

Preparation of PEO-*b*-P2VPH⁺-S₂O₈²⁻ micelles in water and their reversible UCST and redox-responsive behavior†

Xuan Jia, Daoyong Chen* and Ming Jiang

Received (in Cambridge, UK) 20th January 2006, Accepted 20th February 2006

First published as an Advance Article on the web 10th March 2006

DOI: 10.1039/b600859c

We report here the preparation of PEO-*b*-P2VPH⁺-S₂O₈²⁻ micelles and their reversible multi-responsive behavior.

Polymeric micelles whose formation and disruption can be reversibly controlled by temperature have attracted much attention due to their great potential in the preparation of controlled drug-delivery systems,¹ catalysts² etc. Among them, the polymeric micelles with a lower critical solution temperature behavior (termed as LCST micelles here) have been extensively studied. The LCST micelles (e.g. the micelles with poly(*N*-isopropylacrylamide) (PNIPAM) as the core) will undergo dissociation when the temperature decreases to the critical temperature, and form again when the temperature rises above it.³ Contrary to LCST micelles, UCST micelles (the polymeric micelles with an upper critical solution temperature behavior) form when the temperature is below a critical temperature and dissociate when the temperature is above it. The UCST micelles reported include the water born micelles formed by a zwitterionic block copolymer,⁴ and the micron-scale spherical aggregates formed in chloroform driven by H-bonding between a copolymer and a complementary bifunctional cross-linker.⁵ Different from LCST micelles whose core is usually formed by a LCST polymer like PNIPAM,⁶ UCST micelles reported have a core composed of a polymer complex.^{4,5} Actually, the formation of UCST micelles is induced by the complexation between the core-forming components, and their dissociation results from the thermal induced decomplexation. Although the micelles formed by inter-polymer complexation induced micellization have been widely studied, most of them are not UCST micelles since in most cases the core-forming polymer-polymer complex keeps stable even when the temperature increases to the boiling point of the solvent. As a result, although UCST micelles are expected to be very promising in applications, the number of UCST micelle systems reported is limited.

In this communication, we will report the preparation of water soluble micelles based on poly(ethylene oxide)-*b*-(protonated P2VP) (PEO-*b*-P2VPH⁺)-potassium persulfate (K₂S₂O₈) complex. The ion-ion interaction leads to the ionic cross-linking of P2VPH⁺ block chains by the divalent anion S₂O₈²⁻, which leads to the micellization of the block copolymer PEO-*b*-P2VPH⁺, forming the micelles with P2VPH⁺-S₂O₈²⁻ complex as the core and PEO block chains as the shell. Our study also demonstrates that the micelles have reversible multi-responsive behavior: they are UCST micelles

and the critical temperature for dissociation can be adjusted in the range of 40 to 70 °C; the micelles are sensitive to a reductant, *i.e.* the micelles dissociate promptly when mixed with a small amount of reductant, and after further addition of K₂S₂O₈, the micelles form again. We believe that this reversible multi-responsive behavior will make the micelles promising in addressing related theoretical and practical problems.

It is known that in aqueous solution of PEO-*b*-P2VP, there is a critical pH value above which the copolymer chains associate. Usually, the critical pH value is in the range of 4 to 6,^{7,8} depending on the structural parameters of the copolymer. In the present study, PEO₃₂₉-*b*-P2VP₁₂₈ (the subscripts are the average number of the repeat units) was dissolved in pH 1.3 aqueous solution at a copolymer concentration of 1.0 mg mL⁻¹. At such a low pH,† the copolymer is molecularly dispersed and almost all of the pyridine units of the P2VP block chains are protonated (the protonated P2VP block is denoted as P2VPH⁺ in this paper). However, when the aqueous copolymer solution was mixed with K₂S₂O₈ at the molar ratio of K₂S₂O₈ to the pyridine units of 1 : 1, blue opalescence appeared spontaneously. The resultant mixture solution was characterized by dynamic light scattering (DLS). The characterization data demonstrate the formation of aggregates. The average hydrodynamic radius <R_h> of the aggregates is 105 nm. The aggregates have a narrow size distribution with a regular spherical morphology as indicated by the relatively low polydispersity index ($\mu_2/\langle I \rangle^2 = 0.09$),⁹ and a linear relation of $\Gamma \sim q^2$ obtained by our investigation of the angular dependence of laser light scattering of the aggregates.¹⁰ In our control experiment, we carried out the micellization of PEO₃₂₉-*b*-P2VP₁₂₈ in aqueous solution at pH > 6.0 by dialyzing the copolymer solution in THF against water. The <R_h> of the resultant micelles is 45 nm, which is much smaller than that of the micelles obtained in the present study. We have reported in our previous study that the average size of the micelles formed by cross-linking one of the blocks of a block copolymer in its common solvent is remarkably larger than that of the micelles formed by the same block copolymer in its selective solvent.¹¹ It was also reported by Kabanov *et al.* that the <R_h> of PEO₁₇₀-*b*-PMA₁₈₀ (poly(methacrylate acid)) micelles with the cross-linked PMA as the core can be as large as 144 nm at a relative high pH.¹²

It is known that the average size of particles observed by electron microscopy may be either similar to or different from the average size of the same particles measured by DLS. The causes for the difference were analyzed in the reported studies.^{13,14} In the present study, the average size and the size distribution of PEO₃₂₉-*b*-P2VP₁₂₈-S₂O₈²⁻ micelles observed by SEM are close to the corresponding results obtained by DLS characterization. Our

Department of Macromolecular Science and the Key Laboratory of Molecular Engineering of Polymers, Fudan University, Shanghai 200433, China. E-mail: chendy@fudan.edu.cn; Fax: 86 21 65640293; Tel: 86 21 65643989

† Electronic supplementary information (ESI) available: experimental details. See DOI: 10.1039/b600859c

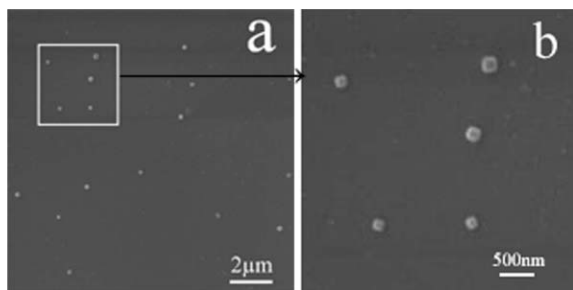


Fig. 1 (a) SEM image of PEO-*b*-P2VPH⁺-S₂O₈²⁻ micelles reduced to 3/10 of the original image. (b) The particles shown at the magnification of the original SEM image.

SEM observations demonstrate that the micelles have an average radius around 100 nm and a narrow size distribution.

¹H NMR measurements confirm the core-shell structure of the aggregates with PEO as the shell and P2VPH⁺-S₂O₈²⁻ as the core. The spectrum of PEO-*b*-P2VPD⁺ in D₂O (pD = 1.3) and that of the PEO-*b*-P2VPD⁺-K₂S₂O₈ mixture in D₂O at 25 °C (pD = 1.3) are presented in Fig. 2 as spectra A and B, respectively. In spectrum A, the peaks b, c and d are assigned to the protonated P2VP block (P2VPD⁺), as indicated in the inset. Compared with spectrum A, after mixing of the copolymer with K₂S₂O₈ in D₂O at 25 °C, all the signals assigned to the P2VPD⁺ block (peaks b, c and d) disappear (spectrum B). As demonstrated in our previous study,^{15,16} the disappearance of the P2VPD⁺ signals is the result of the aggregation of the P2VPD⁺ block chains, since the aggregation leads to the loss in the mobility and the disappearance of the signals of the P2VPD⁺ block chains in the liquid ¹H NMR spectrum. On the contrary, the PEO signal (peak a) at 3.5 ppm is nearly unchanged after the mixing. Therefore, it is concluded that the aggregates are core-shell structured polymeric micelles with PEO as the shell and the aggregated P2VPD⁺ as the core. Obviously, the aggregation of the P2VPD⁺ block chains is caused by the interaction with S₂O₈²⁻, which drives the micellization of the copolymer.

In pH 1.3 aqueous solution, the copolymer PEO-*b*-P2VPH⁺ is molecularly dispersed. As the solution is relatively dilute, when mixed with K₂S₂O₈, an S₂O₈²⁻ anion may interact with one of the protonated pyridine cations at first, forming a 2VPH⁺-S₂O₈²⁻ ion pair (in fact, the ion pair is a univalent anion, denoted as (2VPH⁺-S₂O₈²⁻)⁻¹ here). (2VPH⁺-S₂O₈²⁻)⁻¹ anions will further interact with other protonated pyridine units, leading to the ionic cross-linking of P2VPH⁺ block chains. As 2VPH⁺-S₂O₈²⁻ ion pairs are

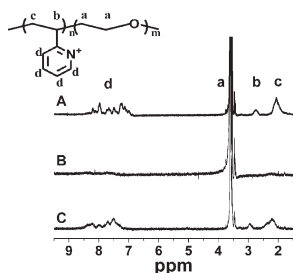


Fig. 2 ¹H NMR spectra of: (A) pure PEO-*b*-P2VP solution at a concentration of 1.0 mg mL⁻¹; (B) the solution of PEO-*b*-P2VPD⁺-K₂S₂O₈ at 25 °C; and (C) the solution of PEO-*b*-P2VPD⁺-K₂S₂O₈ at 45 °C; (in D₂O, pD = 1.3).

negatively charged, they are expected to be soluble in the aqueous solution and no aggregation between them can be observed. The solubility of 2VPH⁺-S₂O₈²⁻ ion pairs is supported by the results of our control experiments where no precipitates were observed by mixing K₂S₂O₈ with equal moles of pyridine or 2-vinylpyridine under identical conditions. Therefore, we believe that it is the ionic cross-linking of P2VPH⁺ block chains that drives the micellization. The micellization of a block copolymer resulting from the cross-linking of one of the blocks has been reported by Yashida¹⁷ and by us.¹⁶

The as-prepared PEO₃₂₉-*b*-P2VPH⁺₁₂₈-S₂O₈²⁻ micelles in pH 1.3 aqueous solution change little in the structure and the size after storing at room temperature for weeks. However, they dissociate promptly when the temperature increases to 40 °C,† as evidenced by the fact that no aggregates can be detected by DLS characterization at the temperature of 40 °C. The dissociation of the micelles is confirmed by our ¹H NMR measurement (spectrum C, Fig. 2). When the solution temperature increases to a temperature above 40 °C from 25 °C, the spectrum of the solution changes from spectrum B to spectrum C. In spectrum C, all the signals associated to the P2VPD⁺ block chains appear again, and the relative intensity of the signals in spectrum C is close to that of the respective ones in spectrum A (using the PEO signal at 3.5 ppm as internal standard), indicating that most of the block copolymer chains are molecularly solubilized in the solution, *i.e.* the micelles dissociate at such a temperature. Our further experiments demonstrate that the association and dissociation of the micelles are reversible. Reversibility was exhibited by our turbidity measurements (Fig. 3). Heating the solution at 40 °C resulted in a total loss of turbidity. Upon cooling to room temperature (25 °C), the turbidity was restored. From Fig. 3 one can see that after the first heating-cooling cycle, the turbidity of the solution at 25 °C (the turbidity at point 2) is higher than that of the original micelle solution (the turbidity at point 1). According to Rotello *et al.*, the change arises from the annealing of the initial kinetically formed structures to thermodynamically more stable aggregates upon thermal cycling.⁵ Afterwards, no remarkable change of turbidity was found at either temperature. Apparently, the as-prepared micelles are UCST micelles.

Biggs and Vincent reported that P2VP could be completely oxidised by reacting with peroxyacetic acid at 70 °C for 24 hours.¹⁸ The oxidation is accompanied by a shift in the UV spectrum of the oxidised polymer. However, in the present study, although K₂S₂O₈ is a strong oxidant, we did not find considerable oxidation of the P2VP block, as no such shift was observed in the UV-vis spectrum of the P2VP after the mixing with K₂S₂O₈ for 24 hours and the heating-cooling cycles. This is further supported by our iodimetry measurement.† The measurement detects no remarkable change in the concentration of K₂S₂O₈ after the mixing and the

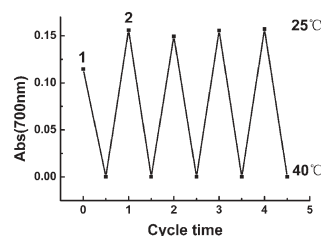
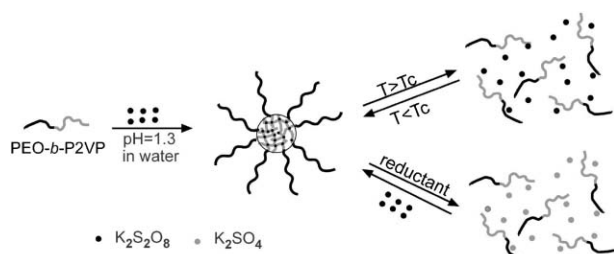


Fig. 3 Solution turbidity of micelles during heating-cooling cycles.



Scheme 1 The schematic presentation of the reversible multi-responsive behavior of PEO-*b*-P2VP- $\text{K}_2\text{S}_2\text{O}_8$ micelles in water. T_C : the upper critical solution temperature.

heating-cooling cycles. Therefore, we believe that the dissociation of the micelles should be the result of the thermal induced decomplexation of the $\text{P2VP}^+\text{-S}_2\text{O}_8^{2-}$ complex rather than the decomposition of $\text{K}_2\text{S}_2\text{O}_8$. As the individual core-forming components P2VP^+ and $\text{S}_2\text{O}_8^{2-}$ are hydrophilic, they will be molecularly solubilized in water after the decomplexation. This leads to the micelle dissociation (as indicated in Scheme 1). Additionally, the critical temperature can be altered through changing the structure parameter of the copolymer. For example, when the copolymer $\text{PEO}_{134}\text{-}b\text{-P2VP}_{251}$ is mixed with $\text{K}_2\text{S}_2\text{O}_8$ under the same conditions, the critical dissociation temperature rises to $70\text{ }^\circ\text{C}$; while when $\text{PEO}_{59}\text{-}b\text{-P2VP}_{14}$ was applied, no micelles can be formed.

As mentioned before, UCST micelles have the cores formed by solvent-philic components complexed with each other. The interaction or complexation between the core-forming components keeps the integrity of the micelles below the critical temperature. We did a lot of research work concerning the polymer-polymer complexation in solution.¹⁹ To our knowledge, most of polymer-polymer complexes are too stable to be decomplexed by raising the temperature to a value below the boiling point of the solvent, so most of the micelles formed by inter-polymer complexation induced micellization are not UCST micelles. Meanwhile, almost none of the micelles formed due to complexation between the polyanion block of a double hydrophilic block copolymer and multi-valent metallic cations (the ionic cross-linking is the driving force) are UCST micelles either, since the interaction is usually strong possibly due to the fact that it is the combination of ion-ion electric interaction and metal-ligand coordination. It seems that the micelles with a core formed by polycations/multi-valent small molecular anions are promising in preparing UCST micelles. In the present work, we found that the interaction between respective CO_3^{2-} , PO_4^{3-} , SO_4^{2-} anions and the polycation P2VP^+ were too weak to drive the micellization of $\text{PEO-}b\text{-P2VP}^+$ with different structural parameters, as no aggregates were formed by the mixing under the identical conditions. On the other hand, the interaction between P2VP^+ block chains of $\text{PEO-}b\text{-P2VP}^+$ and amaranth containing 3 sulfonic groups in each of the molecules is too strong, as the micelles with PEO as the shell and $\text{P2VP}^+\text{-amaranth}$ as the core in water are stable even at $100\text{ }^\circ\text{C}$.

The as-prepared $\text{PEO-}b\text{-P2VP}^+\text{-S}_2\text{O}_8^{2-}$ micelles possess multi-responsive behavior. Besides their thermal response, the micelles are sensitive to reductant as well. Mixed with a small amount of reductant such as oxalic acid, the micelles dissociate promptly as proved by our DLS and turbidity measurements. It is known that the persulfate ions are reduced to SO_4^{2-} by the

reductant. As mentioned before, the interaction between SO_4^{2-} and the P2VP^+ block chains is too weak to drive the micellization. After the addition of $\text{K}_2\text{S}_2\text{O}_8$, the micelles formed again (as indicated in Scheme 1). Such redox-sensitive micelles have the potential to be used as reductant sensors, which, to our knowledge, has never been reported. Besides, the micelles with a core containing a strong oxidant may serve as the microreactor for a redox reaction.

In summary, at ambient temperature, the ionic cross-linking of P2VP^+ by $\text{S}_2\text{O}_8^{2-}$ in water can lead to the micellization of $\text{PEO-}b\text{-P2VP}^+$, forming micelles with PEO as the shell and $\text{P2VP}^+\text{-S}_2\text{O}_8^{2-}$ complex as the core. These are UCST micelles since they dissociate at a temperature above a critical temperature and their formation and thermal induced dissociation are reversible. When the block copolymer $\text{PEO}_{329}\text{-}b\text{-P2VP}_{128}$ is used, the critical temperature is $40\text{ }^\circ\text{C}$. However, the critical temperature can be adjusted by changing the structural parameter of the block copolymer. For example, when $\text{PEO}_{134}\text{-}b\text{-P2VP}_{251}$ is used, the critical temperature is *ca.* $70\text{ }^\circ\text{C}$. Besides, the as-prepared micelles are responsive to a reductant, *i.e.* the micelles dissociate when mixed with a small amount of reductant, and form again after adding $\text{K}_2\text{S}_2\text{O}_8$ to the solution. We believe that these reversible multi-responsive micelles whose formation and dissociation can be reversibly controlled by temperature or by alternate addition of a reductant and $\text{K}_2\text{S}_2\text{O}_8$ will generate much interest in the fields of polymer science and materials.

Notes and references

‡ Actually, the critical temperature fluctuates within the range of $38\text{ }^\circ\text{C}$ ~ $40\text{ }^\circ\text{C}$, as kinetic factors may have a certain effect on the structure of the micelles.

- 1 A. Chilkoti, M. R. Dreher, D. E. Meyer and D. Raucher, *Adv. Drug Delivery Rev.*, 2002, **54**, 613–630.
- 2 D. E. Bergbreiter, B. L. Case, Y. S. Liu and J. W. Caraway, *Macromolecules*, 1998, **31**, 6053–6062.
- 3 M. Shibayama and T. Tanaka, *Adv. Polym. Sci.*, 1993, **109**, 1–62.
- 4 J. V. M. Weaver, S. P. Armes and V. Butun, *Chem. Commun.*, 2002, 2122–2123.
- 5 R. J. Thibault, P. J. Hotchkiss, M. Gray and V. M. Rotello, *J. Am. Chem. Soc.*, 2003, **125**, 11249–11252.
- 6 H. G. Schild, *Prog. Polym. Sci.*, 1992, **17**, 163–249.
- 7 T. J. Martin, K. Prochazka, P. Munk and S. E. Webber, *Macromolecules*, 1996, **29**, 6071–6073.
- 8 J. F. Gohy, S. K. Varshney, S. Antoun and R. Jerome, *Macromolecules*, 2000, **33**, 9298–9305.
- 9 B. Chu, Z. L. Wang and J. Q. Yu, *Macromolecules*, 1991, **24**, 6832–6838.
- 10 W. A. Zhang, X. C. Zhou, H. Li, Y. Fang and G. Z. Zhang, *Macromolecules*, 2005, **38**, 909–914.
- 11 T. R. Hui, D. Y. Chen and M. Jiang, *Macromolecules*, 2005, **38**, 5834–5837.
- 12 T. K. Bronich, P. A. Keifer, L. S. Shlyakhtenko and A. V. Kabanov, *J. Am. Chem. Soc.*, 2005, **127**, 8236–8237.
- 13 H. S. Peng, D. Y. Chen and M. Jiang, *Langmuir*, 2003, **19**, 10989–10992.
- 14 J. F. Gohy, S. Antoun and R. Jerome, *Macromolecules*, 2001, **34**, 7435–7440.
- 15 X. M. Yao, D. Y. Chen and M. Jiang, *J. Phys. Chem. B.*, 2004, **108**, 5225–5229.
- 16 D. Y. Chen, H. S. Peng and M. Jiang, *Macromolecules*, 2003, **36**, 2576–2578.
- 17 E. Yoshida and S. Kunugi, *Macromolecules*, 2002, **35**, 6665–6669.
- 18 S. Biggs and B. Vincent, *Colloid Polym. Sci.*, 1992, **270**, 505–510.
- 19 M. Jiang, M. Li, M. L. Xiang and H. Zhou, *Polymer Synth. Polym. Polym. Complexation*, 1999, **146**, 121–196.