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The direct synthesis of sulfobetaine-containing amphiphilic block copolymers and their self-assembly behavior

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ABSTRACT

Diblock copolymers containing the thermo-responsive sulfobetaine, [2-(methacryloyloxy ethyl) dimethyl-(3-sulfopropyl) ammonium hydroxide (DMAPS)], were synthesized by the aqueous RAFT polymerization of DMAPS, followed by direct chain extension in hexafluoroisopropanol (HFIP) with methyl methacrylate (MMA). This was shown to give lower dispersity polymers than RAFT emulsion polymerization. The diblock copolymers self-assembled in water to form micelles, as analyzed by light scattering (LS) and transmission electron microscopy (TEM). Micelles formed from diblocks bearing a long PDMAPS block were shown to swell with temperature, rather than display a traditional UCST cloud point. This was due to the polymers retaining hydrophilicity, even at temperatures well below the UCST for the corresponding PDMAPS homopolymer, as shown by variable temperature NMR. This swelling behavior was utilized in the release of a hydrophobic dye in response to temperature. This approach has great potential for applications in controlled release whilst maintaining the structure of the carrier nanoparticles.

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1. Introduction

Polymeric betaines are a class of zwitterionic polymers in which the cationic and anionic functional groups are located on the same monomer unit [1]. This unique functionality allows the polymer to undergo different types of self-association, from intramonomer, to intrachain and interchain aggregation, leading to salt-responsive and thermo-responsive behavior [2]. These polymers are often insoluble in pure water, at room temperature, but increase in solubility with the addition of salt [1,3–6]. Betaines can be further subdivided into three classes; sulfobetaines [6], phosphobetaines [7], and carboxybetaines [8], which differ in the chemical nature of the ionic groups. Sulfo- and phosphobetaines have been shown to be biocompatible, [9–14] to reduce bacterial adhesion and protein fouling [10,15] and are potentially finding uses in gene delivery, [16] blood-inert surfaces [17], and wound care [18]. Some sulfobetaines also display an upper critical solution temperature (UCST) thermo-responsive behavior, with the overall molecular weight of the polymer affecting the UCST cloud point [19–22]. An additional benefit of sulfobetaines is that the zwitterionic functionality is essentially independent of pH.

There are several reports of sulfobetaine monomers being polymerized by RAFT polymerization techniques, both as homopolymers and as block copolymers [3,21–28]. An advantage of this direct polymerization of the sulfobetaine monomer is that it can be carried out in water or salt solutions, thereby avoiding the need for organic solvents. The ability to synthesize betaine-containing diblock copolymers leads to interesting self-assembly and thermo-responsive behavior. Donovan et al.,

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utilized RAFT polymerization to synthesize several diblocks consisting of an N-methylacrylamide sulfobetaine and dimethylacrylamide. These were found to self-assemble into micelles in pure water but formed unimers upon dissolution into 0.5 M NaCl solution [23]. We recently reported the thermo-responsive disassembly of di- and triblock copolymers consisting of sulfobetaine monomer and poly(oligoethylene glycol) methyl ether methacrylate (POEGMA) and found that the temperature at which disassembly occurs was a result of the overall hydrophilicity of the polymer, provided by the hydrophilic POEGMA blocks [29]. Arotçaréna et al. synthesized a schizophrenic block copolymer consisting of DMAPS and N-isopropylacrylamide, NIPAM, by Atom Transfer Radical Polymerization (ATRP). Self-assembly at temperatures below the UCST of the sulfobetaine block resulted in micelles with a sulfobetaine core and a hydrated PNIPAM corona, whilst at temperatures above the LCST of the NIPAM block, inverse micelles with the NIPAM block as the core and the sulfobetaine block as the hydrophilic corona were formed [9]. A similar example utilizes a diblock of a methacrylamido sulfobetaine and NIPAM synthesized by RAFT polymerization [21].

These previous examples all demonstrate amphiphilic copolymers where the non-betaine block is, under the correct conditions, hydrophilic. There are fewer examples where a permanently hydrophobic block is utilized. One reason for this is the difficulty in selecting a solvent in which both the betaine block and the hydrophobic block are soluble.

One way to address this problem is to utilize a post-polymerization betainization method, whereby the corresponding tertiary amino-monomer is polymerized in a suitable solvent and then the sulfonate group is introduced by reaction with 1,3 propane sultone or larger ring derivatives [25–27,30,31]. Copolymerization of the tertiary amine monomer with the desired hydrophobic monomer would then give access to sulfobetaine-containing polymers with hydrophobic fractions [25–27,32–34]. However, a disadvantage of this route is the toxicity of the sultones required for modification and often for more hindered tertiary amines, the reaction takes several days and does not go to completion [27,30,35]. Woodfield et al. utilized a slightly different method, whereby they synthesized a homopolymer of pentafluorophenyl acrylate and then modified by post-polymerization methods using a mixture of zwitterionic amine and hydrophobic amines, such as benzyl amine and pentyl amine. The UCST of the resulting polymer increased as the incorporation of benzyl amine, and therefore the overall hydrophobicity of the polymer, increased. However, an increase in the incorporation of pentyl amine did not result in a changing UCST, which was attributed to entropic contribution from the flexible pentyl chains [36].

The direct copolymerization of hydrophobic and sulfobetaine monomers is a tougher synthetic challenge, owing to the poor solubility of the sulfobetaine block. Free radical copolymerization of sulfobetaine and hydrophobic monomers has been attempted in various solvents, including in DMSO [37,38], ethanol [39], trifluoroethanol [40], acetonitrile/water mixtures [41] and in water as an emulsion polymerization [42,43]. However, for these solvents solubility of the growing polymer chain is problematic and can only be achieved at low sulfobetaine loadings. Free radical copolymerization of a sulfobetaine monomer and ethyl acrylate in ethanol resulted in the resulting polymer being insoluble at zwitterionic loadings higher than 10 mol% [44]. Ionic liquids have also been investigated as a better solvent for this type of copolymerization [41,45], and whilst a sulfobetaine homopolymer became insoluble during the polymerization, copolymers of *n*-butyl acrylate and sulfobetaine monomer formed a transparent gel. However purification proved problematic, as separation of the ionic liquid from the zwitterionic polymer was difficult [41].

Herein we report the direct synthesis of sulfobetaine-containing amphiphilic diblock copolymers, in a suitable solvent for both the sulfobetaine macroCTA and the growing hydrophobic chain, by RAFT polymerization and report on their self-assembly and thermo-responsive behavior. This is of interest because it allows easy access to well-defined amphiphilic betaine-containing polymers, and therefore higher order polymer structures, without the need for arduous post-polymerization modification steps.

2. Experimental

2.1. Materials

[2-(Methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide (DMAPS), methyl methacrylate (MMA), 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPTA) and 4,4'-azobis(4-cyanopentanoic acid) (ACVA) were used as received from Aldrich and Fluka unless otherwise stated. AIBN [2,2'-azobis(2-methylpropionitrile)] was recrystallized twice from methanol and stored in the dark at 4 °C. Hexafluoroisopropanol (HFIP) was obtained from Fluorochem and Apollo.

2.2. Characterization

¹H Nuclear magnetic resonance (NMR) experiments were performed on a Bruker 400 FT-NMR spectrometer operating at 400 MHz using deuterated solvents. Chemical shifts are reported in parts per million relative to H₂O (4.79 ppm) or HFIP (4.4 ppm). Spectra were recorded at either 25 °C or 45 °C. Size exclusion chromatography (SEC) measurements were obtained in either HPLC grade HFIP at a flow rate of 1 mL min⁻¹, on a set of two HFIPgel columns plus a guard column or in pH 8.2 phosphate buffer at a flow rate of 1 mL min⁻¹, on a set of one PL aquagel OH 50 and one PL aquagel mixed M plus a PL aquagel OH guard column. Cirrus SEC software was used to analyze the data using poly(methylmethacrylate) (PMMA) or poly(ethylene glycol) (PEG) standards.

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