



A brief review of ‘schizophrenic’ block copolymers

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Available online 1 September 2005

Abstract

Recent progress in the synthesis of so-called ‘schizophrenic’ water-soluble block copolymers is reviewed. The original report in this new sub-field involved a tertiary amine methacrylate-based AB diblock copolymer synthesized by group transfer polymerization that was both pH- and salt-responsive, allowing the formation of either A-core or B-core micelles in aqueous solution. A second example involved a poly(propylene oxide)-tertiary amine methacrylate diblock copolymer synthesized via atom transfer radical polymerization (ATRP) that exhibited both pH- and thermo-responsive behavior. More recently, several examples of wholly pH-responsive zwitterionic diblock copolymers (prepared via ATRP, usually using protecting group chemistry) have been reported, with their aqueous solution behavior being characterized with varying degrees of precision. The synthesis and characterization of purely thermo-responsive diblock copolymers is also discussed, along with the first example of an ABC triblock copolymer that is capable of forming a ‘trinity’ of micelles in aqueous solution at 20 °C simply by adjusting the solution pH. In this remarkable final example, the cores of the three types of micelles are formed by hydrophobic forces, polyion complexation and hydrogen bonding, respectively.

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Keywords: Block copolymer; Micelle; Water-soluble polymers; Schizophrenic; Self-assembly

1. Introduction

Since 1998 numerous examples of novel water-soluble diblock copolymers that exhibit so-called ‘schizophrenic’ character have been reported. That is, the copolymer chains can self-assemble in dilute

aqueous solution in the absence of any organic co-solvent to form *two* distinct micelle structures. In each case, the individual blocks can be independently tuned to become either hydrophilic or hydrophobic by subtle adjustment of the solution temperature, solution pH or ionic strength. The phrase ‘schizophrenic block copolymers’ was coined by our research group to describe this behavior, which is not exhibited by conventional small molecule surfactants.

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2. Experimental

Full experimental details of the synthesis and aqueous solution characterization of each of the various literature examples of ‘schizophrenic’ diblock copolymers (see below) have already been published elsewhere [1–14] and the reader is referred to the original literature for further details. The chemical structures and acronyms of the various ‘schizophrenic’ diblock copolymers described in this review article are shown in Fig. 1.

3. First example of a ‘schizophrenic’ diblock copolymer

In the first reported example [1], the diblock copolymer was based on two tertiary amine methacrylates, namely 2-(diethylamino)ethyl methacrylate [DEA] and 2-(*N*-morpholino)ethyl methacrylate [MEMA] (see Fig. 2). These two monomers contain no labile protons and thus can be directly polymer-

ized using group transfer polymerization [GTP], which is particularly well suited for the synthesis of controlled-structure methacrylic copolymers [15]. At pH 6 this PMEMA–PDEA diblock dissolved molecularly in dilute aqueous solution at 20 °C (under these conditions the neutral PMEMA block is hydrophilic and non-ionic, whereas the PDEA block is protonated and hence soluble as a cationic polyelectrolyte). At pH 8.5, the PDEA block is deprotonated and becomes hydrophobic, leading to PDEA-core micelles, as judged by dynamic light scattering (DLS) studies. On the other hand, if sufficient electrolyte is added to the original solution at pH 6, the PMEMA block can be selectively salted out to produce PMEMA-core micelles. The micelle structures postulated on the basis of chemical intuition (and prior knowledge of the aqueous solution behavior of the PMEMA and PDEA homopolymers) were confirmed using ¹H NMR spectroscopy: no PDEA signals were detected for the PDEA-core micelles and the PMEMA signals were suppressed for the PMEMA-core mi-

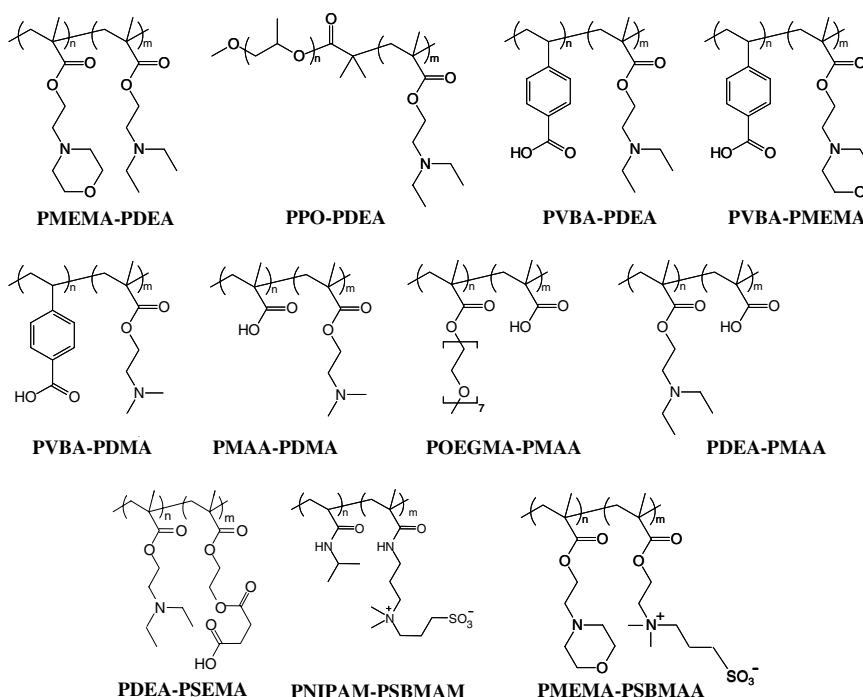


Fig. 1. Chemical structures and acronyms of the various ‘schizophrenic’ diblock copolymers discussed in this review article. In each case micellar self-assembly occurs in dilute solution on adjusting the pH, temperature or ionic strength.

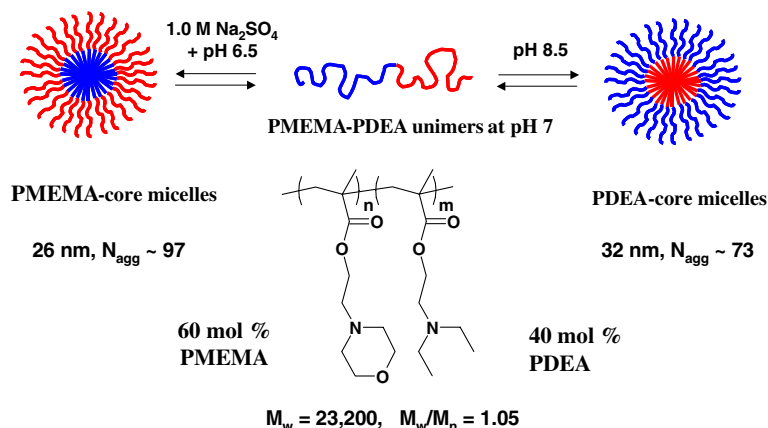


Fig. 2. The ‘schizophrenic’ behavior exhibited by a PDEA–PMEMA diblock copolymer in dilute aqueous solution: PDEA-core micelles are formed above pH 8, whereas PMEMA-core micelles can be formed at around pH 6.5 on addition of sufficient electrolyte.

celles. In a follow-up collaborative paper with Eastoe’s group at Bristol and Tuzar at the IMC in Prague [2] the effect of block asymmetry was examined and the two types of near-monodisperse micelles were characterized by both small-angle neutron scattering (SANS) and laser light scattering (DLS and SLS). For one PMEMA–PDEA diblock copolymer (comprising 60 mol% MEMA; $M_n = 24,700$; $M_w/M_n = 1.10$) micelle aggregation numbers were estimated to be 74 for the PDEA-core micelles and 97 for the PMEMA-core micelles. Since DLS studies indicated that the PMEMA-core micelles had a mean diameter of 26 nm, whereas the PDEA-core micelle diameter was 33 nm, it was concluded that the former micelles must be significantly more compact than the latter. Surface light scattering studies also indicated relatively low surface tensions (around 33 mN m^{-1}) for the aqueous micellar solutions, as expected.

4. A second generation example of a ‘schizophrenic’ diblock copolymer

In 2001, we reported a second-generation schizophrenic diblock copolymer [3]. In this case, atom transfer radical polymerization (ATRP) chemistry was employed for the copolymer synthesis. ATRP is a well-known example of pseudo-living free radical polymerization [16] and is very tolerant of both protic sources and monomer func-

tionality. A poly(propylene oxide) [PPO] ATRP macro-initiator with a degree of polymerization (Dp) of 33 was prepared by esterification of a monohydroxy-capped PPO precursor using 2-bromoisobutyryl bromide. This macro-initiator was used to polymerize DEA in methanol at 55°C to obtain the desired PPO–PDEA diblock copolymer (see Fig. 3). The PDEA block had a mean Dp of 42 as determined by ^1H NMR and GPC analysis indicated an overall M_w/M_n of around 1.20. As already established for the

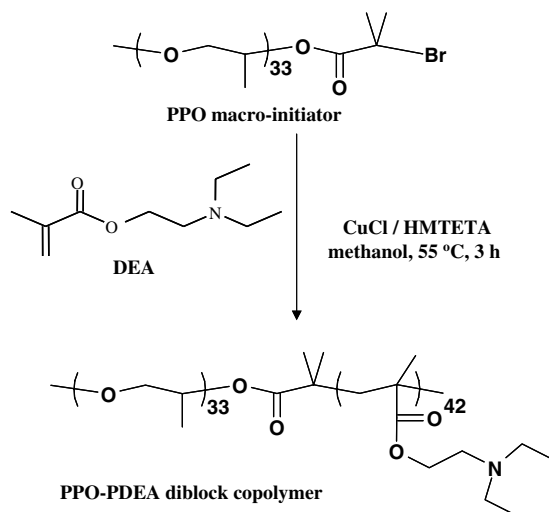


Fig. 3. The ATRP synthesis of a PPO–PDEA diblock copolymer using a PPO-based macro-initiator.

first-generation example, the PDEA block has pH-sensitive water-solubility. The PPO block exhibits inverse temperature solubility behavior: for a D_p of 33 the PPO precursor has an LCST (or cloud point) of around 20 °C in dilute aqueous solution. Thus the PPO–PDEA diblock dissolved molecularly at 5 °C (i.e., below the cloud point of the PPO block) at pH 6, with the PDEA block in its protonated, cationic form. On adjusting the solution pH from 6 to 8.5, DEA-core micelles were formed at 5 °C. Alternatively, warming the original solution at pH 6 up to 40 °C (i.e., well above the cloud point of the PPO block) led to PPO-core micelles. The formation of micelles and their structures were confirmed by DLS and NMR studies. Static light scattering studies indicated micelle aggregation numbers of 650 and 760 for the PDEA-core and PPO-core micelles, respectively.

5. A third generation example of a ‘schizophrenic’ diblock copolymer

Very recently, we reported the ATRP synthesis of a novel zwitterionic diblock copolymer that exhibits ‘schizophrenic’ character merely by adjusting the solution pH [4]. This diblock comprised a weak polyacid, poly(4-vinylbenzoic acid) [PVBA], and a weak polybase, PDEA (see Fig. 4). Both blocks were hydrophobic in their neutral forms and only became water-soluble after ionization [PVBA] or protonation [PDEA]. At intermediate pH, visual inspection indicated that the zwitterionic diblock copolymer was insoluble at around its isoelectric point [IEP] of pH

7.4. ^1H NMR spectra were recorded for the PVBA–PDEA diblock copolymer in d_5 -pyridine, $\text{D}_2\text{O}/\text{DCl}$ and NaOD . In d_5 -pyridine, both blocks were solvated and all the NMR signals expected for the PVBA and PDEA residues were observed. In acidic solution all the PVBA signals were suppressed, suggesting that this block was de-solvated and thus formed the micelle cores. On the other hand, PDEA-core micelles were formed in alkaline media since the PDEA signals were substantially attenuated under these conditions. Both types of micelles were extensively characterized using DLS, SLS, surface tensiometry and zeta potential measurements [4].

Transmission electron microscopy studies of the two types of micelles were also undertaken. The PVBA-core micelles were somewhat larger than the PDEA-core micelles; this may be due to increased spreading and flattening of the former adsorbed micelles on the TEM grid. The rationale here is that the PDEA chains in the micelle coronas are highly cationic and the grid is most likely to have an anionic surface charge. We have previously observed similar effects for adsorbed micelles with cationic coronas on anionic mica surfaces using atomic force microscopy [17].

If the PDEA block is replaced with a PMEMA block the resulting PVBA–PMEMA diblock copolymer also exhibited schizophrenic character but with some differences [5]. In the absence of added salt PVBA-core micelles were formed in acidic media but PMEMA-core micelles were not formed in alkaline media. Also, no precipitation occurred at the IEP, since in this particular case there is only very low charge density on both

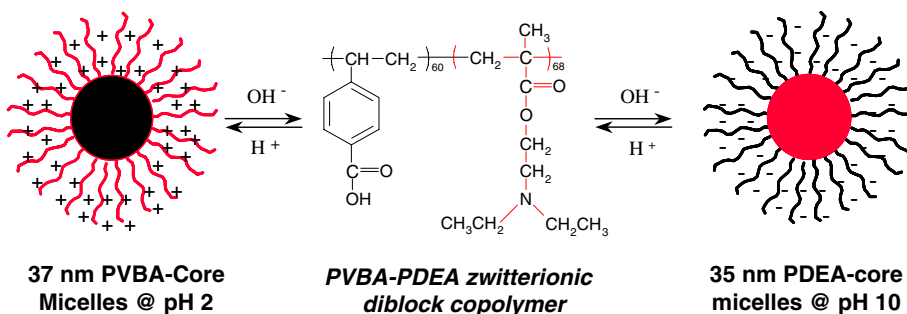


Fig. 4. pH-modulated micellar self-assembly behavior of the PVBA–PDEA zwitterionic diblock copolymer.

blocks, so electrostatic attraction is minimized. However, in the presence of sufficient added salt precipitation at the IEP was observed and PMEMA-core micelles were formed in alkaline media, particularly at elevated temperatures. In as yet unpublished work, we have also examined PVBA–PDMA diblock copolymers, where DMA is 2-(dimethylamino)ethyl methacrylate. The expected schizophrenic character was again observed, with the PVBA block being pH-responsive and the PDMA block being thermo-responsive.

6. Other literature examples of schizophrenic diblock copolymers

There are relatively few well-documented examples of schizophrenic diblock copolymers in the literature. As we have seen from the preceding discussion, a wide range of experimental techniques is required to verify schizophrenic behavior. In particular, ^1H NMR spectroscopy is invaluable since this technique indicates which block becomes de-solvated and is thus located in the hydrophobic micelle core. In this context, Jerome et al. [10] reported that zwitterionic diblock copolymers based on DMA and methacrylic acid [MAA] were capable of forming both PDMA-core and PMAA-core micelles under appropriate aqueous solution conditions. However, the dimensions of the observed colloidal aggregates are probably too large to be considered true micelles and it is very difficult to verify that PMAA-core micelles are formed by ^1H NMR spectroscopy since there are no unique signals due to the MAA residues. Similarly, we have used DLS to show that a diblock copolymer based on MAA and methoxy-capped oligo(ethylene glycol) methacrylate [OEGMA] forms two types of aggregates in aqueous solution but it was not possible to obtain conclusive spectroscopic evidence for PMAA-core micelles [6]. More recently, Gan and co-workers [11] have prepared PMAA–PDEA diblock copolymers using ATRP combined with protecting group chemistry, but again unequivocal confirmation of the formation of PMAA-core micelles was not possible.

7. Technical problems with the synthesis of ‘schizophrenic’ diblock copolymers

Although of considerable academic interest, most of the published examples of ‘schizophrenic’ block copolymers reported to date suffer from one or more problems. For example, GTP chemistry is very moisture-sensitive and requires a relatively expensive silyl ketene acetal initiator, making scale-up syntheses of the PMEMA–PDEA diblock copolymer somewhat problematic. Moreover, the salt-induced micellization of the PMEMA block is a rather inconvenient phase transition from both an academic and an industrial viewpoint and MEMA is a relatively expensive speciality monomer.

The ATRP synthesis of the PPO–PDEA diblock is reasonably convenient but the fact that neither of the micellar forms of this copolymer are stable at room temperature does not augur well for potential applications. Although perhaps the most interesting example from an academic viewpoint, the pH-responsive PVBA–PDEA zwitterionic diblock is probably the least commercially attractive system since its ATRP synthesis is rather inefficient, involves a very expensive monomer (VBA) and also requires protecting group chemistry. Thus there is still considerable scope for more attractive syntheses of schizophrenic diblock copolymers. One notable advance in this regard is the recent report by Bories-Azeau et al. [7], who have shown that well-defined zwitterionic diblock copolymers can be prepared via a relatively atom-efficient two-step synthesis without recourse to protecting group chemistry (see Fig. 5). First, ATRP is used to prepare diblock copolymer precursors from a tertiary amine methacrylate and a hydroxy-functional monomer such as 2-hydroxyethyl methacrylate [HEMA] or 2-hydroxypropyl methacrylate [HPMA] via a one-pot sequential monomer addition synthesis. Then the hydroxy-functional PHEMA block is converted into a carboxylic acid-functional PSEMA block by reacting with excess succinic anhydride in the presence of pyridine at 20 °C. The dilute aqueous solution behavior of the resulting zwitterionic diblock copolymers is quite similar to that of the PVBA–PDEA diblock copolymer described by Liu and

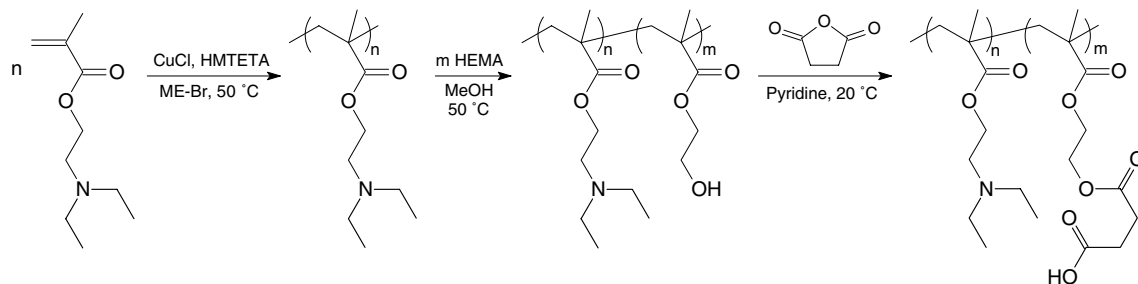


Fig. 5. Preparation of a pH-responsive zwitterionic PDEA-PSEMA diblock copolymer from an ATRP-synthesized hydroxy-functional diblock copolymer precursor using excess succinic anhydride under mild conditions.

Armes [4]. The acidic PSEMA block is hydrophobic in its neutral form at low pH and forms the micelle cores, with the tertiary amine methacrylate block forming a cationic corona. Conversely, the tertiary amine methacrylate-based chains become the hydrophobic core-forming block in alkaline media, with the ionized PSEMA chains forming the anionic micelle corona.

8. Purely thermo-responsive diblock copolymers

Most non-ionic water-soluble polymers exhibit so-called inverse temperature-solubility behavior: they are soluble in aqueous solution at lower temperatures but precipitate from solution on heating to the lower critical solution temperature (LCST; sometimes called the cloud point). However, a number of polysulfobetaines exhibit upper critical solution temperature (UCST) behavior because a certain minimal amount of thermal energy is required to overcome the electrostatic attractive forces operating between the cationic and anionic charges that comprise the sulfobetaine residues [18]. Laschewsky and co-workers used this knowledge to synthesize the first example of a purely thermo-responsive ‘schizophrenic’ diblock copolymer [12,13] using reversible addition fragmentation chain transfer (RAFT) chemistry [19]. The LCST block was prepared first by homopolymerizing *N*-isopropyl acrylamide [NIPAM], followed by chain extension using a commercially available sulfobetaine methacrylamide [SBMAM] to produce the UCST block. The resulting diblock copolymer was molecularly soluble in aqueous

solution between 20 and 34 °C, formed PSB-MAM-core micelles below its UCST of 20 °C and formed PNIPAM-core micelles above 34 °C. However, the RAFT chemistry used for the block copolymer synthesis was far from optimized, as acknowledged by the authors. The final PNIPAM-PSBMAM diblock copolymer polydispersity was relatively high ($M_w/M_n = 1.35$), only rather poor overall conversions were achieved and contamination with *both* homopolymers could not be ruled out. This elegant work made us realize that we had actually synthesized a closely related purely thermo-responsive ‘schizophrenic’ diblock copolymer five years prior to Laschewsky’s reports, although we had not appreciated it at the time. One of my former PhD students, Vural Bütün, had previously used GTP to prepare a PMEMA-PDMA diblock copolymer precursor, which was then selectively quaternized with 1,3-propanesultone to produce a PMEMA-PSBMA methacrylic diblock copolymer [20]. Unlike Laschewsky’s PNIPAM-PSBMAM diblock copolymer, this PMEMA-PSBMA diblock copolymer (51 mol% SBMA; $M_n = 42,500$) was obtained in excellent yield, had a much narrower polydispersity ($M_w/M_n = 1.08$) and suffered from no discernable homopolymer contamination. A phase diagram for this diblock copolymer is shown in Fig. 6. According to our related DLS and variable temperature ^1H NMR studies on this PMEMA-PSBMA diblock copolymer, PSBMA-core micelles are formed below around 20 °C, molecular dissolution occurs between 20 and 50 °C, and PMEMA-core micelles are formed above approximately 50 °C [8]. This latter critical micellization

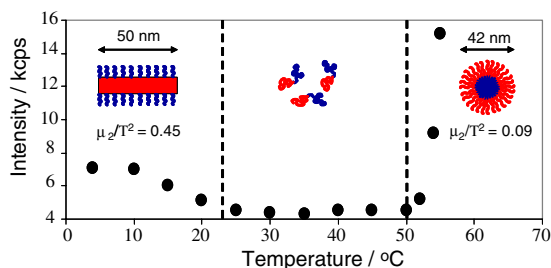


Fig. 6. Micellization behavior of a dilute aqueous solution of a PMEMA–PSBMA thermo-responsive ‘schizophrenic’ diblock copolymer. Below 20 °C, PSBMA-core micelles are formed due to the UCST behavior of the PSBMA block, between 20 and 50 °C the diblock copolymer is molecularly dissolved, and above 50 °C PMEMA-core micelles are formed due to the LCST behavior of the PMEMA block.

temperature is only slightly higher than the known cloud point for PMEMA homopolymer [21]. The latter micelles are spherical, near-monodisperse and around 39–45 nm, whereas the PSBMA-core micelles appeared, on first inspection, to be spherical, polydisperse and around 50 nm. However, subsequent detailed small angle neutron scattering (SANS) studies on a series of PMEMA–PSBMA

diblock copolymers undertaken by Stancik and Gast indicated that the PSBMA-core micelles were actually anisotropic (either rod-like or worm-like), rather than spherical. These SANS studies will be reported elsewhere in due course [22]. The most recent contribution to purely thermo-responsive diblock copolymers is from a Japanese group, who have used FT-IR spectroscopy to monitor changes in hydration with increasing temperature for a RAFT-synthesized diblock copolymer based on SBMA and *N,N*-diethyl acrylamide [14]. Finally, two examples of ‘schizophrenic’ block copolymers with *non-linear* (i.e., Y-shaped) architectures have just been reported by Cai and co-workers [23,24].

9. A ‘trinity’ of micelles formed by a novel ABC triblock copolymer

The inspiration for this work came from our earlier study of the aggregation behavior of a binary mixture of a PEO–PDEA diblock copolymer and a PMAA homopolymer [25]. A PEO-based macro-initiator was used to first polymerize

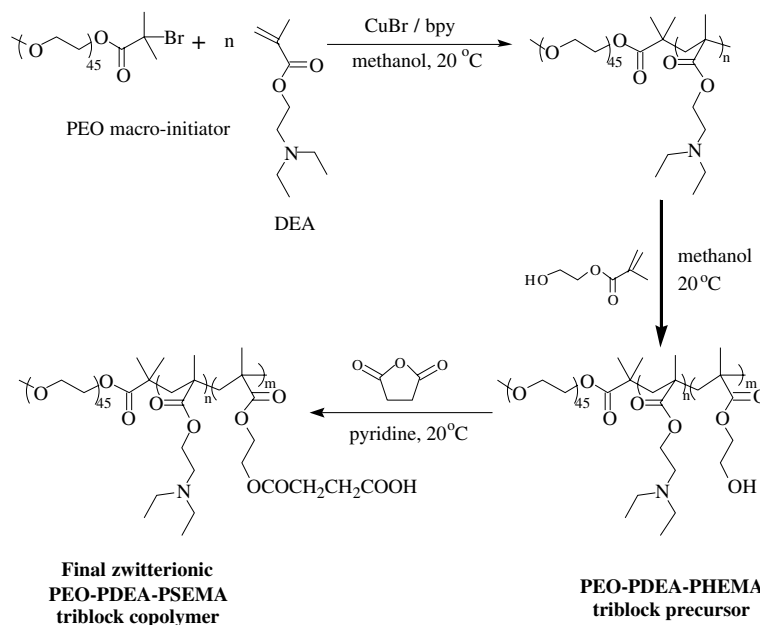


Fig. 7. One-pot ATRP synthesis of a novel ABC zwitterionic triblock copolymer by sequential monomer addition. A PEO-based macro-initiator is used to polymerize first DEA, followed by HEMA. The hydroxy groups of the HEMA block are then esterified using excess succinic anhydride under mild conditions to obtain the final PEO–PDEA–PSEMA triblock copolymer.

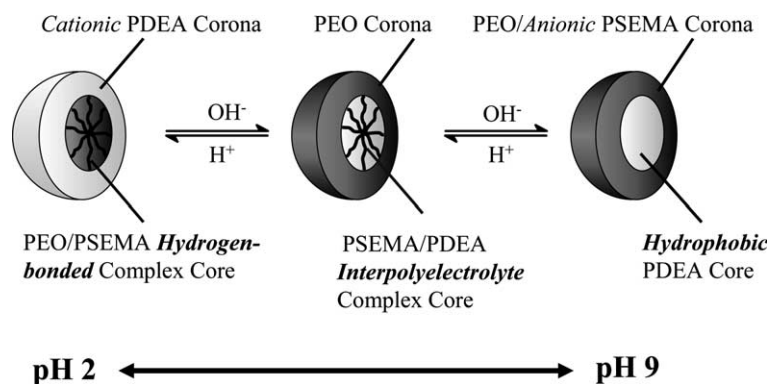


Fig. 8. Unprecedented micellar self-assembly behavior exhibited by a novel zwitterionic PEO–PDEA–PSEMA triblock copolymer: a ‘trinity’ of micelles in aqueous solution at 20 °C may be prepared simply by adjusting the solution pH.

2-(diethylamino)ethyl methacrylate (DEA) and then 2-hydroxyethyl methacrylate (HEMA) in a one-pot synthesis via ATRP in methanol at 20 °C. The resulting PEO–PDEA–PHEMA triblock copolymer precursors were successfully converted into the corresponding PEO–PDEA–PSEMA zwitterionic triblock copolymers by esterification of the hydroxy groups on the HEMA block using excess succinic anhydride in pyridine under mild conditions (see Fig. 7). A ‘trinity’ of micellar aggregates was formed by these PEO–PDEA–PSEMA triblock copolymers in aqueous solution simply by adjusting the solution pH at ambient temperature (see Fig. 8) [9]. The driving forces for forming these three types of micelles were hydrogen bonding at low pH, interpolyelectrolyte complexation at intermediate pH and hydrophobic interactions at high pH, respectively. The hydrogen-bonded PSEMA/PEO-core micelles formed at low pH could be disrupted at higher temperatures or by addition of methanol, leading to PSEMA-core aggregates. The PSEMA/PDEA interpolyelectrolyte micelles formed at around the IEP were very sensitive to the ionic strength of the aqueous solution. The hydrophobic DEA-core micelles formed in alkaline solution had mixed PEO + PSEMA coronas. As far as we are aware, the rich aqueous solution behavior of this new class of ABC triblock copolymers is unprecedented since, for the first time, three types of micelles are formed in aqueous solution by a single component system. The phrase ‘schizophrenic’ seems to be rather inadequate to describe the complexity of this system!

10. Prospect

Schizophrenic water-soluble block copolymers are a fascinating new class of polymeric surfactants that exhibit unique self-assembly behavior in dilute aqueous solution. A wide range of examples has been reported to date, with various synthetic strategies being employed. However, as yet no suitable applications have been identified for these remarkable copolymers, which hitherto remain an academic curiosity. Identifying a realistic application is now considered to be essential if this field is to receive further impetus.

Acknowledgments

EPSRC is thanked for financial support in the form of post-doctoral fellowships for S.L. (GR/N17409) and Y.C. (GR/R64223). X.B.A. thanks Akzo Nobel (Holland) for a PhD studentship and J.V.M.W. acknowledges an EPSRC studentship and CASE support from Cognis Performance Chemicals (Hythe, UK).

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