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LCST behavior of poly(2-ethyl-2-oxazoline) containing diblock and triblock copolymers

Martin Sahn, Leanne M. Stafast, Michael Dirauf, Damiano Bandelli, Christine Weber, Ulrich S. Schubert*

Laboratory of Organic and Macromolecular Chemistry (IOMC), Friedrich Schiller University Jena, Humboldtstr. 10, 07743 Jena, Germany
Jena Center for Soft Matter (JCSM), Friedrich Schiller University Jena, Philosophenweg 7, 07743 Jena, Germany

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ABSTRACT

Mono- and bifunctional macro chain transfer agents were prepared *via* the living cationic ring opening polymerization of EtOx. A series of well-defined P(eTEGA)-*b*-PEtOx-*b*-P(eTEGA) triblock copolymers, PEtOx-*b*-P(eTEGA) as well as PEtOx-*b*-PNiPAm diblock copolymers were obtained by subsequent reversible addition fragmentation chain transfer polymerization of eTEGA or NiPAm, respectively. While the molar mass of the PEtOx was kept constant, the DP of the PNiPAm or P(eTEGA) block was varied and covers a wide range. Turbidimetry, NMR spectroscopy and dynamic light scattering investigations of the aqueous polymer solutions revealed that the lower critical solution temperature behavior of the triblock copolymers is strongly affected by the hydrophobic end groups whereas the presence of hydrogen bond donating moieties does not play any role. For diblock copolymers with a sufficiently long PEtOx block, the PNiPAm blocks collapsed independently, resulting in multiple phase transitions and the formation of well-defined aggregated structures.

1. Introduction

Thermoresponsive polymers are known as “smart materials” and are appealing for a wide range of applications due to their ability to alter the properties by an external trigger [1]. In particular, polymers exhibiting a lower critical solution temperature (LCST) are in focus of interest and well-studied [2]. Poly(*N*-isopropylacrylamide) (PNiPAm) is probably the most investigated polymer that reveals a “switch” from hydrophilic to hydrophobic properties and is considered to be the gold standard in that field [3]. Furthermore, its reversible coil-to globule phase transition temperature at 32 °C [4,5] is slightly below body temperature making it interesting for biomedical applications [6–10]. In this entropy driven process, hydrogen bonds between the polymer and water molecules are weakened at elevated temperatures leading to demixing, *i.e.* to the formation of a biphasic system comprising a higher and a lower concentrated polymer phase [11]. Tuning of the coil-to-globule transition temperature can be achieved by copolymerization of NiPAm with other monomers [12,13].

PNiPAm has been combined with permanently hydrophilic blocks such as, *e.g.,* poly(ethylene oxide) (PEO) in different architectures to adjust the thermoresponsive behavior. In particular, aqueous solutions of PNiPAm-*b*-PEO-*b*-PNiPAm triblock copolymers exhibit a thermally induced reversible sol-gel transition due to the permanent solvation of the middle block [14–16]. Furthermore, PEO-*b*-PNiPAm diblock copolymers undergo thermally induced self-assembly processes forming micelles or vesicles in aqueous solution upon elevated temperature [17,18].

Poly(ethoxytriethyleneglycol acrylate) (P(eTEGA)) represents a biocompatible [19,20] and thermoresponsive polymer with a reported molar mass dependent cloud point temperature (T_{cp}) of 34–39 °C [21–24] in aqueous solution that is similar to PNiPAm (T_{cp} = 32 °C). In contrast to PNiPAm, P(eTEGA) does not feature any hydrogen bond donor moieties. Also P(eTEGA) was combined in di-[25,26] and triblock [27] architectures with PEO and the resulting polymers showed the expected sol-gel transitions. However, the studies focused on P(eTEGA)-based building blocks comprising *o*-nitrobenzyl acrylate or acrylic acid in varying molar fractions [25–27]. To the best of our knowledge, a comprehensive direct comparison between PNiPAm and P(eTEGA) as thermo-responsive building blocks combined with a hydrophilic building block in di- and triblock architectures is missing to date.

For this purpose, we selected a hydrophilic poly(2-oxazoline) (POx) block since it is known that PEO shows some drawbacks such as non-biodegradability or possible accumulation in the body [28]. The hydrophilic poly(2-ethyl-oxazoline) (PEtOx) features appropriate properties, such as stealth effect and biocompatibility [28,29]. The cationic

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* Corresponding author at: Laboratory of Organic and Macromolecular Chemistry (IOMC), Friedrich Schiller University Jena, Humboldtstr. 10, 07743 Jena, Germany.
E-mail address: ulrich.schubert@uni-jena.de (U.S. Schubert).

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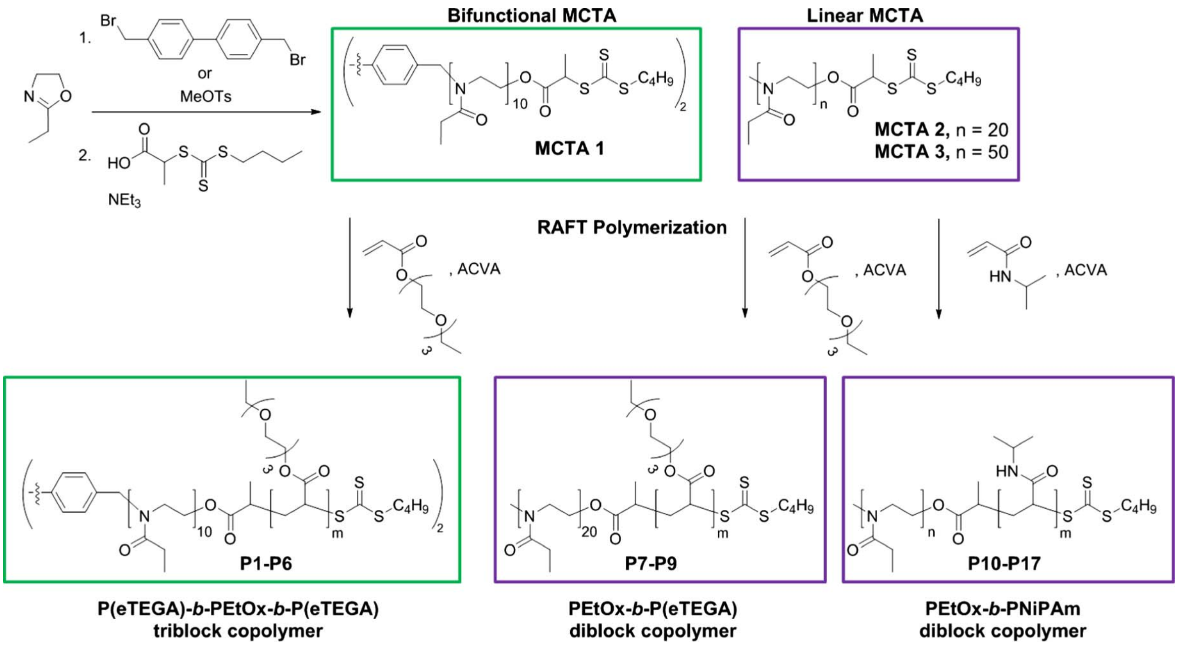

Scheme 1. Schematic representation of the synthesis route towards P(eTEGA)-*b*-PEtOx-*b*-P(eTEGA) triblock copolymers or PEtOx-*b*-P(eTEGA) and PEtOx-*b*-PNiPAm diblock copolymers, respectively.

ring-opening polymerization (CROP) provides access to tailor-made POx. Its livingness enables the introduction of various functionalities into the polymer by using functional initiators [30] and end capping-agents [31], respectively. Sequential monomer addition [32–35] or crossover techniques [36,37] enable the preparation of block copolymers. In particular, block copolymers comprising PEtOx and PNiPAm building blocks have been obtained *via* a crossover of CROP and radical addition fragmentation transfer (RAFT) polymerization technique using PEtOx based macro chain transfer agents (MCTA) obtained by quenching the living CROP with a carboxylic acid functionalized CTA [37,38]. The utilization of methyl tosylate as CROP initiator resulted in a monofunctional MCTA providing access to diblock copolymers [37]. Bifunctional MCTA and the according symmetrical BAB triblock copolymers can be obtained using the bifunctional CROP initiator 4,4′-bis(bromomethyl)biphenyl (BBMBP).

Both MCTA types should be efficient in controlling the polymerization of NiPAm as well as eTEGA, facilitating access to a range of block copolymers suitable to directly compare the influence of hydrogen bond donating moieties and the block copolymer architecture on the LCST behavior (Scheme 1). Featuring hydrogen bond accepting moieties, high molar mass PEtOx exhibits LCST behavior in water at temperatures above 70 °C [39]. The PEtOx building blocks were hence kept rather short, whereas the degree of polymerization (DP) of the PNiPAm and P(eTEGA) blocks, respectively, was varied over a broad range.

2. Experimental part

2.1. Materials

Unless specified otherwise, all chemicals were used without further purification. 2-Ethyl-2-oxazoline (EtOx, Acros Organics) and methyl *p*-toluenesulfonate (MeOTs, Sigma Aldrich) were dried over barium oxide, distilled and stored under argon atmosphere. *N*,*N*-Dimethylformamide (DMF, Sigma Aldrich), acetonitrile (ACN, Sigma Aldrich) and dichloromethane were dried in a solvent purification system (Pure Solv EN, InnovativeTechnology) before use as polymerization or reaction solvent. Triethylamine (NEt_3) was dried over potassium hydroxide overnight and refluxed for three hours. After filtration of potassium hydroxide it was dried over calcium hydride, distilled and stored under argon atmosphere. 4,4′-Bis(bromomethyl) biphenyl (BBMBP, ≥97% purity), *N*-isopropylacrylamide (NiPAm, ≥97% purity), acryloyl chloride (≥97% purity) and 4,4′-azobis(4-cyanovaleric acid) (ACVA, ≥98% purity) were purchased from Sigma-Aldrich. Triethylene glycol monoethylether (> 90.0% purity) was bought from TCI. 2-(Butylthiocarbonothioylthio)-propanoic acid (BTPA) was a kind gift from the BASF and used as received.

2.2. Instruments

The polymerization of EtOx was performed in a Biotage Initiator Sixty microwave synthesizer.

Size exclusion chromatography (SEC) was measured on an Agilent 1200 series equipped with a G1310A pump, a G1315D DA detector, a G1362A RI detector, and PSS GRAM 30 Å/1000 Å (10 μm particle size) columns in series at 40 °C using *N*,*N*-dimethylacetamide (DMAc) with 2.1 $g\,L^{-1}$ LiCl as eluent at a flow rate of 1 $mL\,min^{-1}$. The system was calibrated with PS standards (374–1,040,000 Da).

^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz or a Bruker Avance 400 MHz using the residual solvent resonance as an internal standard. The chemical shifts are given in ppm relative to trimethylsilane. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-ToF) mass spectra were acquired with an Ultraflex III ToF/ToF instrument (Bruker Daltonics, Bremen, Germany). The instrument is equipped with a Nd-YAG laser. All spectra were measured in the positive reflector mode. The instrument was calibrated prior to each measurement with an external PMMA standard from PSS. Samples were spotted using the dried droplet technique applying 2,5-dihydroxybenzoic acid (DHB) as a matrix and NaI as a doping salt.

For the electrospray ionization time-of-flight mass spectrometry (ESI-ToF-MS) measurements, samples were analyzed by using a microToF Q-II (Bruker Daltonics) mass spectrometer equipped with an automatic syringe pump from KD Scientific for sample injection. The mass spectrometer was running at 4.5 kV, at a desolvation temperature of 180 °C and was operated in the positive ion mode. Nitrogen was used as the nebulizer and drying gas. All fractions were injected with a constant flow rate (3 $\mu L\,min^{-1}$) of sample solution. The instrument was calibrated in the *m*/*z* range from 50 to 3000 with a calibration standard