

# Effect of carbon chain length of monocarboxylic acids on cloud point temperature of poly(2-ethyl-2-oxazoline)

Jaweria Ambreen · Jinxian Yang · Xiaodong Ye ·  
Mohammad Siddiq

Received: 29 June 2012 / Revised: 9 September 2012 / Accepted: 11 September 2012 / Published online: 25 September 2012  
© Springer-Verlag Berlin Heidelberg 2012

**Abstract** The temperature-induced phase transition of poly(2-ethyl-2-oxazoline) (PEtOx) aqueous solution under mixing with a series of small carboxylic acids has been studied by turbidity measurements and laser light scattering. It has been found that cloud point temperature ( $T_{cp}$ ) of the PEtOx was changed to varying degrees depending upon the pH, ionic strength, molar ratio of acids to 2-ethyl-2-oxazoline unit, and carbon chain length of small carboxylic acids. Significant change in  $T_{cp}$  was observed in the case of hexanoic acid. At acidic pH, an increase in the molar ratio of hexanoic acid to the 2-ethyl-2-oxazoline unit gradually decreased the phase transition temperature of the polymer as compared to the  $T_{cp}$  of pure PEtOx. At original pH 6 ( $\text{pH} > \text{p}K_a$ ),  $T_{cp}$  shifts to higher value than that of pure PEtOx for lower molar ratios and decreased later on with increasing the molar ratio. The shift in the  $T_{cp}$  is described based on the differences in the driving force of phase transition, including hydrogen bonding between small carboxylic acids and PEtOx polymer and hydrophobic interaction.

**Keywords** Laser light scattering · Phase transition · Stimuli-sensitive polymers · Transmittance · UV–Vis spectrophotometer

J. Ambreen · J. Yang · X. Ye  
Hefei National Laboratory for Physical Sciences at the Microscale,  
Department of Chemical Physics, University of Science and  
Technology of China,  
Hefei, Anhui 230026, China

J. Ambreen · M. Siddiq  
Department of Chemistry, Quaid-I-Azam University,  
Islamabad 45320, Pakistan

X. Ye (✉)  
CAS Key Laboratory of Soft Matter Chemistry,  
University of Science and Technology of China,  
Hefei, Anhui 230026, China  
e-mail: xdye@ustc.edu.cn

## Introduction

The thermally sensitive polymers undergo temperature-induced phase transition in aqueous solution at their cloud point temperature ( $T_{cp}$ ). These thermally sensitive polymers are currently receiving greater attention in view of their variety of applications in drug delivery [1–3], bioengineering [4], and separation science [5]. Poly(2-oxazoline)s (POZ) are one of the widely studied class of thermally sensitive polymers because their properties can be tuned easily by variation of the two substituents of the 2-oxazoline monomer [6]. Many of the POZ are known to exhibit a phase transition behavior [7–9]. They exhibit a reversible, concentration-dependent phase separation with the absence of hysteresis [10]. Among various POZ, poly(2-ethyl-2-oxazoline) (PEtOx) has potential properties as a new functional material [11–16]. It is an amorphous, nonionic, thermally stable, and nontoxic tertiary polyamide that is soluble in water and exhibits a  $T_{cp}$  in the range of 61–64 °C depending on its concentration and molecular weight [17, 18]. Recently, Hoogenboom et al. showed that the effect of Hofmeister salts on the cloud point of three poly(2-oxazoline)s strongly depends on their hydrophilicity. Poly(2-ethyl-2-oxazoline) being more hydrophilic than poly(2-isopropyl-2-oxazoline) and poly(2-*n*-propyl-2-oxazoline) showed more distinctive change in the cloud point temperature by the addition of salts [19].

Interpolymer noncovalent complexation could adjust the hydrophilic–hydrophobic balance in the thermally responsive polymeric systems [20]. Many thermally sensitive polymers could form stable hydrogen-bonded complexes with poly(carboxylic acids) [21–24]. PEtOx also contains specific sites that can potentially form hydrogen bonds with carboxylic acids. The carbonyl oxygen and the nitrogen are two possible binding sites in an oxazoline repeat unit, but preferably carbonyl oxygen is the main site for hydrogen bonding with carboxylic group [25]. Interpolymer hydrogen

bonding of PEtOx and poly(carboxylic acids) has already been reported in an acidic aqueous media [26, 27]. The complexation behavior of polymeric micelles from poly(2-ethyl-2-oxazoline)-*b*-poly( $\epsilon$ -caprolactone) block copolymer with poly(carboxylic acids) as well as with multifunctional carboxylic acids like malonic acid, tricarballic acid, and 1,2,3,4-butanetetracarboxylic acid in aqueous solutions has also been investigated by dynamic light scattering and TEM [28]. Although a significant amount of work has been done on the interaction of PEtOx and poly(carboxylic acids), much less is known about the interaction of PEtOx with monocarboxylic acids. In the present work, we have investigated the carbon chain length dependence of  $T_{cp}$  of complexes of monocarboxylic acids with linear PEtOx as a function of pH, ionic strength, and molar ratio of acids to 2-ethyl-2-oxazoline repeat unit and our objective is to understand the effect of hydrogen bonding and hydrophobic interaction on the  $T_{cp}$  of PEtOx. We have found that the  $T_{cp}$  of complexes changes to varying degrees depending on the alkyl chain length, molar ratios of acids to 2-ethyl-2-oxazoline repeat unit, pH, and ionic strength of the system. On the basis of previous studies done by other researchers in the past with poly(carboxylic acids) and PEtOx complexes [25–28], special attention should be paid during the use of PEtOx for biomedical applications in an environment containing carboxylic acids because of their effect on the  $T_{cp}$  of the polymers.

## Experimental section

**Materials** Poly(2-ethyl-2-oxazoline) linear chains with a weight-average molar mass of 500,000 g/mol was purchased from the Sigma-Aldrich Company, Inc. and used as received as a starting material for fractionation. PEtOx was fractionated by the dissolution/precipitation process in a mixture of dry THF and dry *n*-hexane. All carboxylic acids were purchased from Aladdin Reagents and used as received. Buffer solutions were prepared as follows:  $\text{KH}_2\text{PO}_4$ –85 %  $\text{H}_3\text{PO}_4$  for pH 3.8 and  $\text{KH}_2\text{PO}_4$ – $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$  for pH 6 were used to investigate the effect of buffer ionic strength on phase transition of PEtOx. The concentrations of the reagents were chosen to achieve a value of the ionic strength equal to 0.1 or 0.2 M. For instance, the buffer solution of pH=3.8 and ionic strength 0.1 M was obtained by dissolving 1.36 g of  $\text{KH}_2\text{PO}_4$  and 10  $\mu\text{L}$  of 85 %  $\text{H}_3\text{PO}_4$  in Millipore water and subsequent dilution with water to 100 mL.

**Turbidity measurements** Turbidity measurements were used to evaluate the influence of the different molar ratios of small carboxylic acids to 2-ethyl-2-oxazoline repeat unit and solution ionic strength on the  $T_{cp}$  of PEtOx. PEtOx

aqueous buffered solutions with concentrations of 1 mg/mL were mixed with all carboxylic acids by varying the molar concentration ratio of the COOH group of each carboxylic acid to 2-ethyl-2-oxazoline repeat unit. Mixtures were kept on a shaker and allowed to stand 1 day before the turbidity measurements. In our study, turbidity was measured using a UV–Vis spectrophotometer (UNICO UV/VIS 2802PCS) at a wavelength of 500 nm without stirring. The temperature of the solution was controlled by a circulation water bath (Model THD-1006, Ningbo Tianheng Instrument Factory) and was measured using an electric thermometer with a precision of  $\pm 0.1$  °C. Each sample was allowed to equilibrate for 5 min at each temperature point.  $T_{cp}$  was defined as the temperature corresponding to 50 % of transmittance. The error of the  $T_{cp}$  was within  $\pm 0.1$  °C.

**Laser light scattering** A commercial laser light scattering (LLS) spectrometer (ALV/DLS/SLS-5022 F) equipped with a multi- $\tau$  digital time correlator (ALV5000) and a cylindrical 22-mW UNIPHASE He–Ne laser ( $\lambda_0=632.8$  nm) as the light source was used. A combination of static and dynamic light scattering modes has been used. In static LLS [29, 30], the angular dependence of the absolute excess time-average scattering intensity, known as the Rayleigh ratio  $R_{vv}(q)$ , can lead to the weight-average molar mass ( $M_w$ ), the root-mean-square gyration radius  $\langle R_g^2 \rangle_z^{1/2}$  (or simply written as  $\langle R_g \rangle$ ) and the second virial coefficient  $A_2$  by using

$$\frac{KC}{R_{vv}(q)} \cong \frac{1}{M_w} \left( 1 + \frac{1}{3} \langle R_g^2 \rangle_z q^2 \right) + 2A_2C \quad (1)$$

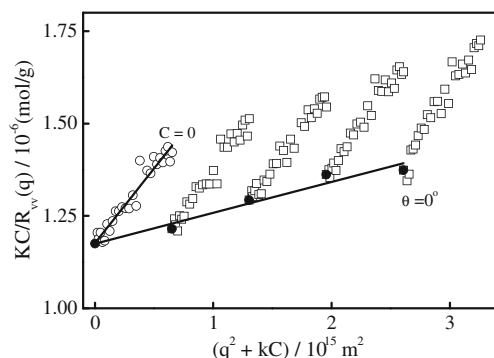
where  $K=4\pi^2(dn/dC)^2/(N_A\lambda_0^4)$  and  $q=(4n\pi/\lambda_0)\sin(\theta/2)$  with  $C$ ,  $dn/dC$ ,  $N_A$ , and  $\lambda_0$  being concentration of the polymer solution, the specific refractive index increment, the Avogadro's number, and the wavelength of light in a vacuum, respectively. The refractive index increment [ $dn/dC=(0.161\pm 0.001)$  mL g $^{-1}$ ] of PEtOx in aqueous solution was determined with a precise differential refractometer [31] at 20 °C and 633 nm, which is the same as the value reported by Bijsterbosch et al. [32]. The extrapolation of  $R_{vv}(q)$  to  $q \rightarrow 0$  and  $C \rightarrow 0$  leads to  $M_w$ . The plot of  $[KC/R_{vv}(q)]_{C \rightarrow 0}$  vs  $q^2$  and  $[KC/R_{vv}(q)]_{q \rightarrow 0}$  vs  $C$  leads to  $\langle R_g^2 \rangle_z$  and  $A_2$ , respectively. In dynamic light scattering [33], the Laplace inversion of a measured intensity–intensity time correlation function  $G^{(2)}(t, q)$  in the self-beating mode can result in a line-width distribution  $G(I)$ . For a pure diffusive relaxation,  $\Gamma$  is related to the translational diffusion coefficient  $D$  by  $\Gamma/q^2=D$  at  $q \rightarrow 0$  and  $C \rightarrow 0$ , or a hydrodynamic radius  $R_h=k_B T/(6\pi\eta D)$  with  $k_B$ ,  $T$ , and  $\eta$  being the Boltzmann constant, absolute temperature, and solvent viscosity, respectively. The PEtOx aqueous solutions at a concentration of 1 mg/mL were

clarified with 0.45- $\mu\text{m}$  Millipore filters to remove the dust. The polydispersity index ( $M_w/M_n$ ) was estimated from the relative width  $\mu_2/\langle I \rangle^2$  of the line-width distribution measured in dynamic LLS by using  $M_w/M_n \sim 1 + 4\mu_2/\langle I \rangle^2$  [30].

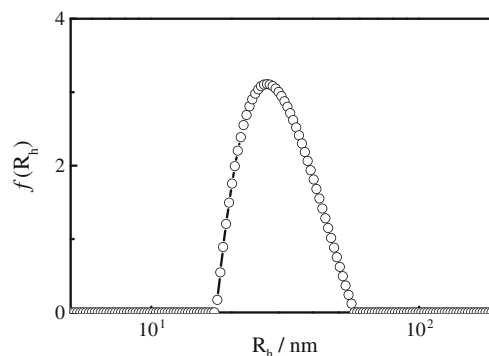
**Size-exclusion chromatography** The relative weight-average molar mass ( $M_w$ ) and polydispersity index ( $M_w/M_n$ ) were also determined by size-exclusion chromatography (SEC, Waters 1515) using a series of three Waters Styragel columns HR2, HR4, and HR6. A refractive index detector (Wyatt WREX-02) was used. The eluent was THF at a flow rate of 1.0 mLmin<sup>-1</sup>, and narrowly distributed polystyrene was used as standards.

### Results and discussion

It is well known that the  $T_{cp}$  of the PEtOx depends on the molecular weight [10, 34, 35]. In general, its cloud point decreases with an increase in molecular weight in the range of 20–500 kDa [16] and exhibits no  $T_{cp}$  below 10 kDa at 0.5 wt% [36]. Therefore, in order to get a narrow distributed sample of PEtOx with fairly high molecular weight, the fractionation method has been used [37]. Figure 1 shows a typical Zimm plot for the fraction of poly(2-ethyl-2-oxazoline) used for our experiments obtained from static light scattering experiment. The weight average molar mass ( $M_w$ ) was  $8.7 \times 10^5 \text{ g mol}^{-1}$  and radius of gyration ( $R_g$ ) was 34 nm. Hydrodynamic radius distribution calculated from the dynamic light scattering experiment has been shown in Fig. 2. The distribution curve shows that the polymer is narrowly distributed with a polydispersity index (PDI) of 1.3 which is consistent with the value obtained from SEC ( $\text{PDI}_{\text{SEC}} = 1.23$ ). However, the  $M_w$  value obtained from SEC is  $5.5 \times 10^5 \text{ g mol}^{-1}$ , which is smaller than the value determined from light scattering experiment due to the fact that sample and the polystyrene standard are different polymers. The second virial coefficient value ( $A_2$ ) obtained from Zimm plot is  $3.2 \times 10^{-7} \text{ mol dm}^3 \text{ g}^{-2}$ . As  $A_2$  is greater than zero, it is



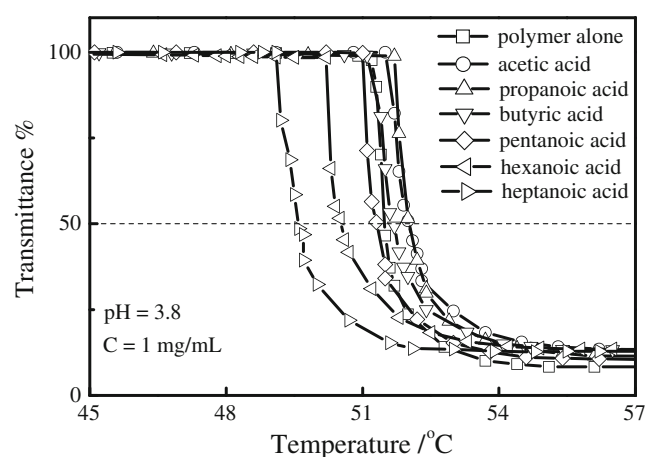
**Fig. 1** Typical Zimm plot of poly(2-ethyl-2-oxazoline) in aqueous solution at 25 °C, where  $C$  ranges from 0.1 to 0.4 mg/mL



**Fig. 2** Hydrodynamic radius distribution of poly(2-ethyl-2-oxazoline) in aqueous solution, where  $C = 0.1 \text{ mg/mL}$

indicative of good interaction strength between water and PEtOx [38]. Because the  $\text{p}K_a$  values of acetic, propanoic, butyric, pentanoic, hexanoic, and heptanoic acids range from 4.76 to 4.89 [39, 40], we have optimized two original pH values, pH 3.8 ( $\text{pH} < \text{p}K_a$ ) and pH 6 ( $\text{pH} > \text{p}K_a$ ) to investigate the  $T_{cp}$  behavior of PEtOx and small acids complexes in aqueous solution as a function of various selected parameters.

Poly(2-ethyl-2-oxazoline) and carboxylic acids can form complexes by means of intermolecular hydrogen bonding between carboxylic and amide groups [16, 25–28], so it is expected that the  $T_{cp}$  of the solution will be changed with the addition of the monocarboxylic acids. Figure 3 illustrates the effect of chain length on the phase transition behavior for 1:1 complexes of PEtOx with acetic, propanoic, butyric, pentanoic, hexanoic, and heptanoic acids, respectively, at pH 3.8 and ionic strength of 0.1 M. At acidic pH ( $\text{pH} < \text{p}K_a$ ), the hydrogen ion concentration in the solution is quite high, which effectively suppresses the ionization of carboxylic acid groups, and the carboxylate groups are in the molecular state (COOH). This would enhance the chances of hydrogen

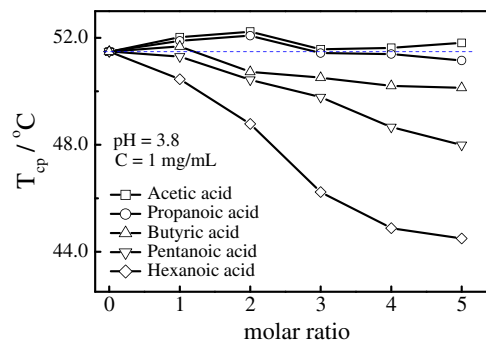


**Fig. 3** Temperature dependence of transmittance at 500 nm obtained for 1.0 mg/mL of poly(2-ethyl-oxazoline) in buffer solution with low molecular weight monocarboxylic acids, where the original pH=3.8, the ionic strength of buffer solution  $I = 0.1 \text{ M}$ , and the molar ratio of acid to 2-ethyl-oxazoline repeat unit was 1

bond formation between the polymer and acids in the solution [41]. Besides, there may be specific hydrophobic hydration of the ethyl side chains by the hydrophobic tails of the small acids, as mentioned by Hoogenboom et al. [9, 42].

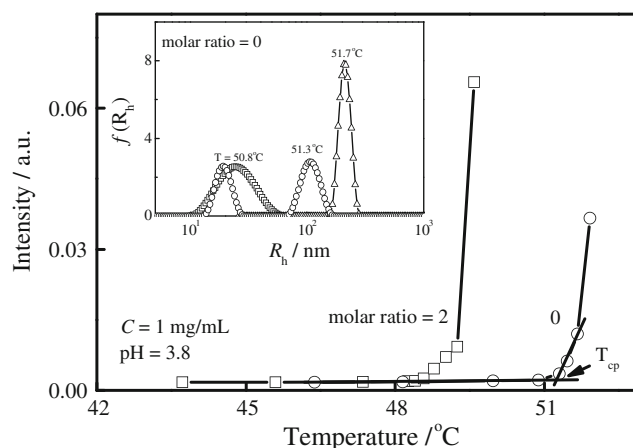
In the case of acetic, propanoic, and butyric acids, the  $T_{cp}$  first increases as compared to pure PEtOx. One of the reasons for this increase can be ascribed to the increase of hydrophilicity and enhanced solubility introduced by these acids. Usually, the  $T_{cp}$  of a polymer can be increased when a hydrophilic comonomer is incorporated into a given homopolymer chain and lowered by a hydrophobic monomer [43–49]. For example, some studies revealed that copolymerization of poly(*N*-isopropylacrylamide) with more hydrophilic acrylamide and acrylic acid monomers leads to the enhancement of  $T_{cp}$  [50, 51], while  $T_{cp}$  decreases for more hydrophobic monomer such as *n*-butyl acrylamide [51]. Also, note that for poly(2-alkyl-2-oxazoline) homopolymers, only few polymers, such as poly(2-methyl-2-oxazolines), poly(2-ethyl-2-oxazoline), poly(2-*n*-propyl-2-oxazoline), and poly(2-isopropyl-2-oxazolines), are soluble in water at room temperature. By varying the composition of random copolymers of 2-ethyl-2-oxazoline and 2-*n*-propyl-2-oxazoline, Hoogenboom et al. have reported that the  $T_{cp}$  of the copolymers can be tuned easily from 24 to 97 °C [10]. Secondly, some steric hindrance caused by methyl, ethyl, and propyl groups of small acids may shift the  $T_{cp}$  to higher temperature after complexation. This explanation is in accordance with the results reported by Zhang and coworkers where they found that poly(*N*-isopropylmethacrylamide) which has one more methyl group than poly(*N*-isopropylacrylamide) (PNIPAM) at each repeating unit has a higher  $T_{cp}$  (~45 °C) as compared to PNIPAM ( $T_{cp}$  ~32 °C) [52]. For higher chain length acids like pentanoic, hexanoic, and heptanoic acids, the formation of hydrogen bond between the COOH group of monocarboxylic acids and carbonyl oxygen of PEtOx as well as hydrophobic interactions may limit the accessibility of water to the polymer chains resulting in an increase in the hydrophobicity of the PEtOx linear chains and  $T_{cp}$  decreases. Besides the solubilization behavior of poly(oxazoline)s, the effect of the length of *n*-alkyl side chains on the thermal properties has also been narrated and summarized by Hoogenboom [53, 54]. A sharp decrease in glass transition temperature of series of poly(2-(*n*-alkyl)-2-oxazoline)s with an increase in the number of carbon atoms in side chain has been reported [53]. Moreover, higher surface energies (~45 mN m<sup>-1</sup>) were observed for polymers with methyl to propyl side chains and low surface energies (~22 mN m<sup>-1</sup>) for longer (propyl to pentyl) side chains [53].

Figure 4 summarizes the effect of different molar ratios of monocarboxylic acids to 2-ethyl-2-oxazoline repeat unit on  $T_{cp}$  of the complexes at pH 3.8 and 0.1 M ionic strength. Due to the lower solubility of heptanoic acid in water at 20 °C (0.244 g/100 g water) [55], the effect of molar ratio of heptanoic acid to 2-ethyl-2-oxazoline has not been investigated. In



**Fig. 4** Dependence of molar ratios of acids to 2-ethyl-2-oxazoline repeat unit on  $T_{cp}$  of poly(2-ethyl-2-oxazoline), where the concentration of polymer was 1 mg/mL, the original pH=3.8, and the ionic strength of buffer solution  $I=0.1$  M

the case of acetic and propanoic acid,  $T_{cp}$  is first increased as compared to the pure PEtOx till the molar ratio of acid to 2-ethyl-2-oxazoline repeat unit is 2 and then decreases later on. Similar explanation could be assigned for increased  $T_{cp}$  as discussed before. The increasing molar ratio effect on  $T_{cp}$  is more pronounced in the case of pentanoic and hexanoic acids. Apparently, an increasing amount of carboxylic acid moieties in the solution at acidic pH led to an increase in the number of hydrogen bonds between acids and PEtOx polymer. The  $T_{cp}$  decreases with the increasing molar ratio of the acids due to the stronger hydrophobic interactions. We also have used LLS to verify the phase transition behavior of PEtOx aqueous solution. Figure 5 shows the temperature dependence of the scattered light intensity of PEtOx solutions with and without the addition of hexanoic acid. As expected, at lower temperatures, scattered light intensity is nearly a constant, indicating the existence of individual PEtOx polymer chains with only

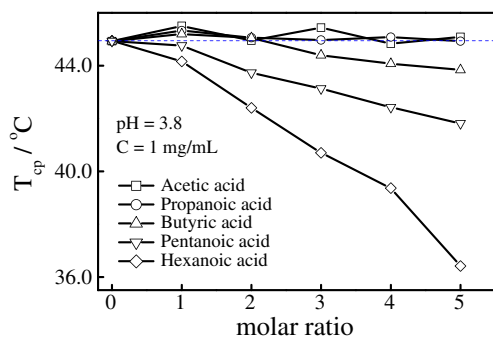


**Fig. 5** Temperature dependence of the scattered light intensity of poly(2-ethyl-2-oxazoline) without the addition of hexanoic acid and with the addition of hexanoic acid (molar ratio of acid to 2-ethyl-2-oxazoline is 2), where the concentration of PEtOx was 1 mg/mL, the original pH=3.8, and the ionic strength of buffer solution  $I=0.1$  M. The inset shows the hydrodynamic radius distribution  $f(R_h)$  of PEtOx solution without the addition of hexanoic acid at different temperatures

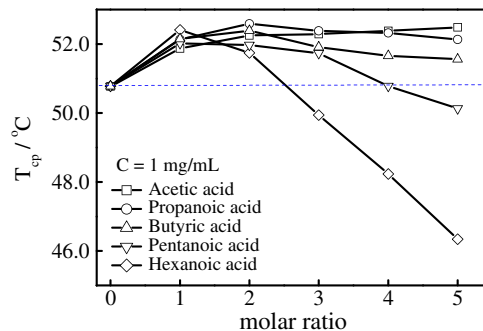
one narrowly distributed peak located at 24 nm. The increase in the scattered light intensity in the higher temperature range reflects the aggregation of the PEtOx. When the temperature is 51.3 °C, the position of the peak at 24-nm shifts to the direction of smaller  $R_h$  (~19 nm), indicating the collapse of a single PEtOx polymer. A new peak located at 106 nm appeared due to the formation of aggregates of the PEtOx polymer chains. With the further increase of the temperature, the  $\langle R_h \rangle$  of the aggregates becomes larger ~211 nm. The peak located at 19 nm disappears because all the individual PEtOx polymer form aggregates. The arrow in Fig. 5 shows how the  $T_{cp}$  is defined in the LLS experiments. It is clear that  $T_{cp}$  decreases with the addition of hexanoic acid. The values determined from LLS experiments without and with the addition of hexanoic acid are 51.3 and 48.4 °C, which are a little smaller than that from turbidity measurements as the LLS is a more sensitive technique.

The effect of ionic strength on the  $T_{cp}$  of pure PEtOx and complexes with different molar ratios of acids at pH 3.8 has been shown in Fig. 6. As compared to Fig. 4, when the ionic strength is increased from 0.1 to 0.2 M, the  $T_{cp}$  of pure PEtOx taken as a reference point decreases from 51.5 to 44.9 °C. In high ionic strength, the solvent quality with respect to the polymer may weaken, leading to the strengthening of segment–segment interaction of polymer chains as well as the association of the PEtOx with carboxylic acids especially for hexanoic acid [56]. Similarly, Staikos et al. [57] and Moharram et al. [58] found that an increase in the ionic strength of solution has a favorable effect upon poly(acrylic acid)–poly(acrylamide) interpolymer association.

Furthermore, we have also investigated the effect of original pH above the  $pK_a$  value of acids. When the  $pH > pK_a$ , the number of hydrogen bonds between acid and polymer becomes relatively small since the carboxylic groups are converted into carboxylate groups due to partial ionization. Only protonated carboxylic groups can form hydrogen bonds with proton-accepting moieties in the polymer chain

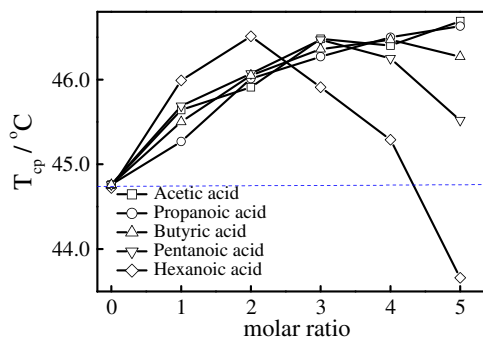


**Fig. 6** Dependence of molar ratios of acids to 2-ethyl-2-oxazoline repeat unit on  $T_{cp}$  of poly(2-ethyl-2-oxazoline), where the concentration of polymer was 1 mg/mL, the original pH=3.8, and the ionic strength of buffer solution  $I=0.2$  M



**Fig. 7** Dependence of molar ratios of acids to 2-ethyl-2-oxazoline repeat unit on  $T_{cp}$  of poly(2-ethyl-2-oxazoline), where the concentration of polymer was 1 mg/mL, the original pH=6, and the ionic strength of buffer solution  $I=0.1$  M

[24]. It can be observed in Fig. 7 that when the original pH of the buffer solution was 6, the  $T_{cp}$  of the polymer without acids has been decreased from 51.5 to 50.9 °C. However, for acetic, propanoic, and butyric acids,  $T_{cp}$  has shifted to a higher value as compared to the reference point for all the molar ratios. It is anticipated that the  $T_{cp}$  increase for these acids may be due to the decrease in the ionic strength of the buffer solution with the addition of the acids. For hexanoic acid, after the molar ratio 2, there is a sharp decrease in  $T_{cp}$  with an increase in the molar ratio of acid to 2-ethyl-2-oxazoline repeat unit. The  $T_{cp}$  decrease for hexanoic acid at a higher molar ratio is due to the predominance of the hydrophobic attractive interactions as the pH value of the solution was decreased below the  $pK_a$  value of the acids when the molar ratio was larger than 2. At original pH 6, the effect of molar ratios of acids on  $T_{cp}$  of complexes when the ionic strength was 0.2 M has been shown in Fig. 8. Comparing with Fig. 7, the  $T_{cp}$  of pure PEtOx is shifted down to 44.8 °C from 50.9 °C. For hexanoic acid,  $T_{cp}$  decreases significantly later on for higher molar ratio also due to the stronger hydrophobic interactions as the pH value of the solution was decreased to around 4.8.



**Fig. 8** Dependence of molar ratios of acids to 2-ethyl-2-oxazoline repeat unit on  $T_{cp}$  of poly(2-ethyl-2-oxazoline), where the concentration of polymer was 1 mg/mL, the original pH=6, and the ionic strength of buffer solution  $I=0.2$  M

## Conclusion

In this study, the effect of the carbon chain length of monocarboxylic acids on the phase transition of PEtOx has been investigated at different pH values, ionic strength, and molar ratios of acids to 2-ethyl-2-oxazoline. At original pH=3.8, due to the formation of the hydrogen bond between small carboxylic acids and PEtOx polymer, increasing the molar ratios decreases the  $T_{cp}$  of the complex for pentanoic acid and hexanoic acid. For acetic acid, propanoic acid, and butyric acid, the  $T_{cp}$  increases at lower molar ratio possibly due to the steric hindrance and/or the increase in the hydrophilicity of the polymer. At original pH=6.0 and  $I=0.1$  M, for acetic acid, propanoic acid, and butyric acid, the  $T_{cp}$  of PEtOx increases with the molar ratio and then levels off due to a decrease in the ionic strength of the solution with the addition of the acids; while for pentanoic acid and hexanoic acid, the  $T_{cp}$  decreases when molar ratio is larger than 2 due to the hydrophobic interaction because the acids form hydrogen bonds with the PEtOx as the pH value is decreased below the  $pK_a$  value. The shift in the  $T_{cp}$  is described based on the differences in the driving force of phase transition, including hydrogen bonding between small carboxylic acids and PEtOx polymer and hydrophobic interaction.

**Acknowledgments** The financial support of the National Program on Key Basic Research Project (2012CB933802), the National Natural Scientific Foundation of China (NNSFC) Projects (No. 20804043 and No. 21274140), Third World Academy of Science and Chinese Academy of Science (Twas-CAS), Higher Education Commission of Pakistan, and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry is gratefully acknowledged.

## References

- Bromberg LE, Ron ES (1998) Temperature-responsive gels and thermogelling polymer matrices for protein. *Adv Drug Delivery Rev* 31:197–221
- Jeong B, Kim SW, Bae YH (2002) Thermosensitive sol–gel reversible hydrogels. *Adv Drug Delivery Rev* 54:37–51
- Schmaljohann D (2006) Thermo- and pH-responsive polymers in drug delivery. *Adv Drug Delivery Rev* 58:1655–1670
- Rzaev ZMO, Dincer S, Piskin E (2007) Functional copolymers of *N*-isopropylacrylamide for bioengineering applications. *Prog Polym Sci* 32:534–595
- Kikuchi A, Okano T (2002) Intelligent thermoresponsive polymeric stationary phases for aqueous chromatography of biological compounds. *Prog Polym Sci* 27:1165–1193
- Hoogenboom R (2009) Poly(2-oxazoline)s: a polymer class with numerous potential applications. *Angew Chem Int Ed* 48:7978–7994
- Diehl C, Schlaad H (2009) Thermo-responsive polyoxazolines with widely tuneable LCST. *Macromol Biosci* 9:157–161
- Park JS, Kataoka K (2006) Precise control of lower critical solution temperature of thermosensitive Poly(2-isopropyl-2-oxazoline) via gradient copolymerization with 2-ethyl-2-oxazoline as a hydrophilic comonomer. *Macromolecules* 39:6622–6630
- Thijs HML, Van Kuringen HPC, Van der Put JPW, Schubert US, Hoogenboom R (2010) Temperature induced solubility transitions of various poly(2-oxazoline)s in ethanol–water solvent mixtures. *Polymers* 2:188–199
- Hoogenboom R, Thijs HML, Jochem MJHC, Van Lankvelt BM, Fijten MWM, Schubert US (2008) Tuning the LCST of poly(2-oxazoline)s by varying composition and molecular weight: alternatives to poly(*N*-isopropylacrylamide). *Chem Commun* 44:5758–5760
- Viegas TX, Bentley MD, Harris JM, Fang Z, Yoon K, Dizman B, Weimer R, Mero A, Pasut G, Veronese FM (2011) Polyoxazoline: chemistry, properties, and applications in drug delivery. *Bioconjugate Chem* 22:976–986
- Mero A, Pasut G, Dalla Via L, Fijten MWM, Schubert US, Hoogenboom R, Veronese FM (2008) Synthesis and characterization of poly(2-ethyl 2-oxazoline)-conjugates with proteins and drugs: suitable alternatives to PEG-conjugates. *J Control Release* 125:87–95
- Lee SC, Kim C, Kwon IC, Chung H, Jeong SY (2003) Polymeric micelles of poly(2-ethyl-2-oxazoline)-block-poly( $\epsilon$ -caprolactone) copolymer as a carrier for paclitaxel. *J Control Release* 89:437–446
- Gaertner FC, Luxenhofer R, Blechert B, Jordan R, Essler M (2007) Synthesis, biodistribution and excretion of radio labeled poly(2-alkyl-2-oxazoline)s. *J Control Release* 119:291–300
- Hsiue GH, Wang CH, Lo CL, Wang CH, Li JP, Yang JL (2006) Environmental-sensitive micelles based on poly(2-ethyl-2-oxazoline)-*b*-poly(L-lactide) diblock copolymer for application in drug delivery. *Int J Pharm* 317:69–75
- Wiesbrock F, Hoogenboom R, Abeln CH, Schubert US (2004) Single-mode microwave ovens as new reaction devices: accelerating the living polymerization of 2-ethyl-2-oxazoline. *Macromol Rapid Commun* 25:1895–1899
- Lin PY, Clash C, Pearce EM, Kwei TK, Aponte MA (1988) Solubility and miscibility of poly(ethyl-oxazoline). *J Polym Sci B-Polym Phys* 26:603–619
- Haruna M (2010) Synthesis and characterization of temperature responsive poly(2-ethyl-2-oxazolines). *Bajopas* 3:250–254
- Bloksma MM, Bakker DJ, Weber C, Hoogenboom R, Schubert US (2010) The effect of Hofmeister salts on the LCST transition of poly(2-oxazoline)s with varying hydrophilicity. *Macromol Rapid Commun* 31:724–728
- Burova TV, Grinberg NV, Grinberg VY, Kalinina EV, Lozinsky VI, Aseyev VO, Holappa S, Tenhu H, Khoklov AR (2005) Unusual conformational behavior of complexes of poly(*N*-isopropylacrylamide) with poly(methacrylic acid). *Macromolecules* 38:1292–1299
- Garay MT, Llamas MC, Iglesias E (1997) Study of polymer–polymer complexes and blends of poly(*N*-isopropylacrylamide) with poly(carboxylic acid): 1. Poly(acrylic acid) and poly(methacrylic acid). *Polymer* 38:5091–5096
- Koussathana M, Lianos P, Staikos G (1997) Investigation of hydrophobic interactions in dilute aqueous solutions of hydrogen-bonding interpolymer complexes by steady-state and time-resolved fluorescence measurements. *Macromolecules* 30:7798–7802
- Garay MT, Alava C, Rodriguez M (2000) Study of polymer–polymer complexes and blends of poly(*N*-isopropylacrylamide) with poly(carboxylic acid). 2. Poly(acrylic acid) and poly(methacrylic acid) partially neutralized. *Polymer* 41:5799–5807
- Bian F, Liu M (2003) Complexation between poly(*N*, *N*-diethylacrylamide) and poly(acrylic acid) in aqueous solution. *Eur Polym J* 39:1867–1874
- Kwon IC, Bae YH, Kim SW (1991) Electrically erodible polymer gel for controlled release of drugs. *Nature* 354:291–293
- Lichkus AM, Painter PC, Coleman MM (1988) Hydrogen bonding in polymer blends. 5. Blends involving polymers containing methacrylic acid and oxazoline groups. *Macromolecules* 21:2636–2641

27. Chen FL, Pearce EM, Kwei TK (1988) Intermacromolecular complexes by in situ polymerization. *Polymer* 29:2285–2289
28. Kim C, Lee SC, Kwon IC, Chung H, Jeong SY (2002) Complexation of poly(2-ethyl-2-oxazoline)-block-poly( $\epsilon$ -caprolactone) micelles with multifunctional carboxylic acids. *Macromolecules* 35:193–200
29. Zimm BH (1948) The scattering of light and the radial distribution function of high polymer solutions. *J Chem Phys* 16:1093–1099
30. Chu B (1991) Laser light scattering, basic principles and practice, 2nd edn. Academic, New York, chapter 2 and 8
31. Wu C, Xia KQ (1994) Incorporation of a differential refractometer into a laser light-scattering spectrometer. *Rev Sci Instrum* 65:587–590
32. Bijsterbosch HD, Cohen Stuart MA, Fleer GJ, van Caeter P, Goethals EJ (1998) Nonselective adsorption of block copolymers and the effect of block incompatibility. *Macromolecules* 31:7436–7444
33. Berne BJ, Pecora R (1976) Dynamic light scattering. Plenum, New York
34. Diab C, Akiyama Y, Kataoka K, Winnik FM (2004) Microcalorimetric study of the temperature-induced phase separation in aqueous solutions of poly(2-isopropyl-2-oxazolines). *Macromolecules* 37:2556–2562
35. Park JS, Akiyama Y, Winnik FM, Kataoka K (2004) Versatile synthesis of end-functionalized thermosensitive poly(2-isopropyl-2-oxazolines). *Macromolecules* 37:6786–6792
36. Christova D, Velichkova R, Loos W, Goethals EJ, Du Prez F (2003) New thermo-responsive polymer materials based on poly(2-ethyl-2-oxazoline) segments. *Polymer* 44:2255–2261
37. Zhou S, Fan S, Au-yeung SCF, Wu C (1995) Light-scattering studies of poly(*N*-isopropylacrylamide) in tetrahydrofuran and water. *Polymer* 36:1341–1346
38. Mattoussi H, O'Donohue S, Karasz FE (1992) Polyion conformation and second virial coefficient dependences on the ionic strength for flexible polyelectrolyte solutions. *Macromolecules* 25:743–749
39. Lide DV (2009) Handbook of chemistry and physics, 90th edn. CRC, Boca Raton
40. Namazian M, Halvani S (2006) Calculations of  $pK_a$  values of carboxylic acids in aqueous solution using density functional theory. *J Chem Therm* 38:1495–1502
41. Jones MS (1999) Effect of pH on the lower critical solution temperatures of random copolymers of *N*-isopropylacrylamide and acrylic acid. *Eur Polym J* 35:795–801
42. Van Kuringen HPC, De la Rosa VR, Fijten MWM, Heuts JPA, Hoogenboom R (2012) Enhanced selectivity for the hydrolysis of block copoly(2-oxazoline)s in ethanol–water resulting in linear poly(ethylene imine) copolymers. *Macromol Rapid Commun* 33:827–832
43. Weber C, Becer CR, Hoogenboom R, Schubert US (2009) Lower critical solution temperature behavior of comb and graft shaped poly[oligo(2-ethyl-2 oxazoline)methacrylate]s. *Macromolecules* 42:2965–2971
44. Weber C, Becer CR, Guenther W, Hoogenboom R, Schubert US (2010) Dual responsive methacrylic acid and oligo(2-ethyl-2-oxazoline) containing graft copolymers. *Macromolecules* 43:160–167
45. Huber S, Jordan R (2008) Modulation of the lower critical solution temperature of 2-alkyl-2-oxazoline copolymers. *Colloid Polym Sci* 286:395–402
46. Park JS, Kataoka K (2007) Comprehensive and accurate control of thermosensitivity of poly(2-alkyl-2-oxazoline)s via well-defined gradient or random copolymerization. *Macromolecules* 40:3599–3609
47. Hoogenboom R, Thijs HML, Wouters D, Hoepfener S, Schubert US (2008) Tuning solution polymer properties by binary water–ethanol solvent mixtures. *Soft Matter* 4:103–107
48. Weng YM, Ding YW, Zhang GZ (2006) Microcalorimetric investigation on the lower critical solution temperature behavior of *N*-isopropylacrylamide-*co*-acrylic acid copolymer in aqueous solution. *J Phys Chem B* 110:11813–11817
49. Feil H, Bae YH, Feijen J, Kim SW (1993) Effect of comonomer hydrophilicity and ionization on the lower critical solution temperature of *N*-isopropylacrylamide copolymers. *Macromolecules* 26:2496–2500
50. Chen G, Hoffmann AS (1995) Graft copolymers that exhibit temperature-induced phase transitions over a wide range of pH. *Nature* 373:49–52
51. Hofmann AS et al (2000) Really smart bioconjugates of smart polymers and receptor proteins. *J Biomed Mater Res* 52:577–586
52. Tang YC, Ding YW, Zhang GZ (2008) Role of methyl in the phase transition of poly(*N*-isopropylmethacrylamide). *J Phys Chem B* 112:8447–8451
53. Hoogenboom R (2007) Poly(2-oxazoline)s: alive and kicking. *Macromol Chem Phys* 208:18–25
54. Hoogenboom R (2011) Poly(2-oxazoline)s based on fatty acids. *Eur J Lipid Sci Technol* 113:59–71
55. Ralston AW, Hoerr CW (1942) The solubilities of the normal saturated fatty acids. *J Org Chem* 7:546–555
56. Nurkeeva ZS, Mun GA, Khutoryanskiy VV, Sergaziev AD (2001) Complex formation between poly(vinyl ether of diethylene glycol) and poly(acrylic acid). I. Effect of low molecular salts and phenol additives. *Eur Polym J* 37:1233–1237
57. Staikos G, Tsitsilianis C (1991) Viscometric investigation of the poly(acrylic acid)–polyacrylamide interpolymer association. *J Appl Polym Sci* 42:867–872
58. Moharram MA, Balloomal LS, El-Gendy HM (1996) Infrared study of the complexation of poly(acrylic acid) with poly(acrylamide). *J Appl Polym Sci* 59:987–989