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# Double-responsive core–shell–corona micelles from self-assembly of diblock copolymer of poly(*t*-butyl acrylate-*co*-acrylic acid)-*b*-poly(*N*-isopropylacrylamide)

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## Abstract

Self-assembly of poly(*t*-butyl acrylate-*co*-acrylic acid)-*b*-poly(*N*-isopropylacrylamide) [P(*t*BA-*co*-AA)-*b*-PNIPAM], which was obtained from part hydrolysis of P*t*BA-*b*-PNIPAM synthesized by sequential atom transfer radical polymerization (ATRP) was studied. Thermo- and pH-responsive core–shell–corona (CSC) micelles with different structures were formed from (P*t*BA-*co*-PAA)-*b*-PNIPAM in aqueous solution. At pH 5.8 and 25 °C, the block copolymer self-assembled into spherical core–shell micelles with hydrophobic P*t*BA segments as the core, hydrophilic PAA/PNIPAM segments as the mixed shell. Increasing temperatures, core–shell micelles converted into CSC micelles with P*t*BA as the core, collapsed PNIPAM as the shell and soluble PAA as the corona. Moreover, decreasing pH at 25 °C, PAA chains collapsed onto the core resulting in CSC micelles with P*t*BA as the core, PAA as the shell and PNIPAM as the corona.
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## 1. Introduction

Stimuli-responsive copolymers whose behaviors depend strongly on the external chemical and physical stimuli, such as temperature, pH, ionic strength, light and electric field, have attracted increasing research attentions for their wide range of applications in gene and drug delivery, chemical and biological sensors, etc. [1–9]. Poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most studied thermo-responsive polymers that exhibits a lower critical solution temperature (LCST) in water around 32 °C [10,11]. Below the LCST, PNIPAM is soluble in aqueous solution, while above the LCST, PNIPAM shows a sharp phase transition and precipitates. It is this unusual phase transition temperature and its related solution properties that have attracted great theoretical and technological interests [12–17]. The pH-responsive polymers can respond to pH changes to adjust their morphology and conformation due to the protonation–deprotonation equilibrium in aqueous solution [18].

Block copolymers containing both of thermo- and pH-responsive segments can respond to combined external stimuli [19–22]. Armes et al. reported a diblock copolymer of poly(propylene oxide)-*b*-poly(2-(diethylamino)ethyl methacrylate), which dissolved molecularly in cold aqueous solution and self-assembled into PPO-core micelles or DEA-core micelles by adjusting pH and temperature [21]. Muller et al. studied the self-assembly of thermo- and pH-responsive PNIPAM-*b*-PAA diblock copolymer in water [22]. All these studies focused on the reversible changes of core–shell micelles.

Apart from core–shell micelles [23,24], core–shell–corona (CSC) micelles that have more defined structures have been extensively studied. Usually, CSC micelles are prepared from amphiphilic ABC triblock copolymers [25–29] or mixtures of AB block copolymer and C homopolymer or two diblock copolymers AB and BC or AB and CD [30–32]. For example, Jerome et al. prepared CSC micelles with a pH-responsive shell from polystyrene-*b*-poly(2-vinyl pyridine)-*b*-poly(ethylene oxide) (PS-*b*-P2VP-*b*-PEO) [25]. Our group reported a thermo- and pH-responsive triblock copolymer of poly(ethylene glycol)-*b*-poly(4-vinylpyridine)-*b*-poly(*N*-isopropylacrylamide) (PEG-*b*-P4VP-*b*-PNIPAM), which existed as unimers at 25 °C pH 2.0 and self-assembled into CSC micelles with increasing of temperature and pH [26]. So far, double-responsive CSC micelles with responsive shell and corona have been

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scarcely investigated. Understanding the dynamics of these micelles are also important to broaden the potential applications of polymeric micelles.

Very recently, Eisenberg et al. reported on the formation of bowl-shaped aggregates from the self-assembly of an amphiphilic random copolymer of poly(styrene-co-methacrylic acid) [P(S-co-MAA)], where most of short hydrophilic segments are buried inside the core due to hydrogen bonding; the hydrophobic segments form the continuous matrix and part of hydrophilic segments provide an exterior corona for the aggregates [33]. If the random copolymers consist of responsive segments, the morphology of the aggregates may be more easily adjusted. In this paper, we report the formation of thermo- and pH-responsive CSC micelles from self-assembly of a asymmetric diblock copolymer of poly(t-butyl acrylate-co-acrylic acid)-b-poly(N-isopropylacrylamide) [P(tBA-co-AA)-b-PNIPAM].

## 2. Experimental section

### 2.1. Materials

1-Chlorophenylethane (1-PECl) (Acros Organics, USA). t-Butyl acrylate (tBA) (Aldrich, AR) was dried with CaH$_2$ and then distilled under vacuum. N,N,N',N'',N''-Pentamethyl diethylenetriamine (PMDETA) (AR, Acros Organics, USA). N-Isopropylacrylamide (NIPAM) (Acros Organics USA) was purified by recrystallization in benzene/n-hexane mixtures and dried in a vacuum. Tris[2-(dimethylamino)ethyl]amine (Me$_6$-TREN) was synthesized from tris(2-amino)ethyl amine (TREN) (Aldrich) [34]. CuCl was synthesized in our laboratory. Other analytical reagents were used as received.

### 2.2. Synthesis of block copolymer

The macroinitiator of poly(t-butyl acrylate) (PtBA-Cl) was prepared according to the published report [35] using 1-PECl as initiator and CuCl/PMDETA as catalyst at 100 °C for 6 h in the mixture solvent of butanone and 2-propanol (7:3 by volume).

Block copolymer of PtBA-b-PNIPAM was obtained through PtBA-Cl initiating polymerization of NIPAM. A typical polymerization procedure is as follows: PtBA-Cl (3.0 g) was added to a reaction flask and then 6 mL mixture solvent of butanone and 2-propanol (6:4 by volume) was added. The sample was first stirred and then degassed under nitrogen purge. Subsequently, CuCl and Me$_6$TREN were introduced into the reaction flask. At last, NIPAM (9.0 g) was added into the flask and degassed under nitrogen purge again. Polymerization was performed at 40 °C for 48 h. The product was purified by passing through Al$_2$O$_3$ column and then deposited in a methanol/water mixture.

The block of poly(t-butyl acrylate) in copolymers was hydrolyzed to poly(acrylic acid) by using p-toluenesulfonic acid as the catalyst in refluxing toluene at 110 °C.

### 2.3. Characterizations

Molecular weights and polydispersity index (PDI) of PtBA-Cl and PtBA-b-PNIPAM were characterized by a Waters 600E gel permeation chromatography (GPC) analysis system, where THF was used as the eluent and narrow-polydispersity polystyrene as the calibration standard.

The composition of block copolymers before and after hydrolysis was recorded using a Bruker AV300 spectrometer ($^1$H NMR) in CDCl$_3$ or DMSO.

Dynamic laser scattering (DLS) and static laser scattering (SLS) measurements were performed on a laser light scattering spectrometer (BI-200SM) equipped with a digital correlator (BI-10000AT) at 514 nm. The block copolymer P(tBA-co-AA)-b-PNIPAM was directly dissolved in water at room temperature. The copolymer solution with a given pH value was adjusted with HCl and NaOH. All samples with the same concentration of 0.2 mg/mL were first prepared by filtering about 1 mL of the aqueous solution with a 0.45 μ Millipore filter into a clean scintillation vial and heating at a given temperature for about 1 h and then characterized by DLS and SLS.

In DLS measurements, the measured intensity–intensity time correlation function $G^{(2)}(t,q)$ in the self-beating mode can result in a line-width distribution $G(\Gamma)$. For a pure diffusive relaxation, $G(\Gamma)$ is related to the translational diffusion coefficient $D$ by $G(D)$ since $D = \Gamma/q^2$ at $\theta \rightarrow 0$ and $C \rightarrow 0$ or a hydrodynamic diameter distribution $f(D_h)$ via the Stokes-Einstein equation $D_h = k_b T/(3\pi\eta D)$, where $k_b$, $T$, and $\eta$ are the Boltzmann constant, the absolute temperature and the solvent viscosity, respectively. In the present study, $D^0$ of the resultant micelles at given concentration is calculated by extrapolating $q^2$ to 0, and then the hydrodynamic diameter $D_h^0$ or the hydrodynamic radius $R_h^0$ and the hydrodynamic diameter distribution $f(D_h)$ at given polymer concentration are calculated.

On the basis of SLS theory, for a given dilute polymer solution at concentration $C$ (g/mL) and at the scattering angle $\theta$, the angular dependence of the excess absolute average scattered intensity, known as the excess Rayleigh ratio $R(\theta,C)$, can be approximated as

$$\left[\frac{KC}{R(\theta,C)}\right] = \left[\frac{1}{M_w}\right]\left[1 + \frac{(R_g^2 q^2)}{3}\right] \tag{1}$$

where $K$ is the optical constant and $K = 4\pi^2 n^2 (dn/dc)^2/(N_A \lambda_0^4)$ with $N_A$, $n$, $\lambda_0$ being Avogadro's number, the solvent refractive index and the wavelength of laser, respectively; $dn/dc$ is the specific refractive index increment, $q$ is the magnitude of the scattering wave vector and $q = (4\pi n/\lambda_0)\sin(\theta/2)$, respectively. After measuring $R(\theta,C)$ at a set of $\theta$, the value of gyration radius $R_g$ and apparent weight-average molecular weight $M_W$ are determined based on the Eq. (1).

The specific refractive index increment $(dn/dc)$ was determined using the Wyatt Optilab DSP interferometric refractometer at a wavelength of 514 nm at 25 °C.

Transmission electron microscopy (TEM) measurement was performed on a Philips EM400ST electron microscopy at