



“Schizophrenic” self-assembly of dual thermoresponsive block copolymers bearing a zwitterionic and a non-ionic hydrophilic block



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ARTICLE INFO

Article history:

Received 29 April 2017

Received in revised form

23 June 2017

Accepted 24 June 2017

Available online 27 June 2017

Keywords:

RAFT polymerization

Block copolymer

Sulfobetaine methacrylate

Responsive polymer

LCST

UCST

Schizophrenic self-assembly

ABSTRACT

Several series of presumed dual thermo-responsive diblock copolymers consisting of one non-ionic and one zwitterionic block were synthesized via consecutive reversible addition-fragmentation chain transfer (RAFT) polymerization. For all copolymers, poly(N-isopropylmethacrylamide) was chosen as non-ionic block that shows a coil-to-globule collapse transition of the lower critical solution temperature (LCST) type. In contrast, the chemical structure of zwitterionic blocks, which all belonged to the class of poly(sulfobetaine methacrylate)s, was varied broadly, in order to tune their coil-to-globule collapse transition of the upper critical solution temperature (UCST) type. All polymers were labeled with a solvatochromic fluorescent end-group. The dual thermo-responsive behavior and the resulting multifarious temperature-dependent self-assembly in aqueous solution were mapped by temperature-resolved turbidimetry, ¹H NMR spectroscopy, dynamic light scattering (DLS), and fluorescence spectroscopy. Depending on the relative positions between the UCST-type and LCST-type transition temperatures, as well as on the width of the window in-between, all the four possible modes of stimulus-induced micellization can be realized. This includes classical induced micellization due to a transition from a double hydrophilic, or respectively, from a double hydrophobic to an amphiphilic state, as well as “schizophrenic” behavior, where the core- and shell-forming blocks are inverted. The exchange of the roles of the hydrophilic and hydrophobic block in the amphiphilic states is possible through a homogeneous intermediate state or a heterogeneous one.

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1. Introduction

Block copolymer synthesis and self-assembly have been particularly fertile research fields of macromolecular science during the past decades. While for long being mostly limited to living anionic and cationic polymerizations, the advent of reversible deactivation radical polymerization (RDRP) enabled also the rather facile synthesis of block copolymers bearing highly functional moieties, including systems that are suited for so-called responsive (“smart”) materials [1–7]. This includes also block copolymers

comprising zwitterionic structures. Polyzwitterions are a priori highly hydrophilic polymers that bear the same number of anionic and cationic moieties within the same constitutional repeat unit (CRU) [8–10]. Due to this structural similarity to cell membranes that are made mostly of zwitterionic phospholipids, they have been studied intensely for the development of highly biocompatible, non-immunogenic and low-fouling materials. Amidst the various families of polyzwitterions known, poly(sulfobetaine)s stand out by virtue of their chemical stability, as well as the pH-independence of their zwitterionic character [10]. Importantly, many poly(-sulfobetaine)s exhibit a coil-to-globule collapse transition in aqueous media upon cooling with the occurrence of an upper critical solution temperature (UCST) [11–20]. This particular thermo-responsive behavior differs from the behavior of the other

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main classes of polyzwitterions, namely of poly(carboxybetaine)s [21–24] and poly(phosphatidylcholine)s [25–29], for which no such a phase transition in aqueous solution has been reported. It also is in sharp contrast to the behavior of most thermoresponsive non-ionic polymers, which show typically a coil-to-globule collapse transition with a lower critical solution temperature (LCST) in aqueous solution [30–34].

Recently, we studied the thermo-responsive behavior of several series of polysulfobetaines in detail, with the aim to correlate it to the molecular structure [20,35]. Though the behavior of these polymers seems to evade simple structure property-relationships, we succeeded in covering a wide range of transition temperatures only by implementing minimal changes in the chemical structure. Pursuing the use of such poly(sulfobetaine)s as versatile building blocks for “smart” and biocompatible polymers, we derived now a series of double-hydrophilic block copolymers, which are dual thermoresponsive [36–39] (Scheme 1). The new copolymers are composed of a zwitterionic and a non-ionic block, and can feature a UCST as well as an LCST transition [40–43]. When adjusting the structure of the polymer blocks properly, this enables stepwise thermal switching of the copolymer self-assembly. If the UCST transition occurs at lower temperatures than the LCST transition, the polymer changes from an amphiphilic character at low temperature, to a fully soluble double-hydrophilic state at intermediate temperatures, and again back to an amphiphilic one at even more elevated temperatures (Scheme 1b). If the UCST transition however is higher than the LCST transition, the polymers are amphiphilic at low or high temperatures, but insoluble at intermediate ones (Scheme 1c). In the course of these transformations, the roles of the hydrophilic and hydrophobic blocks are switched, and the micellar structures turn inside-out. For this particular pattern of self-assembly, the term “schizophrenic” had been coined [44–46]. While schizophrenic micellization of block copolymers can be induced by diverse triggers (such as changes of the pH or addition of electrolytes) [45–51], its implementation via UCST and LCST governed dual thermal switching has the advantage to be applicable in closed systems. Since the first report in 2002, only sporadic examples of such systems have been published, generally focusing in detail on one particular system [40–43,52–64].

In the present study, in the attempt to screen self-assembly patterns, we prepare a large set of presumed dual thermo-responsive block copolymers (Fig. 1) and explore their temperature-dependent self-assembly in aqueous solution. Polymers are synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization, varying systematically the

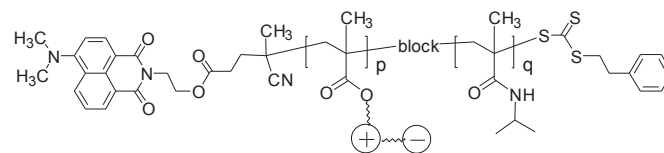


Fig. 1. General structure of the polyzwitterion block copolymers $\text{pSB-}x_p\text{-}b\text{-NIPMAM}_q$ studied, with $\text{SB-}x$ being $\text{SB-}1$ to $\text{SB-}8$, and p and q being the number average degree of polymerizations DP_n of the respective blocks. For the structure of the zwitterionic monomers employed, cf. Fig. 2.

poly(sulfobetaine) block, while the non-ionic block, namely poly(N-isopropylmethacrylamide) pNIPMAM , is kept constant (Fig. 2). The latter polymer is chosen because it features a rather insensitive LCST transition in the range of 45 °C, which is - for still disputed reasons - considerably higher than the LCST of about 32 °C of its much more studied analogue poly(N-isopropylacrylamide) pNIPAM [31,65,66], and therefore appears to be more practical for our investigations. The investigations in solution were conducted uniformly in the concentration range of 10–50 g L⁻¹, in order to facilitate direct comparisons not only of the various measurements within this study, but also of our findings with the results of structural investigations on closely related systems [20,42,43].

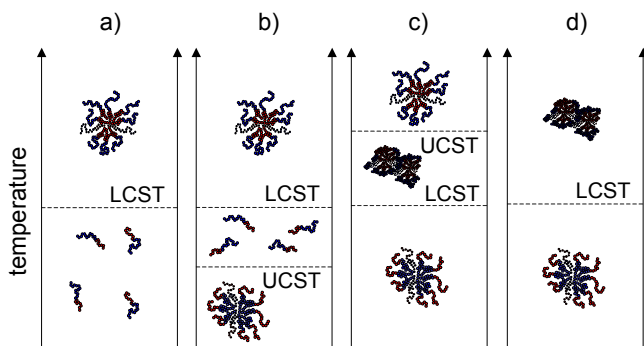
2. Experimental part

2.1. Materials

Synthesis and molecular characterization of the zwitterionic and non-ionic macromolecular chain transfer agents (macro CTAs) are described elsewhere [20,43]. Block copolymers were synthesized by chain extension of the previously prepared macro CTAs with NIPMAM , and exceptionally with $\text{SB-}1$, via reversible addition-fragmentation chain transfer (RAFT) polymerization in trifluoroethanol (TFE). In a typical procedure, a TFE solution of macro CTA, monomer, and initiator V-501 (total concentration about 25 wt%) was purged with N₂ for 30 min and sealed. Subsequently, the yellow mixture was polymerized at 75 °C for a given time. The reaction was stopped by allowing air into the reaction vessel, and cooled to ambient temperature. The block copolymer formed was collected by precipitation into diethyl ether. Dissolution in TFE and precipitation into diethyl ether was repeated 3 times. The precipitate was washed with dichloromethane, isolated, and dried *in vacuo*. The purified block copolymers were obtained as amorphous yellow solids. They were characterized by ¹H NMR, UV–vis, fluorescence, and IR spectroscopies, as well as by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Details of the chemicals used and the synthetic procedures are given in the [Electronic Supplementary Material \(ESM\)](#).

2.2. Methods

Molecular characterization. ¹H nuclear magnetic resonance (NMR) spectra were recorded with a Bruker Avance 300 spectrometer (300 MHz) at ambient temperature in D₂O or dichloromethane for structure determination. The solvent signals were set to 4.79 ppm and 5.32 ppm, respectively. ¹H NMR spectra of the crude reaction mixtures were used to calculate the conversions by comparing the integral of the signals of the olefinic double bond to the integral of the signals of the methyl protons of the ammonium group in the case $\text{SB-}1$, or of the methine proton of the isopropyl group in the case of NIPMAM , respectively. Temperature-dependent studies of 50 g L⁻¹ solutions in D₂O were performed on a



Scheme 1. Schematic scenarios for the solution self-assembly of dual thermo-responsive diblock copolymers, which have of a fixed LCST- and a variable UCST-transition: a) UCST < freezing point (simple micellization triggered from the soluble state), b) UCST < LCST (“schizophrenic” micellization via soluble transition zone), c) LCST < UCST (“schizophrenic” micellization via insoluble transition zone), d) UCST > boiling point (simple micellization triggered from the insoluble state).

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