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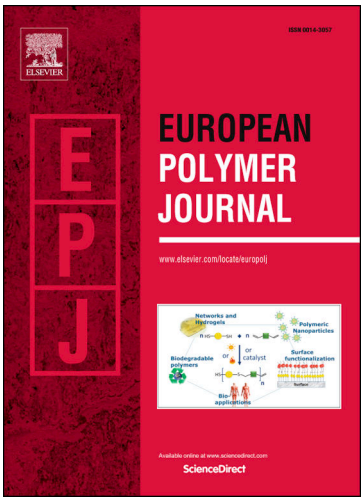

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Effect of end-groups on sulfobetaine homopolymers with the tunable upper critical solution temperature (UCST)

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KEYWORDS: zwitterionic polymers, RAFT polymerization, thermo-responsive, end-group effects

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Abstract

One-step syntheses of well-defined Poly(3-((2-(Methacryloyloxy) ethyl) (dimethyl) ammonio)-1-propanesulfonate) (PDMAPS) with a carboxylic acid end-functional reversible addition-fragmentation chain transfer (RAFT) agent and further end-group modification were described. The upper critical solution temperature (UCST) of homo-zwitterions can be precisely adjusted by the surrounding pH due to the presence of a carboxyl end-group. Meanwhile, after esterification of the carboxylic acid group by methyl, ethyl, hexyl, phenethyl alcohol, UCST of all resulted PDMAPS with ester terminated groups showed more significant increases. Dynamic light scattering (DLS), Zeta-potential and small-angle X-ray scattering (SAXS) results demonstrated that the ionization/protonation from the carboxylic end-group and hydrophobicity of ester groups contribute significantly to the tunability. This end-group modification technique provides an easy and economical way of synthesizing temperature-responsive homo-polyzwitterions with precise and controllable temperature range owing to the designability of RAFT polymerization, where the products are suitable for biomedical and environmental engineering applications.

Introduction

The Zwitterionic polymer is a kind of polyelectrolyte with equivalent positive and negative charge groups on a single chain unit. In recent years, advanced techniques such as “controlled radical polymerization” [1-4] have rapidly promoted research on zwitterionic polymers to a new stage for facile preparation and ease of tunability.[5-11] These polymers have been widely used in anti-fouling and biomedical applications due to their great biocompatibility and responsiveness in temperature.[12-19] Poly(3- ((2-(methacryloyloxy) ethyl) (dimethyl) ammonio) -1-propanesulfonate) (PDMAPS) is one of the most widely studied temperature-responsive polyzwitterions, and shows an upper critical solution temperature (UCST) in aqueous solution. Specifically, at low temperature, the attractive electrostatic interaction leads to significant chain

aggregation behavior and forms a collapsed insoluble state in water. However, increasing the temperature weakens this inter- and intra- interaction, releasing the chains into the solution and leading a phase change. From the thermodynamic view, with solubility surpassing the critical temperature, the mixing entropic ($-T\triangle S_{mix}$) of the Gibbs free energy overcomes the enthalpic contribution ($\triangle H_{mix}$) and, as a result, polymers become soluble.[20] The UCST of PDMAPS is highly related to several factors, including the concentration, molar mass and branching coefficient.[21,22] Nevertheless, two major barriers to PDMAPS responsiveness limit the applicability: (i) As with most UCST systems, the UCST of the PDMAPS increases as the molar mass increases. As a result, it is difficult to reach a practical phase transition temperature suitable for ambient temperature applications in low molar mass.[23] (ii) The anti-polyelectrolyte effect means that responsiveness works only in the condition of extremely low ionic strength.[24-26]

Therefore, developing more effective methods to increase the UCST of polyzwitterions has always been key to broadening the applications of this “smart” materials. A number of ways exist to change the UCST of PDMAPS, which include: gradually increasing the length of one linear alkyl substituent on the nitrogen atom to transfer the UCST to the lower critical solution temperature (LCST);[27] using a hydrophilic spacer group to increase the cloud point (CP) and thereby separate the cationic and anionic moieties;[28] hydrophobically modifying sulfobetaine to make the UCST more accessible;[29] and co-polymerizing the 2-(diisopropylamino)ethyl methacrylate (DPA) with PDMAPS to give the polymer dual thermo-responsiveness.[30] However, the chemistry required to synthesize such responsive monomers or copolymers is complicated and costly; the hydrophobically modified monomer affects the biocompatibility of materials in the biomedical field; the monomer feed ratio and the conversion need to be strictly controlled to achieve multiple responsiveness; increasing UCST compromises response time due to the large proportion of the other component; lacks reproducibility of UCST and adjustable temperature range because of the complicated steps in copolymerization. Accordingly,

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PDMAPS homopolymers with predictable and tunable thermo-responsive properties over a wide temperature range show promise for prospective applications.

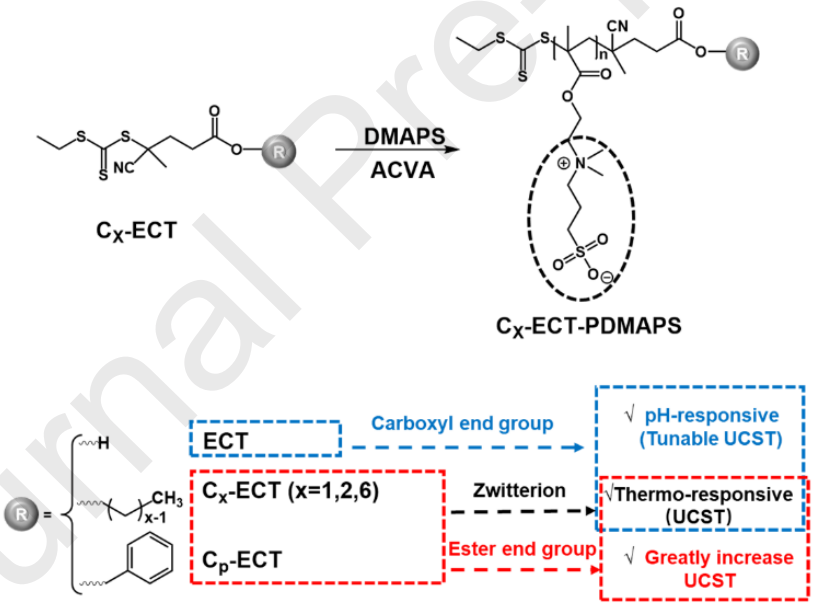
Additionally, end-group effects neglected for decades are beginning to be taken seriously by materials scientists.[31-33] A typical example is poly(*N*-isopropylacrylamide) (PNIPAM) which exhibits a LCST in aqueous solution, where hydrophilic end-group can increase the LCST, while hydrophobic end-group tend to decrease it. Moreover, increasing the molar mass of the polymer with hydrophilic end-group results in a decrease of LCST, but an increase with hydrophobic end-group.[34-35] Unlike PNIPAM, although there has been a good deal of research into the end-group effect on UCST of PDMAPS, the latest progress indicates that there is still a great value in further study in this direction. Armes et al. reported that the terminal carboxyl group can affect the morphology of the non-ionic diblock copolymer assembly by changing the solution's pH.[36] In addition, Davis's group was the first to demonstrate that increasing the end-group hydrophobicity by replacing the carboxylic acid end-group with a methyl ester group led to the formation of vesicles during a polymerization-induced self-assembly (PISA) process.[37] Therefore, it can be seen that with the rapid development of reversible addition-fragmentation chain transfer (RAFT) polymerization, the influence of end groups on polymers should be valued. The "living" and "controlled" advantages of RAFT polymerization give end-group various meaningful potentials: (i) the functional group can be selectively located on the R or Z group of RAFT agent, thus the functional groups' positions in topological polymers could be specified. (ii) The functional end-group could be easily modified after polymerization due to the high end-group fidelity of RAFT polymerization. (iii) The tunability caused by the end-group can be precisely controlled by controlling the length of the polymer or the number of end groups. (iv) The better the molar mass control, the more predictable will be the adjustable range of the polymer caused by end groups.

In this article, to overcome the main barriers of PDMAPS in responsiveness by simple chemistry, RAFT polymerization can be used to prepare PDMAPS

homopolymers with different functionalized end-groups. For the first time, we present the observation that the UCST of PDMAPS with carboxylic acid end-group can be precisely manipulated in a wide range of pH values in aqueous solution, and especially increasing the UCST under extreme acidic condition (pH= 3), moreover, after the simple esterification of the carboxyl end-group, a significant high UCST can be observed even in a salty solution. We are the first to use end-group modification to get the PDMAPS homopolymers which show practical UCST upon the lowest molar mass. We believe that this discovery offers considerable scope for the design of new stimuli-responsive polymers and to widen the applicability of these zwitterionic "smart" materials

Results and discussion

RAFT Polymerization of DMAPS by C_x-ECT



Scheme 1. Synthesis of C_x-ECT-PDMAPS by RAFT polymerization with ECT and C_x-ECT

ECT-PDMAPS and C_x-ECT-PDMAPS with different end-groups were polymerized via the method shown in Scheme 1. Carboxyl end-group was introduced by ECT RAFT agent (synthesized according to the previous report [38]), and different ester end-groups were introduced by esterification of ECT by alcohol with different alkyl chain length.

The functional groups were all located at the R group to ensure that the functional groups are always on the outside of the segment even after further crosslinking and copolymerization. The characteristics of ECT agent and ECT-PDMAPS$_n$ were determined by ^{1}H NMR (Figure S1) spectra and Size Exclusion Chromatography (SEC) analysis (Figure S2, a). The SEC results of C_x-ECT-PDMAPS were shown in Figure S2, b. All the results are listed in Table S1. The molar mass of polymers obtained by the SEC was smaller than that obtained by ^{1}H NMR which could be due to the interaction between the polymers and column materials.[39]

pH responsiveness of ECT-PDMAPS aqueous solution

UV-visible spectrophotometer and DLS were used to characterize the phase-transition behavior and polymer chain association of the ECT-PDMAPS at various molar mass. As expected, UCST exhibited by ECT-PDMAPS positively correlated with molar mass, while polymers with a DP below 80 did not exhibit UCST (Figure S3). On the other hand, the swelling of the polymer segments was accompanied by a gradual rather than an abrupt change in the phase transition (Figure S4). The increase in temperature gradually destroyed the electrostatic force leading to a gradual release to the solution to polymer chains and enlarging chain mobility and entropy.

Besides the thermo-responsiveness, pH responsiveness was also proved in this system, which contributed to the smart dual responsive system. Due to the presence of the carboxyl end-group, we found that the pH of the aqueous solution facilitated manipulation of the UCST of the resulting ECT-PDMAPS$_{145}$ (10 mg mL^{-1}) (Figure 1a, b). The stock solution's pH value was adjusted by HCl and NaOH before preparing the polymer solution samples. UV-Vis spectroscopy was carried out to verify the end-group fidelity of polymers at different DPs before the UCST measurements (3 mg mL^{-1}) (Figure S5). The peak at around 310 nm is characteristic of the absorption of the trithiocarbonate functional group forming part of the ECT RAFT agent. The adsorption decreased with the increase of DP, indicating that at the same concentration of polymers, the end-group concentration decreased with extension of chain length. However, due to

the limitations of polymer solubility and characterizations, the quantitative analysis of the terminal carboxyl groups is not discussed in depth here.

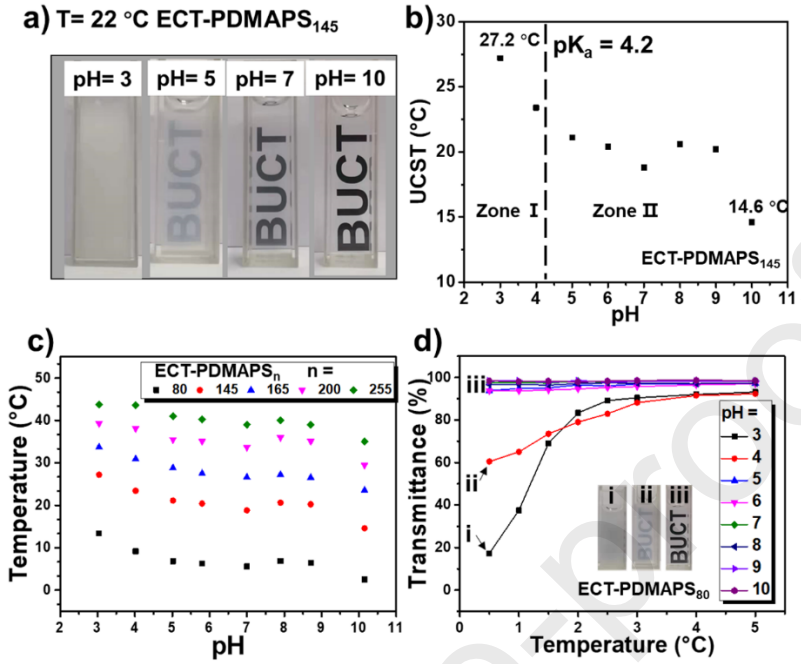


Figure 1 (a) pH-induced phase transition behavior of ECT-PDMAPS$_{145}$ at different pH values at ambient temperature (22 °C). (b) UCST of the ECT-PDMAPS$_{145}$ aqueous solution (10 mg mL^{-1}) under different pH values. (c) Thermo-responsive properties of the ECT-PDMAPS with different DP at the aqueous solution (10 mg mL^{-1}) with different pH values. (d) Thermo-responsive properties of the ECT-PDMAPS$_{55}$ at the aqueous solution (10 mg mL^{-1}) with different pH values.

At ambient temperature (22 °C), the pH-responsiveness of ECT-PDMAPS$_{145}$ resulted from the carboxyl end-group. ECT-PDMAPS$_{145}$ showed complete dissolution under neutral conditions, and underwent a phase transition with increasing acidity (Figure 1a, Figure 1b (zone Ⅰ)). Acid titration studies of the ECT agent in aqueous solution (Figure S6) indicated that the pK_a of the terminal carboxylic acid group is approximately 4.2. We hypothesized that this responsiveness should come from the change of solubility and ionization degree of the carboxyl end-group under different pH values. To confirm this end-group effect, the UCST of the ECT-PDMAPS with DP range from 80 to 255 in aqueous solutions at different pH were measured (Figure 1c). As the pH gradually decreased from 7 to 3, the UCST of each polymer showed an

upward trend, which trend began to slow as the DP increased. When the DP reaches 255, the end group effect is weak, and the adjustable range is less than 5 degrees. Because of the decrease of end-group content, the increase in hydrophobicity caused by deionization of the terminal carboxylic acid group is no longer sufficient to induce polymer chain aggregation. Conversely, as the pH increased gradually from 7 to 10, the UCST of ECT-PDMAPS exhibited a strange tendency to move up-wards and then move downwards (Figure 1b, zone Ⅱ), although the latter movement can be considered as the result of ionization of the terminal carboxylic acid group in-creasing the polymer chains' hydrophilicity. The overall abnormal trend at pH 7 to pH 9 can be explained by electrostatic interaction between cationic zwitterionic moieties with ionized carboxyl end-group. It has been reported previously that adding a small amount of inorganic sodium salt to a solution can increase the UCST.[40] Beyond that, according to Jiang et al., the sulfonate group of DMAPS moiety has low charge density and is likely to prefer to interact with the chaotropic cations, which also contain low charge densities.[41] The charge densities of charged groups not only influenced the zwitterion–ion interactions, but also altered the associations among zwitterionic moieties themselves.[42,43] At pH 8, the terminal carboxyl group reacted with the sodium hydroxide and maintained a certain degree of ionization. At this stage, the ionized carboxyl group generated an electrostatic interaction with the ionic unit on the zwitterionic polymer segment and lead to an increase in UCST.

More evidence to support the carboxylic end-group effect was obtained by adding salt, as NaCl and $CaCl_2$ were added to disturb the carboxylic end-group system (Figure 2a, Figure S7). Consequently, the UCST of ECT-PDMAPS should be reduced sharply at each level of pH because of the electrostatic shielding effect, but the deionization of the carboxyl group in acidic conditions also caused an increase in UCST (from 11 °C at pH 7 to 13.5 °C at pH 3), relieving the salt intolerance of PDMAPS. Besides this, the effects of Na^+ and Ca^{2+} on thermo-responsive behaviors under the basic condition were also examined. Under the basic condition, there was no significant change in the UCST of the polymer in $CaCl_2$ solution, compared to the polymer in the NaCl solution which

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showed the same change as before. This difference in responsive behavior can be ascribed to the specific interaction between carboxylic acid group and Ca^{2+},[34] and this also further indicated that the change of polymer conformation was induced by carboxylic acid end-group.

Based on this discovery, we hoped to enable phase transitions at lower molar mass in acidic aqueous solutions. It is also accepted that PDMAPS will have no thermo-responsive properties when the DP is less than 70[29]. The effect of pH on the UCST of the ECT-$PDMAPS_{55}$ was investigated (Figure 1d). For the first time at this molar mass, a visible phase separation phenomenon can be observed under the environment of pH 3 and 4, wherein the solution at pH 3 has higher turbidity than pH 4 in low temperature.

Additionally, we tried the esterification of the ECT RAFT agent in order to examine this end-group effect. Controlled polymerizations were performed by using C_1-ECT RAFT agent to prepare C_1-ECT-$PDMAPS_{135}$. The UCST of C_1-ECT-$PDMAPS_{135}$ samples were stable under different pH values when compared with ECT-$PDMAPS_{145}$ (Figure 2b). Zeta-potential studies were conducted as a function of solution pH for both polymers beyond UCST (Figure 2c, d). C_1-ECT-$PDMAPS_{135}$ samples were found to present a stable negative zeta-potential which is a typical character of polysulfobetaine.[44] On the other hand, for ECT-PDMAPS, carboxyl group deionization resulted in higher cationic character (from -23 mV at original to 8.5 mV at pH 3); in contrast, ionizing the carboxyl group gave rise to a lower anionic character (from -23 mV at original to -30 mV at pH 10). The phenomenon of UCST increasing from pH 7 to pH 8 and decreasing from pH 8 to pH 10 indicates that the interaction between carboxylic ions and zwitterions counteracted part of the negative charge. It is also emphasized that the conformation (size and dispersion information) of ECT-PDMAPS polymer chains should be examined by DLS. The hydrodynamic size of the polymer segments in aqueous solution decreased with increasing carboxyl group ionization, and free polymer chains may stretch better due to the electrostatic repulsion generated by carboxylic ions. Moreover, the dispersion of aggregates decreased as the

degree of ionization increased, indicating that the polymer conformation changed from an aggregating state to an expanding state. Therefore, the decrease in the degree of ionization of the terminal carboxylic acid group in a low pH environment is accompanied by an increase in hydrophobicity, thereby promoting aggregation of polymer segments and increased UCST.

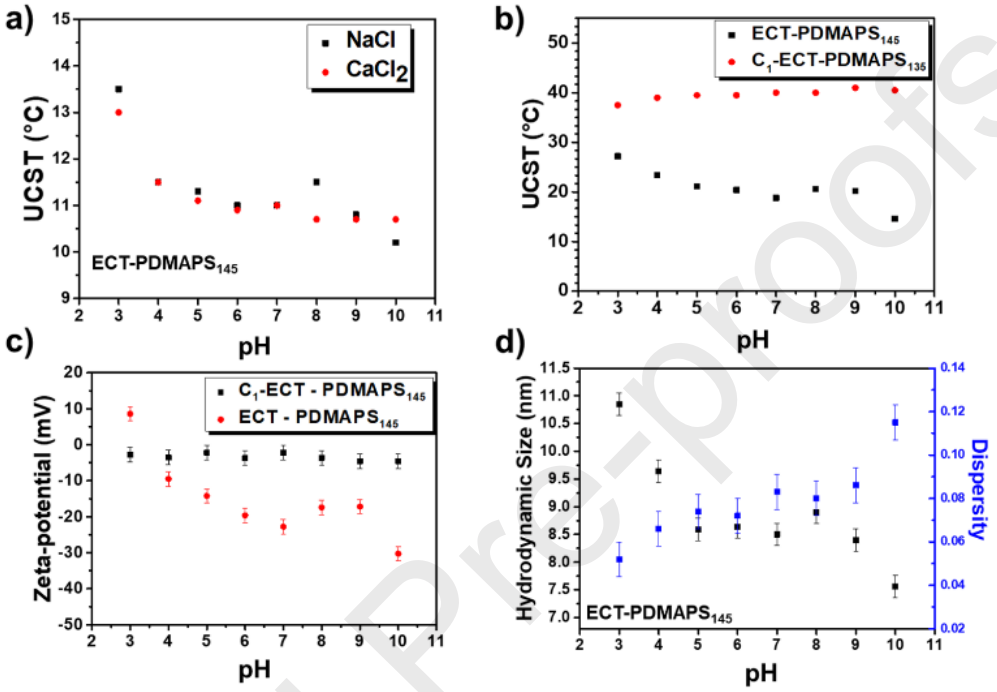

Figure 2 (a) UCST of ECT-PDMAPS$_{145}$ at NaCl and $CaCl_2$ aqueous solution (20 mM). (b) UCST of ECT-PDMAPS$_{145}$ and C_1-ECT-PDMAPS$_{135}$ aqueous solution (10 mg mL^{-1}) at different pH values. (c) Zeta-potential of the ECT-PDMAPS$_{145}$ and C_1-ECT-PDMAPS$_{135}$ aqueous solution (10 mg mL^{-1}) at different pH values. (d) Variation of hydrodynamic particle diameters and dispersity of the ECT-PDMAPS$_{145}$ aqueous solution (10 mg mL^{-1}) at different pH values.

Significantly increase the UCST of PDMAPS by carbomethoxy end-group modification

Up to now, the terminal carboxyl group endowed PDMAPS dual thermo-responsiveness, made a "smarter" zwitterionic material than a conventional single

thermo-responsive one. The UCST of PDMAPS can be adjusted by controlling the surrounding pH, but the increase of UCST at the acidic condition is still limited. It is known that the UCST of PDMAPS homopolymer with a DP around 150 can't reach 30 °C. For example, Roth et al. have investigated the UCST of sulfobetaine (co)polymers with different molar mass systematically. It is showed that the UCST of $PDMAPS_{161}$ with phenyl end-group is around 13°C,[45] this UCST value is also similar to that of the ECT-$PDMAPS_{145}$ (19°C) we synthesized. Therefore, utilizing the end-group effect to greatly boost the UCST of the zwitterionic homopolymer is the next target. We have examined the idea that the C_1-ECT-$PDMAPS_{135}$ has no pH-responsiveness, and were surprised to find that, the UCST could be increased from 19 °C to 40 °C of C_1-ECT-$PDMAPS_{135}$ by only changing the end group from carboxyl to carbomethoxy group (Figure 3a) after end-group esterification (Scheme 1).

As shown in Figure 3a, compared to ECT-$PDMAPS_{145}$, the UCST of C_1-ECT-$PDMAPS_{135}$ had increased by 20 °C. Even at the lowest DP of ECT-$PDMAPS_{80}$ to show thermo-responsiveness, C_1-ECT-$PDMAPS_{75}$ could still maintain an ideal UCST around 25 °C. According to previous reports, PDMAPS can exhibit an anti-polyelectrolyte effect which means that the addition of a small amount of salt causes UCST to collapse.[46] Here we noticed that (Figure 3b), although the UCST of C_1-ECT-$PDMAPS_{135}$ showed a sharp decrease when the polymer solution was prepared in 20 mM NaCl, the C_1-ECT-$PDMAPS_{135}$ showed a considerable UCST at 22 °C. The phase transition behavior of the C_1-ECT-$PDMAPS_{135}$ was slower when compared with ECT-$PDMAPS_{255}$ even though the latter had a longer chain length. This is likely to indicate that a more intense entanglement existed between the segments of C_1-ECT-$PDMAPS_{135}$ (Figure S8, a). Rheological behavior measurement was performed at various temperatures to further investigate the chain conformation details (Figure S9). At all temperature ranges, both G′ and G″ of C_1-ECT-$PDMAPS_{135}$ are higher than ECT-$PDMAPS_{145}$, suggesting stronger physical interactions between C_1-ECT-$PDMAPS_{135}$ chains.

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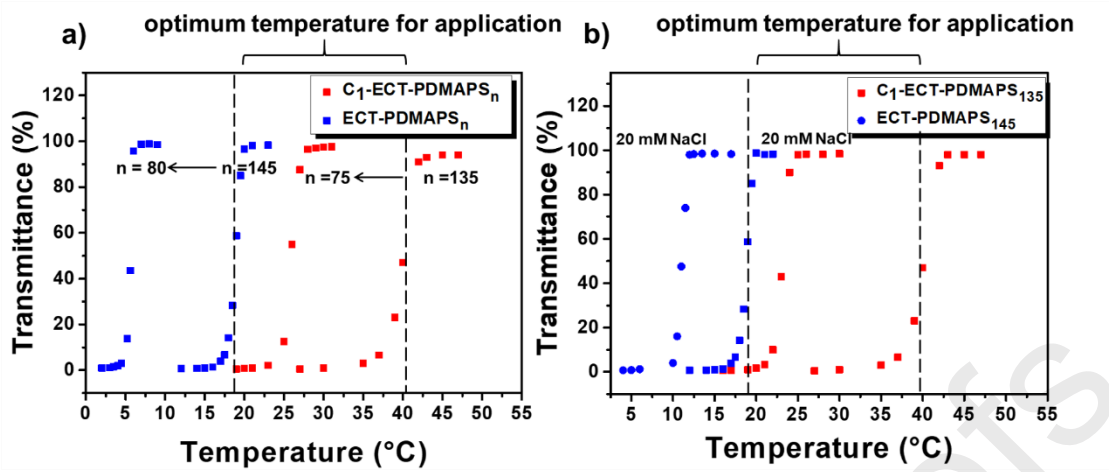

Figure 3 (a) Comparison of thermo-responsiveness of the ECT-PDMAPS$_n$ and C_1-ECT-PDMAPS$_n$ aqueous solution (10 mg mL^{-1}) with different DP. (b) Comparison of thermo-responsiveness of the ECT-PDMAPS$_{145}$ and C_1-ECT-PDMAPS$_{135}$ at NaCl solution (20 mM).

Manipulation of the thermo-responsiveness of PDMAPS by using an ester end-group RAFT agent

If the carboxyl protonation which results in an increase of hydrophobicity can increase the UCST, is there a limitation to this increase in UCST? We investigated the effect of end-group hydrophobicity on UCST in PDMAPS to find the critical value. To this end, RAFT agents with different alkyl chain lengths were prepared by esterification of the ECT RAFT agent (Scheme 1). A total of twelve samples of C_x-ECT-PDMAPS$_n$ were obtained by using different C_x-ECT with low dispersity (Đ≈1.35).

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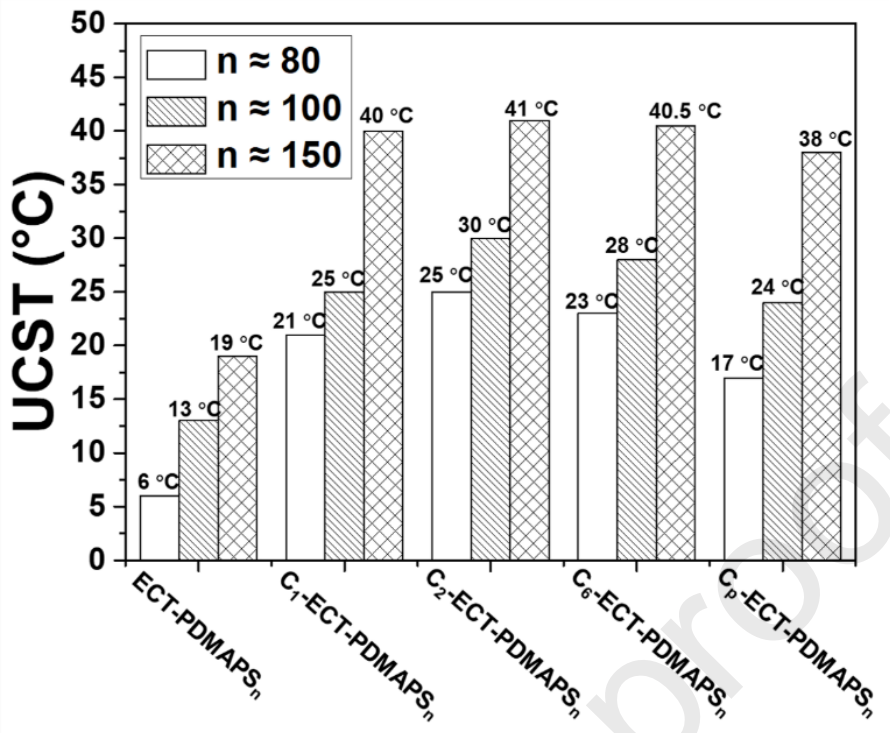
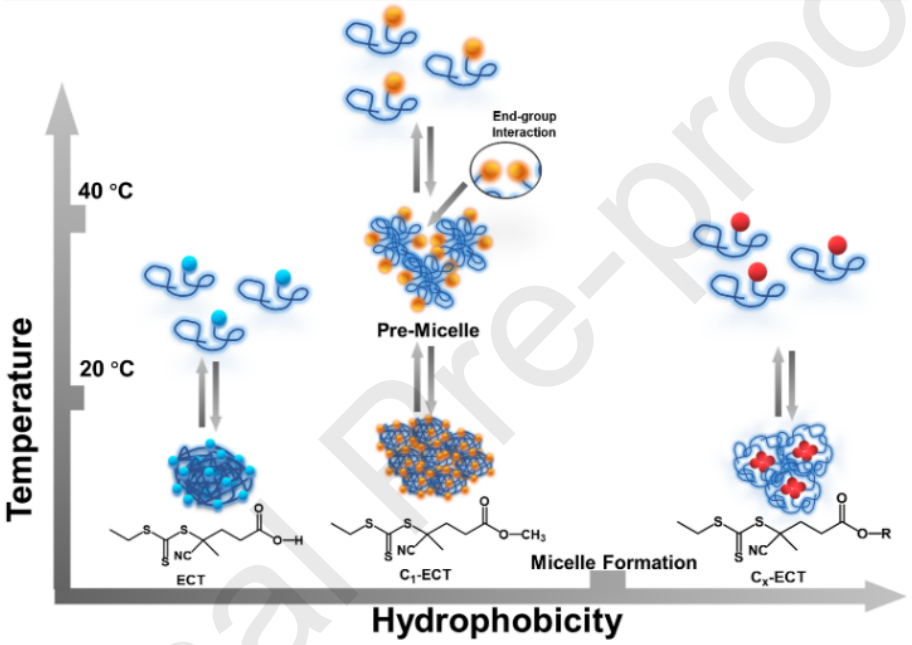


Figure 4 PDMAPS with the variation of UCST at designed DP with different C_x-ECT RAFT agents under neutral condition.

Figure 4 shows the UCST data for the 15 polymers with different end-groups and DPs. Evidently, C_2-ECT-PDMAPS exhibited the highest UCST transition in water, whereas C_6-ECT-PDMAPS and C_p-ECT-PDMAPS displayed decreasing UCST. In addition, as hydrophobicity increases, there is an upper limit of C_x-ECT's ability to reduce the solubility of PDMAPS in water. Over this critical limit, the UCST even decreased, which was beyond our expectations. From our knowledge, if we continued to increase the hydrophobicity of the end group until the end group is wrapped in the core and formed a micellar structure, the end group effect should be decreased. Therefore, a pre-micelle conformation may exist with the increased hydrophobicity of the ester-end group on the RAFT agent and lead to an increase of UCST.[47] The pre-micelle structure could amplify the effect of the end groups' hydrophobicity on the polymer segments. In some applications and studies, the pre-micelle structure exhibits such unexpected phenomena as, among others, amplifying the catalysis[48] and accelerating the electron transfer rate.[49] We have tried to detect the pre-micelle confirmation by traditional pyrene fluorescent probes, but could not obtain worthwhile

results due to the end-groups' extremely small content. We observed the phase transition behavior of the C_1-ECT-PDMAPS$_{75}$ and C_p-ECT-PDMAPS$_{70}$ (Figure S8, b). Consistent with our hypothesis, the C_p-ECT-PDMAPS$_{70}$ which contains more hydrophobic end group shows a sharper transition behavior than C_1-ECT-PDMAPS$_{75}$. The pre-micelle state transitioned towards the micelle state as the hydrophobicity grew, then weakened the end-group effect and the entanglement between the polymer segments (Scheme 2). The largest increase of UCST is obtained at this stage, in the case where the alkyl chain of RAFT agent is critically short.



Scheme 2 Hypothesis scheme of the end-group effect of pre-micelle and micelle on temperature responsiveness.

SAXS provides a much more detailed account of the true nature of the solution state of the polymers. SAXS studies were performed on ECT-PDMAPS$_{80}$, C_2-ECT-PDMAPS$_{75}$ and C_p-ECT-PDMAPS$_{70}$ polymer solutions (experimental details in supporting information) and similar results were observed (Figure 5a). The polymers with DP around 80 were selected and tested at a temperature of 30 °C (higher than the solutions' UCST). A GausPoly unimer model was found to fit well, which indicates that the polymer in the solution does not form a true micelle conformation. This may be because the contribution of the end-groups to the conformation of the entire polymer segment was tiny at specific DP, resulting in the polymer not forming a micelle

conformation in solution.

For a better understanding of the end-group effect's contribution to the conformation of the polymer segments, a plot of ln(I(q)) versus q^2 transforms the Guinier region into a plot (Figure 5b). R_g is determined by using the Guinier approximation[50] for the low-resolution scattering ($qR_g < 1.1$, or $qR_g < 1.3$ for globular scatters):

$$I(q) \approx I(0) \exp(-q^2R_g^2/3) \quad (1)$$

where I(q) is the scattering intensity, I(0) is the forward scattering intensity and the scattering vector magnitude $q = (4\pi/\lambda) \sin\theta$ (θ is the scattering angle and λ is the wavelength of the incident radiation)

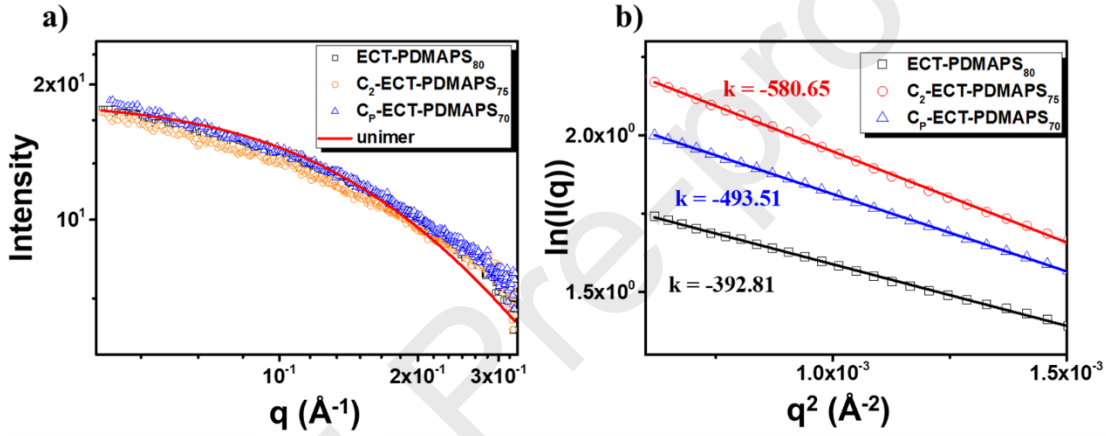


Figure 5 (a) SAXS fit results of ECT-PDMAPS$_{80}$, C_2-ECT-PDMAPS$_{75}$ and C_p-ECT-PDMAPS$_{70}$. (b) Guinier transformation results of ECT-PDMAPS$_{80}$, C_2-ECT-PDMAPS$_{75}$ and C_p-ECT-PDMAPS$_{70}$.

The difference is most easily observed in the slopes for all sets of samples, with the C_2-ECT-PDMAPS$_{75}$ polymer exhibiting a steeper slope (k) at the Guenier regime (Figure 5b), which is indicative of higher R_g (42 Å) and looser object (in agreement with our hypothesis). The R_g from C_2-ECT-PDMAPS$_{75}$ (42 Å) to C_p-ECT-PDMAPS$_{70}$ (38 Å) decreased because of the increased alkyl size of polymer segment end-group leading to pre-micelle conformation caused by the hydrophobicity of larger alkyl groups. The UCST measurement data under variable concentration provide support from another perspective (Figure S10). As the DP increases, the UCST difference of PDMAPS with different end-group becomes smaller at each concentration, indicating that the end-group effect is weakening. Furthermore, as the concentration decreases to

1 mg mL^{-1}, the UCST of the C_p-ECT-$PDMAPS_{135}$ sample becomes higher than C_1-ECT-$PDMAPS_{135}$. This result shows that another influencing factor of the end-group effect is the concentration. Dilution will weaken the pre-micellar degree of the C_p-ECT-$PDMAPS_{135}$ which means at low concentrations, the hydrophobic phenyl end-group contributes more to the aggregation of polymer segments.

Based on the results obtained, we hypothesized that the significant increase in UCST from 20 °C to 40 °C of PDMAPS was due to enhanced hydrophobicity of the ester end-group. From a thermodynamic point of view,[20] when a hydrophobe was placed into an aqueous environment, such a structure restricted the translational and rotational motion of water molecules, leading to a loss of entropy. According to this, hydrophobic end-group modification to C_2-ECT-PDMAPS also caused a leftward shift on the ΔH_m-ΔS_m plot, and their UCST would be elevated. Additionally, topological irregularity of the polymer chains may hinder the hydrophobic interaction, and ΔS_m and ΔH_m would be affected as a result. In terms of materials in this project, the repeating unit on the polymer backbone is composed of methacrylate with an ester group. When the terminal group changed from carboxyl to ester, the regularity of the polymer segment was improved and this, in turn, increased the UCST.

Conclusion

With the aid of RAFT polymerization, we demonstrated that zwitterionic homopolymers can exhibit the pH-responsive behavior that not previously achieved or confirmed. The UCST can even be precisely manipulated by pH value in aqueous solution, as the hydration state of PDMAPS chains is affected by ionization/protonation of the single terminal carboxylic acid end-group. Moreover, it is emphasized that utilizing the ester end-group RAFT reagent can effectively increase the UCST of zwitterionic polymers, which can be attributed to the end-group's higher hydrophobicity introduced by the RAFT agent. Based on this discovery and methodology, the applications of these end-group modified polymers need to be further explored. For example, preparing hybrid materials using the electrostatic effect of ionized end groups; electrospinning zwitterionic materials; synthesizing star polymers

by RAFT polymerization to control the number of end groups to improve responsiveness, and, ultra-fast responsive polymers with super-hydrophilic end-groups. Conclusively, end-group modification is a novel method for effectively manipulating and improving the responsiveness of zwitterionic homopolymers, with the advantages of being easy to operate and easy to maintain the polymers' original component. This strategy broadens the application prospects of stimuli-responsive homopolymers in the fields of analytical industry, controlled drug delivery, surface modification, bio-separation science and engineering.

Experimental

Materials. 3-((2-(Methacryloyloxy) ethyl) (dimethyl) ammonio) -1-propanesulfonate (DMAPS, 99%), 4,4'-azobis(4-cyanopentanoic acid) (ACVA, V-501; 99%), *N*,*N*-dicyclohexylcarbodiimide (DCC, 99%), 4-(dimethylamino)pyridine (DMAP, 99%), ethanol, methanol, n-hexanol, 2-phenylethanol, 2,2,2-trifluoroethanol and dichloromethane (99%, anhydrous grade) were purchased from Sigma-Aldrich and were used as received. The RAFT agent 4-cyano-4- (ethylthiocarbonothioylthio) pentanoic acid (ECT) was synthesized according to the previous report.[38] All other reagents and chemicals were purchased from commercial sources and were used as received without further purification.

Characterizations. ^{1}H NMR spectra for structural assignments and polymer conversion were obtained on a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm), using a residual deuterated solvent as internal standard (D_2O at 4.79 ppm, $CDCl_3$ at 7.26 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. The molar mass was measured by using a Shimadzu SEC system equipped with a SIL-20A autosampler, a refractive index detector, three Shodex KF-805L columns (8 × 300 mm, 10 μm, 5000 Å) and one Shodex KF-801 column (8 × 300 mm, 6 μm, 50 Å) using water (containing 0.1 M sodium chloride) as the eluent at 40 °C with a flow rate of 0.5 mL min^{-1}. The SEC calibration was accomplished with low dispersity dextran standards. Turbidity

measurements were performed on a Hitachi U-3900H UV-vis spectrophotometer equipped with a temperature controller in quartz cuvettes at a wavelength of 550 nm with heating/ cooling rates of 1 °C min^{-1}. The samples (10 mg mL^{-1}) were gradually heated from a low temperature to a high temperature and equilibrated at each selected temperature for 1 min prior to transmittance measurement. The transmittance value was read at every 0.5/1 °C increment for each sample. Transmittance (%) was plotted against temperature, and the UCST was determined as the temperature at the maximum slope of the curve. The average size and zeta-potential of polymers were analyzed by a Brookhaven Nanobrook Omni (DLS) at 45 °C using a monochromatic coherent He–Ne laser (640 nm) as the light source and a detector that detected the scattered light at an angle of 90°. At 45 °C, the polymers were well dissolved in the solution and the electrostatic interaction between polymer segments was weakened to better examine the effect of end-group on polymer segments. All data were averaged over three consecutive runs. The dynamic viscoelasticity was measured with a Kinexus Pro rheometer (Malvern Instruments Ltd.) using 25 mm diameter parallel plates at a plate-to-plate distance of 1 mm. The temperature dependence of the storage modulus (G′) and loss modulus (G″) was determined by oscillatory shear deformation with the temperature range from 10 °C to 60 °C. The frequency and strain were fixed at 10 Hz and 1 % respectively. The polymer solutions' concentrations were 50 g L^{-1}, and the pH was neutral.

RAFT polymerization of 3-((2-(Methacryloyloxy) ethyl) (dimethyl) ammonio)-1-propanesulfonate) (DMAPS) by ECT. DMAPS (0.14 g, 0.5 mmol), ACVA (0.0003mmol, prepared by 93 μL of a stock solution of 1 mg mL^{-1}), and ECT (0.85 mg, 0.0033 mmol) were dissolved in sodium chloride solution (0.1 M). The solution was added into the Schlenk tubes after titration of sodium hydroxide solution (0.1 M), with the molar ratio of [M]: [CTA]: [I] =1500: 10: 1. The tubes were sealed and the oxygen was removed by a series of three freeze-evacuate-thaw cycles. Then the tubes were heated and maintained at 70 °C for 15 h. After the given time, the reaction was stopped by cooling in liquid nitrogen and exposure to air. The polymers were purified by

dialysis (MWCO of 3000) against Milli-Q water and freeze-dried before SEC measurement. The DP of the PDMAPS was systematically varied from 35 to 255 to produce different molar mass polymers.

Esterification of C_x-ECT chain transfer agent. C_1-ECT was synthesized by the following steps. ECT (0.20 g, 0.76 mmol) was dissolved in anhydrous dichloromethane (1.50 mL) in a 10 mL round-bottomed flask, which was cooled in an ice bath to 0 °C in advance. DMAP (0.014 g, 0.12 mmol) and excess anhydrous methanol (0.10 g) were added to the stirred solution at 0 °C. DCC (0.16 g, 0.76 mmol) was added dropwise over 5 min. This reaction mixture was warmed up to 20 °C and stirred continuously for 16 h prior to filtration to remove the insoluble side-product (*N*, *N*'-dicyclohexyl urea). The filtrate was then washed twice with acidic water (pH= 3) and de-ionized water to remove the excess of ECT before being dried over anhydrous magnesium sulfate. Finally, dichloromethane was evaporated under vacuum to produce an orange oil. The products were further purified by recrystallization at -20 °C. ^{1}H NMR (400 MHz, CD_3Cl) : δH (ppm) = 1.36 (t, J = 7.4, 3H), 1.89 (s, 3H), 2.35-2.60 (m, 2H), 2.73-2.65 (m, 2H), 3.35 (q, J = 7.4, 2H), 3.73 (s,3H).

The esterification of ECT with ethanol (C_2-ECT), n-hexanol (C_6-ECT), and 2-phenylethyl alcohol (C_p-ECT) were carried out in the same manner. ^{1}H NMR (400 MHz, CD_3Cl) of C_2-ECT: δH (ppm) = 1.27 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.4, 3H), 1.89 (s, 3H), 2.35-2.60 (m, 2H), 2.65-2.73 (m, 2H), 3.35 (q, J = 7.4, 2H), 3.73 (s, 3H). 4.16 (q, J = 7.1 Hz, 2H). ^{1}H NMR (400 MHz, CD_3Cl) of C_6-ECT: δH (ppm) = 0.9 (t, J = 6.7 Hz, 3H), 1.22-1.41 (m, 6H), 1.89 (s, 3H), 2.35-2.60 (m, 2H), 2.65-2.73 (m, 2H), 3.35 (q, J = 7.4, 2H), 3.73 (s, 3H). 4.10 (q, J = 6.4 Hz, 2H). ^{1}H NMR (400 MHz, CD_3Cl) of Cp-ECT: δH (ppm) = 1.36 (t, J = 7.4, 3H), 1.84 (s, 3H), 2.30-2.55 (m, 2H), 2.55-2.70 (m, 2H), 3.34 (q, J = 7.4, 2H), 5.30 (s, 2H), 7.26 (s, 5H).

RAFT polymerization of DMAPS by C_x-ECT. C_x-ECT-PDMAPS were synthesized by C_1-ECT, C_2-ECT, C_6-ECT, and C_p-ECT chain transfer agents following the same synthetic steps as the ECT-PDMAPS. Trifluoroethanol was used as a solvent to ensure complete dissolution of the RAFT reagents. The DP of the PDMAPS was

systematically designed as 80, 100 and 150. The polymers were purified by dialysis (MWCO of 3000) against Milli-Q water and freeze-dried before SEC measurement.

Conflicts of interest

There are no conflicts to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online

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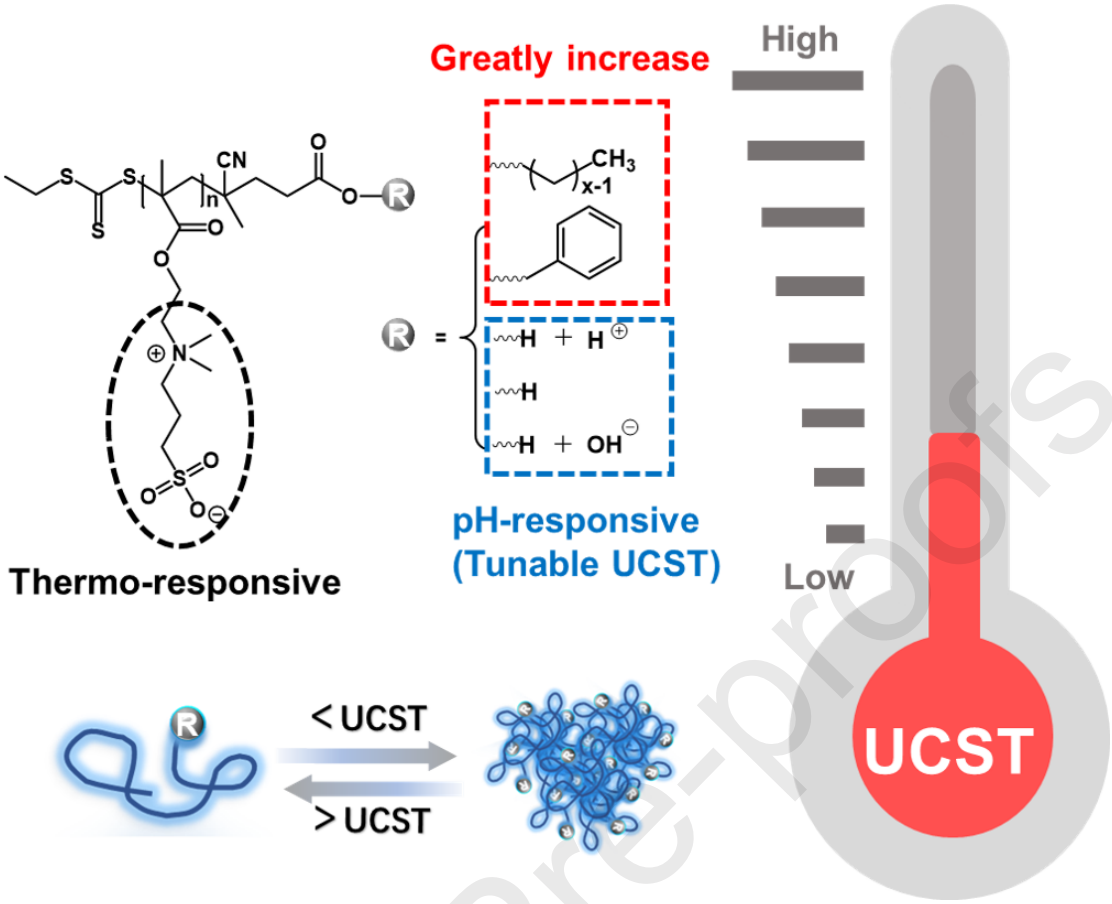

Manipulation of temperature responsiveness of poly-sulfobetaine by using end-group modification of trithio-carbonate RAFT agent.

Highlights

1. Polyzwitterions were prepared by carboxyl and ester group functionalized RAFT agents via RAFT polymerization.

2. Carboxyl end homo-polyzwitterions were pH- and thermo-responsive.

3. The UCST of homo-polyzwitterions are able to achieve the maximum value through ester functionalized RAFT agent polymerization.

4. A pre-micelle conformation of ester-end homo-polyzwitterions could exist.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Zhi Li: Conceptualization, Methodology, Investigation. Writing- Original draft preparation. **Botao Hao**: Methodology, Investigation. **Yijing Tang**: Methodology, Investigation. ***Hao Li****:* Methodology, Investigation. **Tung-Chun Lee**: Software, Formal analysis. **Anchao Feng:** Writing- Reviewing and Editing, Resources, Supervision. **Liqun Zhang:** Resources, Project administration, Funding acquisition**. San H. Thang**: Writing- Reviewing and Editing, Resources.

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