



# Synthesis and temperature-induced self-assembly of a positively charged symmetrical pentablock terpolymer in aqueous solutions

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## ABSTRACT

A novel linear cationic ABCBA pentablock terpolymer composed of a positively charged poly (3-acrylamidopropyl trimethyl ammonium chloride) (PAMPTMA (+)) block at both ends and two thermoresponsive poly (*N*-isopropylacrylamide) (PNIPAAm) blocks separated by a hydrophilic poly(ethylene glycol) (PEG) block was synthesized via a “one-pot” atom transfer radical polymerization procedure (ATRP). The chemical composition of the pentablock terpolymer was confirmed by nuclear magnetic resonance (NMR) and asymmetric flow field-flow fractionation (AFFFF). Depending on the polymer concentration in aqueous solution, this terpolymer forms unimers and self-assembled structures at elevated temperatures. The effect of concentration and temperature-induced self-assembling behavior of the pentablock terpolymer in aqueous solution was examined by using turbidimetry, shear viscosity, rheo-small angle light scattering (rheo-SALS), dynamic light scattering (DLS), and small angle neutron scattering (SANS). The turbidity measurements demonstrated that the formation of intermicellar structures and compaction of the complexes are function of both polymer concentration and temperature. The viscosity and rheo-SALS experiments elucidated the intricate interplay between building-up and breaking-up of interchain complexes under the influence of shear flow. The DLS experiments show the coexistence of small entities and interchain complexes at low temperatures and the evolution of large intermicellar structures at higher temperatures. At the highest temperatures, compaction of the complexes occurred. The results from SANS revealed significant temperature-induced changes of the copolymer structure on a semi-local dimensional scale.

## 1. Introduction

Amphiphilic block copolymers with different architectures and chemical composition that self-assemble into micelles and form gels in the semidilute concentration regime in response to external stimuli are an important class of materials with many applications, including drug delivery systems, gene therapy, and “smart” surface coatings [1–5]. Among the triggering mechanisms for responsive block copolymers, temperature and pH are considered as the most important stimuli for various biological applications, such as drug or gene delivery, smart bioactive surfaces, and molecular recognition agents [6,7]. Especially, the cationic block stimuli-responsive copolymers can interact

electrostatically with anionic proteins at physiological condition, which may not only lead to a sustained release without initial burst, but also protect the proteins from denaturing effects. In addition, the positively charged block copolymers may also form electrostatic complexes with the negatively charged plasmid DNA and cell membranes under physiological condition. The DNA-loaded responsive copolymers formed in situ may lead to a sustained, local gene-delivery system [8].

It is worth noting that the main challenges for a broad application of stimuli-induced self-assembling copolymers depend on factors such as the copolymer composition, molecular architecture, and hydrophobicity of the copolymer, as well as molecular weight and solution concentration. These factors play an essential role for the specific

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properties of copolymers, such as micellar structure of the copolymer in solution, proper assembly features, and biocompatibility, etc. [9]. There are relatively few papers describing the fundamental relationships between the architecture and chemical design of multifunctional block copolymers, and in what way these features will influence how they self-assemble and what kind of mesoscopic structures are formed. Furthermore, the interplay between electrostatic and hydrophobic/hydrophilic interactions of block segments on the aggregation behavior of copolymers has not been established for complex copolymers.

During the past decade, great attention has been paid to the field of self-assembly of responsive diblock and triblock copolymers, which exhibit aggregation behavior in aqueous solution upon tuning external solution conditions, such as temperature and pH [10–14]. In the past years, some studies have been reported on the adsorption of multifunctional pentablock terpolymers onto surfaces [15,16] and the behaviors of the pentablock copolymers in bulk solution [17–21]. However, there is a lack of investigations on the temperature-induced self-association behavior of multifunctional copolymers in solution. The reason for this shortage is probably that these copolymers have intricate morphologies due to the complexity of the macromolecular structure.

In recent years, some studies have been reported on self-assembly behavior of responsive pentablock terpolymers with functional groups added at both ends of the chain [22,23]. For instance, Agarwal et al. [1] and Determan et al. [17] prepared thermo-responsive gel-forming pentablock terpolymers as a self-assembling polymeric gene delivery vector, composed of commercially available Pluronic® F127 (PEO-*b*-PPO-*b*-PEO) triblock copolymers in the center, and cationic poly(amine methacrylate) diblocks at both ends of the chain by using the atom transfer radical polymerization (ATRP) method. These copolymers exhibit temperature dependent micellization because of the block architecture and the copolymer displays a lower critical solution temperature (LCST). Huynh et al. [24,25] prepared pH/temperature-sensitive injectable hydrogels of poly( $\beta$ -amino ester)-poly( $\epsilon$ -caprolactone)-poly(ethylene glycol)-poly( $\epsilon$ -caprolactone)-poly( $\beta$ -amino ester) (PAE-PCL-PEG-PCL-PAE) pentablock terpolymers; the gels were used for controlled insulin delivery. The cationic nature of PAE is used to make ionic complexes with the anionic insulin.

Poly(*N*-isopropylacrylamide) (PNIPAAm) is one of the most studied temperature responsive polymers, and it exhibits a LCST in aqueous solution at around 32 °C [26]. The closeness of the LCST of PNIPAAm to the physiological temperature makes it an appealing polymer for drug and gene delivery applications. By increasing the solution temperature towards the transition temperature, the hydrogen bonds stabilizing the structure at lower temperatures are disrupted and hydrophobic interactions are generated through the isopropyl groups, and formation of aggregates occurs. In this way, we have a copolymer with tunable self-assembling features [27].

In recent years, studies have appeared on the use of PNIPAAm as an ingredient block in multi-block copolymers, consisting of hydrophilic, hydrophobic, and charged block sequences. Our group has for some time worked on pentablock terpolymers of the type ABCBA, where C is the PEG-spacer, B the NIPAAm block, and A is a charged block [28,29]. The results from previous studies on pentablock copolymers indicate that the charged end-groups play a vital role for the structural and rheological properties of the polymers in aqueous media. In addition, the length of the PEG-spacer is important for the type of micelles that are formed and how the micelles are interconnected at higher polymer concentrations and temperatures [28]. Our understanding of the temperature-induced supramolecular features of multifunctional copolymers is quite limited and a more detailed understanding of the self-organized structures is necessary. The aim of the present study is to gain more insight into the self-assembling behavior of pentablock copolymers with charged end-groups.

To accomplish this, a cationic ABCBA pentablock terpolymer with a different type of charged end-group than employed previously [29] was synthesized by ATRP. The self-assembling features of the pentablock

copolymer poly(3-acrylamidopropyl) trimethyl ammonium chloride-*block*-poly(*N*-isopropylacrylamide)-*block*-poly(ethylene glycol)-*block*-poly(*N*-isopropylacrylamide)-*block*-poly(3-acrylamidopropyl) trimethyl ammonium chloride, abbreviated as P(AMPTMA)<sub>14</sub>-*b*-P(NIPAAm)<sub>66</sub>-*b*-P(EG)<sub>77</sub>-*b*-P(NIPAAm)<sub>66</sub>-*b*-P(AMPTMA)<sub>14</sub>, were characterized in aqueous media with the aid of turbidimetry, shear viscosity, dynamic light scattering (DLS) and small-angle neutron scattering (SANS) as function of polymer concentration and temperature. The results from these experimental methods will elucidate the competition between hydrophobic interactions and electrostatic forces to get a better understanding of the self-assembling process and how this process is influenced by temperature-induced changes of structure, size, and size distribution.

## 2. Experimental methods

### 2.1. Materials

The monomer *N*-isopropylacrylamide (NIPAAm, Acros) was recrystallized from a toluene/*n*-hexane mixture twice and dried under vacuum prior to use. Poly(ethylene glycol) ( $M_n$  value of 3400), 2-bromoisobutyl bromide and copper(II) chloride were all purchased from Sigma-Aldrich Co. 3-Acrylamidopropyl trimethylammonium chloride (AMPTMA, Aldrich) was purified from the inhibitor rest present in the sample by precipitating it into cold acetone, followed by washing with cold acetone, and finally drying under vacuum overnight. Triethylamine (TEA, Aldrich) was dried over anhydrous magnesium sulfate (Aldrich), filtered, distilled under  $N_2$ , and stored over 4 Å molecular sieves. Copper (I) chloride (Aldrich) was washed with glacial acetic acid (Aldrich), followed by washing with methanol, diethyl ether and finally dried under vacuum and kept under  $N_2$  atmosphere. *N,N,N',N'',N''',N''''*-(hexamethyl triethylene tetramine) (Me<sub>6</sub>TREN) was synthesized according to a procedure described by Ciampolini [30]. The bis-functional macro-initiator from PEG derivative (Br-PEG<sub>3400</sub>-Br) was prepared via reaction of PEG<sub>3400</sub> with 2-bromoisobutyl bromide in the presence of triethylamine as depicted in Fig. 1. The repeating units of ethylene glycol (EG) are estimated from the proton NMR spectra of the fully esterified product (as described in details elsewhere [28,29,31]) to be 77 units for PEG<sub>3400</sub>, and it was denoted as P(EG)<sub>77</sub>. All water used in this study was purified with a Millipore Mill-Q system with a resistivity of 18 M  $\Omega$  cm.

### 2.2. Synthesis of the pentablock terpolymer

A simple “one-pot” two step ATRP was carried out for preparation of the pentablock copolymer with some modifications (Fig. 1) [12,28,29,32]. Briefly, the polymerization was performed in a water/DMF (50:50, v/v) mixture at 25 °C, and the initiator/catalyst system in the mixture contained PEG-bis-functional macroinitiator (PEG-Bis-MI), CuCl, CuCl<sub>2</sub>, and Me<sub>6</sub>TREN (with molar feed ratio of ([NIPAAm] = 2 M, [NIPAAm]/[AMPTMA]/[PEG-Bis-MI]/[CuCl]/[CuCl<sub>2</sub>]/[Me<sub>6</sub>TREN] = 140/60/1/2/1.2/3.2). The polymer was prepared and purified under similar conditions as described in detail previously [28,29,33].

The chemical structure and composition of the pentablock terpolymer was determined from its <sup>1</sup>H NMR spectrum as shown in Fig. 2. The number-average molecular weight and the unit numbers of *o*, *m*, and *n* in P(AMPTMA)<sub>*o*</sub>-*b*-P(NIPAAm)<sub>*m*</sub>-*b*-P(EG)<sub>*n*</sub>-*b*-P(NIPAAm)<sub>*m*</sub>-*b*-P(AMPTMA)<sub>*o*</sub> were determined by comparing the integral area of the methylene proton peak (1) of EG ( $\delta$  = 3.70 ppm,  $-OCH_2CH_2O$ ), the methylene proton peak (5) of PNIPAAm ( $\delta$  = 3.85 ppm,  $CH(CH_3)_2$ ), and the methylene proton (12) of AMPTMA ( $\delta$  = 3.1 ppm,  $-N(CH_3)_3$ ) obtained from its <sup>1</sup>H NMR spectrum. The entire repeating units of AMPTMA/NIPAAm/EG (2*o*/2*m*/*n*) are estimated to be 28/132/77, based on our previous calculation results [12,28,29,32,34] that the number of repeating units of the ethylene glycol of PEG bis-MI is 77 for PEG<sub>3400</sub>. Hence, the composition of the pentablock terpolymer is

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