



Functional star block copolymers with a cholane core: Thermo-responsiveness and aggregation behavior



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ABSTRACT

Star block copolymers composed of hydrophilic poly(ethylene glycol) (PEG) as an inner block and tuneable poly(allyl glycidyl ether) (PAGE) as an outer block were made by sequential anionic polymerization on a cholane core. The 4-armed CA(EG_n-b-AGE_m)₄ star block copolymers show dual thermo-responsive behavior in aqueous solutions, where the two cloud points (CPs) vary in the range of 10–34 °C for the first CP and 16–39 °C for the second CP, depending on the length of the PEG and PAGE segments. ¹H NMR spectroscopy, dynamic light scattering and atomic force microscopy all indicate a two-step aggregation process of flower-like micelles, where the micelles form through the association of the hydrophobic PAGE blocks and the bile acid core. The allyl groups of the star copolymers were further functionalized by radical thiol-ene coupling to introduce NH₂ or COOH groups in the outer block. As a result, star-shaped block copolymers with dual pH- and thermo-sensitivity were obtained with different aggregation characteristics corresponding to the pK_a of the functionalized blocks. Interestingly, the deprotonated NH₂-bearing polymers showed dual thermo-responsive characteristics different from their allyl group-bearing precursor.

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1. Introduction

Star polymers are a class of branched polymers with several arms attached to a central core. They have lower hydrodynamic volumes and intrinsic viscosities than their linear counterparts of equal molecular weight, depending on the number and length of arms, and they allow the incorporation of a large number of functional groups, both in the chain ends and within the star architecture [1–3]. Amphiphilic star polymers can form unimolecular micelles in aqueous solutions and their micellization behavior may depend on the number of arms [4,5]. Their potential applications include the encapsulation and delivery of compounds such as drugs, dyes, anticorrosion agents, flavors, and fragrances [6–8].

Cholic acid (CA), a naturally occurring bile acid, has a rigid steroid skeleton and four functional groups and is a good starting point for preparing a variety of star polymers. Bile acids are facially amphiphilic biosurfactants that participate in the digestion lipids through the formation of mixed micelles [9], and many of their polymeric derivatives have shown interesting aggregation properties and good biocompatibility [10–19]. The use of oligomers and polymers derived from cholesterol or bile acids include the

transport of DNA, oligonucleotides and therapeutic peptides [20–22]. In our earlier work, well-defined star polymers and block copolymers were made by anionic polymerization of ethylene oxide and/or allyl glycidyl ether onto various bile acids, including cholic acid [13,14,18,23]. Poly(ethylene glycol) (PEG) star polymers with 2–4 arms aggregated in aqueous media and the cores of the aggregates had different polarities [9,18]. When the arms were relatively short, the hydrophobicity of the steroid ring of bile acids had a great effect on the hydrophobic/hydrophilic balance of the polymers and as a result, the otherwise high cloud point (CP) of oligomeric PEG decreased significantly. The most hydrophobic 2-armed bile acid derivative formed elongated thermo-sensitive self-assemblies capable of gelation [24,25]. Thermo-responsiveness was also shown for 4-armed poly(allyl glycidyl ether) (PAGE) stars based on cholic acid when amino groups (NH₂) were introduced in the allyl moieties [13], but such behavior was not observed for the corresponding allyl precursor or carboxylic acid (COOH) derivative. Recently, star block copolymers based on cholic acid with poly(allyl glycidyl ether)-block-poly(ethylene glycol) arms, or CA(AGE_m-b-EG_n)₄, showed interesting thermo-responsive properties over a broad temperature range (13–55 °C) and the polymers with short PEG blocks displayed a two-step transition, which resulted from the formation of micelles, followed by their aggregation into larger clusters because of the association of terminal PEG chains [23].

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The tunable thermo-responsiveness and natural origin of the cholic acid core makes these polymers interesting candidates particularly for biomedical or pharmaceutical applications. For this purpose, the pendent allyl groups provide a platform for bio-conjugation aiming at targeted delivery of therapeutic molecules. Recently, a series of linear random poly(EG-co-AGE) copolymers was synthesized and conjugated with cysteine or peptides for targeted drug delivery [26]. In another work, the modification of allyl groups of triblock terpolymer poly(ethylene glycol)-*block*-poly(allyl glycidyl ether)-*block*-poly(*tert*-butyl glycidyl ether) with cysteine or sugar moieties led to a change in micellar morphologies from spherical core-shell-corona micelles to worm-like ones above the cloud point [27]. In a star polymer, attaching the targeting moieties to the terminal groups or sequences would be desirable. In this work, we used cholic acid as the core to prepare a series of 4-armed star polymers CA(EG_{*n*}-*b*-AGE_{*m*})₄ (Scheme 1) bearing allyl groups in the outer block, onto which NH₂ and COOH functional groups were introduced. The thermo-responsiveness and self-assembling characteristics of the new star block copolymers were investigated.

2. Materials and methods

2.1. Synthesis of CA(EG_{*n*}-*b*-AGE_{*m*})₄

CA(EG_{*n*}-*b*-AGE_{*m*})₄ star block copolymers were made by sequential anionic polymerizations according to previous reports [14,23,26] with some modifications. A cholane precursor with four hydroxyl groups ((2-hydroxyethylene)-3 α ,7 α ,12 α -trihydroxy-5 β -cholanoamide) was used as an initiator for the polymerization of ethylene oxide, followed by the polymerization of AGE to yield 4-armed star block copolymers with a PEG inner block and a PAGE outer block. The products were dialyzed (MWCO 3500 Da) against water and then freeze-dried (yield > 80%). The polymers were analyzed by ¹H NMR spectroscopy, MALDI-TOF mass spectroscopy, size exclusion chromatography (SEC) and differential scanning calorimetry (DSC) to confirm the structures and molecular weights (Supporting Information). The results are presented in Table 1.

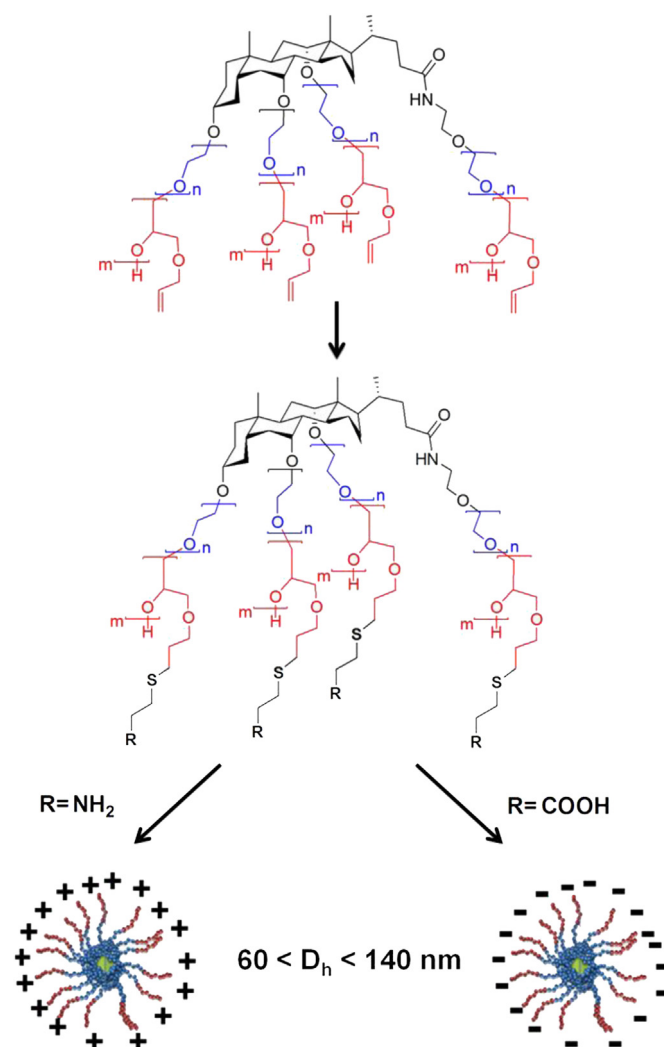
2.2. Functionalization of the star block copolymers

The modifications of allyl groups were conducted following an earlier procedure [13]. To obtain CA(EG_{*n*}-*b*-AGE_{*m*}-COOH)₄, the addition of 3-mercaptopropionic acid on CA(EG_{*n*}-*b*-AGE_{*m*})₄ was performed by dissolving 1 g polymer in 10 mL dry THF. Then, 8 molar equivalent of 3-mercaptopropionic acid and 0.30 equiv. AIBN per double bond were successively added, and the solution was refluxed for 5 h. The most volatile compounds were removed with a rotary evaporator and the resulting viscous liquid was purified by dialysis for 3 days (MWCO 3500 Da) with a yield of 75%. To obtain CA(EG_{*n*}-*b*-AGE_{*m*}-NH₂)₄, CA(EG_{*n*}-*b*-AGE_{*m*})₄ was dissolved in dry methanol (10 mL), 8 equiv. of cysteamine hydrochloride and 1 equiv. of AIBN per double bond were added and let to reflux for 36 h. Methanol was evaporated and the residual syrup of CA(EG_{*n*}-*b*-AGE_{*m*}-NH₂)₄ was purified by dialysis for 3 days (MWCO of 3500 Da) with a yield of 75%. ¹H NMR spectra (Figure S3) confirmed that the efficiency of the addition of thiolated compounds was above 95% (disappearance of vinyl proton peaks of the AGE groups, according to an earlier report [13]).

3. Results and discussion

3.1. Aggregation and thermo-responsiveness of CA(EG_{*n*}-*b*-AGE_{*m*})₄

Since both the PAGE block and the steroid ring of CA core are hydrophobic, CA(EG_{*n*}-*b*-AGE_{*m*})₄ polymers show strong tendency for



Scheme 1. Structures of CA(EG_{*n*}-*b*-AGE_{*m*})₄ star block copolymers, and the functionalized star polymers bearing carboxylic acid and amine functional groups, CA(EG_{*n*}-*b*-AGE_{*m*}-COOH)₄ and CA(EG_{*n*}-*b*-AGE_{*m*}-NH₂)₄, and a schematic of their micellization in aqueous solution. *n* = 11, 21, 28, or 31; *m* = 6 or 11.

aggregation in aqueous solutions. This has been demonstrated by the low critical aggregation concentrations (CAC, Table 1) of the most hydrophilic polymers at 5 °C; 0.5 mm for CA(EG₂₈-*b*-AGE₁₁)₄ and 0.9 mm for CA(EG₃₁-*b*-AGE₆)₄. For the ease of adjusting the polymer concentration of the sample, molal concentration is used where 1 mm indicates 1 mmol of solute per 1 kg of solvent [18]. CA(EG_{*n*}-*b*-AGE₁₁)₄ samples with *n* = 11 and 21 do not have measurable CACs because of their high hydrophobicity. The obtained values are significantly lower than those for CA(EG₁₅₋₃₀)₄ or CA(AGE_{8-*b*-EG₁₅₋₄₀)₄ with comparable PEG chain lengths; 15 and 10 mm, respectively [14,18,23]. This difference arises from the hydrophobic PAGE outer block that induces intermolecular aggregation at lower polymer concentrations.}

The aqueous solutions of CA(EG₁₁-*b*-AGE₁₁)₄ become turbid already at 4 °C, while the other CA(EG_{*n*}-*b*-AGE_{*m*})₄ stars show two cloud points upon slow heating (0.1 °C/min) (Fig. 1A, values listed in Table 1), both within a narrow temperature range. We reported earlier that the CPs of different inverse CA(AGE_{*m*}-*b*-EG_{*n*})₄ stars can be tuned over a broad range of temperatures by varying the length of the PEG segments [23]. For CA(EG_{*n*}-*b*-AGE_{*m*})₄ in this case, the CPs increase with the PEG/PAGE molar ratio. The two-step transitions are reversible, but during cooling or upon heating at lower rate

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