responsive PNIPAM blocks. Below the *lower critical solution temperature* (LCST) of PNIPAM segment, both blocks are water-soluble and the copolymer exists as uniform solutions. Above LCST, the PNIPAM blocks become water-insoluble and further form aggregates. Thus, the nanodomains of the collapsed PNIPAM chains are bridged by the hydrophilic blocks to establish three-dimensional network, i.e. hydrogel. Meanwhile, we employed the biocompatible β-CD host as a core for this thermosensitive star polymer, which makes the star polymer potentially useful in drug delivery system.

## 2. Experimental

### 2.1. Materials

β-Cyclodextrin (β-CD) was purchased from Kermel (China) and purified by recrystallization from water before use. *N*,*N*-dimethylacrylamide (DMA, Aldrich) was distilled under reduced pressure before use. *N*-isopropylacrylamide (NIPAM, Acros) was recrystallized twice from toluene and hexane (1:3). 2,2-Azobis(isobutyronitrile) (AIBN, Beijing Chemical Reagent Co., Ltd) was recrystallized from ethanol three times. Dimethylformamide (DMF, Beijing Chemical Reagent Co., Ltd) was distilled from $CaH_2$ under reduced pressure. Ethyl 2-bromobutyrate (Acros) and Rhodamine B (Acros) were used as received.

### 2.2. Characterization

$^1$H NMR spectra were recorded with a JEOL JNM-ECA400 NMR spectrometer with DMSO-$d_6$ as the solvent. Gel permeation chromatography (GPC) measurements were carried out on a Waters e2695 GPC instrument with three column set (Styragel HR3 + HR4 + HR5), equipped with refractive index detector (Waters 2414), and DMF (containing 1 g $L^{-1}$ LiBr) as eluent at 45 °C. PMMA was used as the calibration standard. UV–vis spectra were measured on a UV 2100 spectrophotometer (SHIMADZU, Japan). Time-of-flight (MALDI-TOF) mass spectrum was recorded on ABI MALDI-TOF mass spectrometry, using a nitrogen laser (337 nm) and α-cyano-4-hydroxycinnamic acid (CCA) as matrix. Transmission electron microscope (TEM) observations were performed on a JEOL JEM-2010 electron microscope operated at an acceleration voltage of 120 kV. TEM samples were prepared by spreading a droplet of diluted solution and dried under vacuum overnight at 40 °C on copper grids with standard carbon-coated Formvar films on copper grids. The samples were prepared without staining.

Rheology measurements were conducted using an AR-G2 Rheometer (TA Instruments) with a 40 mm parallel-plate geometry. An insulated ring was placed around the geometry to prevent water evaporation. The gel formation process was investigated by increasing temperature at a rate of 1 °C/min. The study of the thermal reversibility of samples was performed by increase and decrease of temperature at a rate of 1 °C/min. Steady rheology measurements were performed by steady-step temperature-ramp test (strain controlled) at the same sheer rate (10 $s^{-1}$). Dynamic rheology measurements were performed by oscillatory temperature sweeps (stress-controlled) at the oscillation frequency of 1 Hz and the deformation of 0.1.

### 2.3. Synthesis of β-CD-(xanthate)$_3$ and β-CD-xanthate

A typical procedure employed for the synthesis of β-CD (xanthate)$_3$ with a target degree of substitution of 3 was as follows [71]. The β-CD (6.00 g, 5.29 mmol) was dissolved in 100 mL 20 wt% NaOH aqueous solution. $CS_2$ (1.2 mL, 19.8 mmol) was added slowly. The solution turned orange gradually. After further stirring for 4 h at room temperature, the solution was precipitated in ethanol. Then the crude resultant was dissolved in water and precipitated in ethanol three times. The product was dried under vacuum at 50 °C as sodium β-CD xanthate (β-CD-$(XNa)_3$) in 90% yield. Then, β-CD $(XNa)_3$ (4.00 g) was dissolved in 20 mL distilled water. Ethyl 2-bromobutyrate (2.6 mL) was added dropwise and the reaction mixture kept stirring at 35 °C until light yellow precipitate appeared. The suspension was filtrated and washed with water and diethyl ether repeatedly. The product was obtained as β-CD-(xanthate)$_3$ (21%). Following similar procedures, β-CD-xanthate with a target substitution degree of 1 was also synthesized by adjusting the β-CD/$CS_2$ molar ratio.

### 2.4. Synthesis of β-CD-g-(PDMA)$_3$ and β-CD-g-PDMA

β-CD-xanthate (0.227 g, 0.133 mmol), DMA(2.00 g, 20 mmol), AIBN (4.40 mg, 0.0266 mmol) and 10 mL DMF were added into a 25 mL round-bottom flask, followed by three freeze-vacuum-thaw cycles. The flask was immersed into an oil bath at 80 °C with magnetic stirring. After reaction for 16 h, the polymerization was terminated by quickly cooled in liquid $N_2$, and the resultant mixture was precipitated into an excess diethyl ether. The precipitate was dissolved in DMF and then precipitated again into an excess of diethyl ether. The above dissolution–precipitation cycle was repeated three times. The final product was dried in vacuum, yielding a light yellow solid (1.2 g, 54%). β-CD-*g*-PDMA was synthesized through the same procedures as described above with β-CD-xanthate as the chain transfer agent. Yield: 69%.