



Light/temperature dual-responsive ABC miktoarm star terpolymer micelles for controlled release



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ABSTRACT

A novel light- and temperature-responsive amphiphilic ABC miktoarm star terpolymer consisting of hydrophilic poly(ethylene glycol) (PEG), light-responsive poly(2-nitrobenzyl methacrylate) (PNBM), and temperature-responsive poly(N-isopropylacrylamide) (PNIPAM) arms, PEG(-*b*-PNBM)-*b*-PNIPAM, was synthesized via a combination of atom transfer radical polymerization (ATRP) and click reaction. In aqueous solution, the obtained miktoarm star terpolymer self-assembled into spherical micelles with PNBM cores and hybrid PEG/PNIPAM coronas. When heating above the phase transition temperature of PNIPAM, larger aggregates with mixed PNBM/PNIPAM cores and PEG coronas were formed. Upon UV light irradiation, the initial micelles were disrupted and reassembled into some large micelle complexes. Fluorescence emission measurements showed that Nile red encapsulated in the polymeric micelles could be released by stimuli of UV light or temperature change. More interestingly, the UV triggered release could be strengthened in basic conditions but weakened in acidic conditions. The prepared light- and temperature-responsive polymeric micelles may have great potential in applications such as nanocarriers and biotechnology for controlled drug and bioagent delivery.

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1. Introduction

During the past decades, stimuli-responsive polymeric micelles that respond to environment changes such as temperature, pH, redox and light have attracted increasing attention due to their tremendous potential applications in the fields of sensors [1], diagnostics [2], biotechnology [3], and drug delivery [4]. Among them, polymeric micelles that can be disrupted by light are especially attractive owing to the possibilities of remote motivated spatial and temporal release of loaded molecules from these micelles [5]. Based on the photolysis of photolabile chromophores on the core-forming hydrophobic block, the hydrophilic-hydrophobic balance of the micelles will be disrupted, thus inducing the dissociation of the micelles. Early works by Zhao and co-workers explored the use of pyrenylmethyl esters, which can be cleaved under UV light irradiation to yield carboxylic acid group and the corresponding 1-pyrenemethanol [6]. However, the photosolvolytic cleavage of pyrenylmethyl esters needs the presence of water or a protonic solvent [7], which greatly limits their applications. In contrast, the photocleavage of 2-nitrobenzyl moieties proceeds via a Norrish II type intramolecular rearrangement that needs no water and can readily occur in the solid state such as the core of the micelle [8,9]. Consequently, 2-nitrobenzyl moieties should be a better candidate for constructing the light-dissociable micelle systems. Accordingly, Zhao and co-workers introduced 2-nitrobenzyl moieties into an amphiphilic block copolymer as side groups of the hydrophobic block to prepare light-dissociable micelles

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[10]. Upon UV light irradiation, the 2-nitrobenzyl moieties were cleaved and the micelles were disrupted quickly. Combining light with other stimuli can significantly broaden the scope of applications of such micelle systems. In particular, temperature-responsive polymers have been incorporated with photocleavable polymers containing 2-nitrobenzyl moieties to construct copolymers and self-assemble into dual-responsive micelles [11–13]. For instance, Jiang et al. reported a temperature- and light-responsive double hydrophilic block copolymer [11]. Upon UV irradiation, the thermo-induced self-assembled micelles were dissociated owing to the increase of LCST of the temperature-responsive polymer. Yang et al. synthesized a thermo- and light-responsive amphiphilic block copolymers, micelles self-assembled from which could be disrupted by light and shrunk at high temperature [12].

Previous reports concerning light-dissociable micelle systems mainly focused on the synthesis and self-assembly of linear block copolymers [10–17]. It can be expected that if more than two types of polymer chains are arranged into a nonlinear block copolymers, their self-assembly and responsive behaviors should be more complex and fascinating [18,19]. ABC miktoarm star terpolymers, as a typical type of the above system, can be regarded as three different polymer chains emanating from a central core [20–24]. Compared with AB and ABC linear block copolymers, the unique chain sequence arrangement in ABC miktoarm star terpolymers endows them with quite different properties in solution and bulk states [25–27]. For instance, Lodge et al. reported the self-assembly of a series of ABC miktoarm star terpolymers in water [28,29]. It was found that the aggregated morphologies could be tuned from discrete multicompartment micelles to extended wormlike structures *via* altering the relative block lengths of the hydrophobic blocks. Liu et al. synthesized the double hydrophilic ABC miktoarm star terpolymers with three different water-soluble and responsive arms [18,27], which showed intriguing “schizophrenic” micellization behavior in aqueous solution. To explore the influence of chain architectures of the light/temperature dual-responsive ABC miktoarm star terpolymer on the responsive self-assembly and disassembly behaviors, the synthesis of the model ABC miktoarm terpolymer are much desired.

Herein, we developed a light- and temperature-responsive amphiphilic ABC miktoarm star terpolymer consisting of hydrophilic poly(ethylene glycol) (PEG), light-responsive poly(2-nitrobenzyl methacrylate) (PNBM), and temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAM) arms, PEG(*-b*-PNBM)-*b*-PNIPAM, *via* a combination of atom transfer radical polymerization (ATRP) and click reaction. In aqueous solution, the obtained miktoarm star terpolymer could self-assemble into spherical micellar nanoparticles with PNBM cores and hybrid PEG/PNIPAM coronas. At high temperature, PNIPAM segments within the micellar coronas were getting insoluble, which broke the hydrophilic-hydrophobic balance of the initial micelles; thus the PNBM-core micelles tended to undergo structural rearrangement and formed aggregates with mixed PNBM/PNIPAM cores and PEG coronas. Upon UV light irradiation, the photolysis of 2-nitrobenzyl moieties detached the 2-nitrobenzaldehyde molecules from the polymer and converted the hydrophobic core-forming PNBM blocks into hydrophilic poly(methacrylic acid) (PMAA), which led to the dissociation of the micelles. Finally, the temperature- and UV-triggered release of the encapsulated molecules from the miktoarm star terpolymer micelles were investigated.

2. Experimental

2.1. Materials

2-Nitrobenzyl methacrylate (NBM) was prepared according to the literature [30]. *N*-Isopropylacrylamide (NIPAM, Aladdin, 98%) was purified by recrystallization from a mixture of toluene and *n*-hexane (3/8, v/v) three times prior to use. Poly(ethylene glycol) monomethyl ether (PEG₄₅-OH, $M_n = 2000$, TCI) was dried over anhydrous toluene by azeotropic distillation. Epichlorohydrin, 2-bromoisobutyryl bromide, propargyl alcohol, 4-dimethylaminopyridine (DMAP), CuBr₂ (99%) and *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDETA, 99%) were purchased from Aladdin and used as received. Tris(2-dimethylaminoethyl)amine (Me₆TREN, 99%) was purchased from J&K and used as received. Sodium azide (NaN₃, 99%) was purchased from Zhengzhou Paini Chemical Reagent Factory and used as received. Copper(I) chloride (CuCl) and copper (I) bromide (CuBr) were purified by washing with acetic acid, ethanol, and diethyl ether, and then dried under vacuum. Azido-functionalized Merrifield resin was prepared according to the literature [31]. *N,N'*-Dimethylformamide (DMF), triethylamine (TEA) and dichloromethane (CH₂Cl₂) were dried over CaH₂ and distilled prior to use. Tetrahydrofuran (THF) was dried over sodium/benzophenone and distilled prior to use. All other reagents were of analytical grade and used as received.

2.2. Characterization

Fourier transform infrared (FT-IR) spectra were recorded on a Bruker TENSOR 27 IR spectrometer. ¹H NMR spectra were conducted on a Bruker Avance 400 spectrometer. The samples were dissolved with deuterated CDCl₃, and measured with tetramethylsilane (TMS) as an internal reference. The molecular weight and molecular weight distribution were determined on Waters 1515 gel permeation chromatography (GPC) equipped with Waters 2414 differential refractive index detector and three linear Styragel columns (HT3, HT4, and HT5). The column temperature was maintained at 40 °C. A series of monodisperse polystyrene standards were employed for calibration, and THF was used as the eluent at a flow rate of 1.0 mL/min. The morphologies of the copolymer assemblies were observed with a JEM-2100 transmission electron microscope (TEM) at an acceleration voltage of 200 kV. A 10 μL droplet of aggregate solution was dropped on a copper grid (230 mesh) coated with a carbon film, followed by drying at room temperature. Dynamic light scattering (DLS) measurements were carried out on a

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