

Reversible **Thermoresponsive** Behavior of Poly(2-chloroethyl vinyl ether-*alt*-maleic anhydride) in Mixed Solvent of Tetrahydrofuran/Hexane

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Abstract Poly(2-chloroethyl vinyl ether-alt-maleic anhydride) can exhibit lower critical solution temperature (LCST)-type phase behavior reversibly by tuning the solvent composition in mixed solvent of tetrahydrofuran (THF) and hexane. The effect of solvent composition and polymer concentration on cloud point of polymer solution was investigated. The cloud point temperature for high molecular weight polymer was lower than that for lower molecular weight polymer. High resolution ^1H NMR spectra in mixed solvent of THF- d_8 and hexane were also measured for comprehending thermoresponsive behavior of polymer solution in molecular level, however, any discontinuous change in the NMR signals around the cloud point could not be recognized.

Keywords: *Stimuli-sensitive polymers • Thermoresponsive polymers • Solution properties • Phase Behavior • Lower critical solution temperature • Organic media*

Introduction □

Thermoresponsive polymers can undergo relatively large and abrupt physical or chemical property changes in response to small external changes of temperature in the environment, and those polymers generally have a lower critical solution temperature (LCST) or upper critical solution temperature (UCST). Most interest is related to LCST-type polymers, and based on this kind of polymers many applications have also been developed [1-3].

As for LCST-type phase behavior of polymers in water some theories have been developed in order to predict the thermoresponsive behavior and discover new polymers which can exhibit LCST-type phase behavior [4-6], and water-soluble thermoresponsive polymers have been used in many fields [1, 6, 7-9] such as controlled drug delivery [7], thermoresponsive stabilizers [8] and bioconjugates [1]. However, in the past LCST-type phase behavior of polymers in organic media did not attract so much attention, and one of reasons may be that LCST of conventional polymer systems in organic media occurs at some tough conditions such as near or above boiling point of solvent, so it is not convenient to study this kind of phenomena [10-17]. Nowadays LCST-type phase behavior in organic media at mild conditions has started to attract some interest, but only a few novel examples have been reported [18-20], for example, polymers capped by fluoroalkyl groups [18], heat-set gel-like networks of lipophilic Co(II) triazole complexes [19] and polymers with ionic liquid pendants [20].

Here we report an organic polymer solution system which can exhibit LCST-type phase behavior at mild conditions. In our former article we simply reported the phenomenon that alternating copolymer of 2-chloroethyl vinyl ether and maleic anhydride (P(CVE-MA)) can present LCST-type phase behavior in proper organic media [21]. It is commonly reported that some polymers can exhibit LCST-type phase behavior in mixed solvent of water and organic media [22-31]. However, it is novel that organic polymer solution exhibits LCST-type phase behavior by changing the quality of mixed solvent at mild conditions, and studying this kind of thermoresponsive phase behavior can help us to understand the polymer solution properties deeply. Herein we studied LCST-type behavior of P(CVE-MA) in mixed THF/hexane solvent in detail and investigated ^1H NMR measurements to comprehend the mechanism of thermoresponsive behavior in molecular level.

Experimental part

Materials

Sodium hydroxide (NaOH; Nacalai tesque; 97%), anhydrous sodium sulfate (Na_2SO_4 ; Nacalai tesque; 97%), calcium hydride (CaH_2 ; Nacalai tesque; EP), and 2,2'-azobisisobutyronitrile (AIBN; Wako; >98%), hexane (Kishida Chemical; 96%) were used as received. 2-Chloroethyl vinyl ether (CVE; TCI; >97.0%) was washed three times with equal volume of water made slight alkaline with NaOH, dried with Na_2SO_4 and refluxed in the presence of CaH_2 for 2 hours and distilled under reduced vacuum. Maleic anhydride (MA; TCI; >99.0%) was recrystallized in benzene. Methyl ethyl ketone (MEK; TCI; >99.0%) was refluxed in the presence of CaH_2 for 2 hours, distilled under reduced pressure and kept in the presence of molecular sieve. Tetrahydrofuran (THF; Wako; >99.5%) was distilled before using. THF- d_8 (Nacalai tesque) was used as received.

Synthesis of polymers

Copolymerization of MA and CVE was carried out by free-radical solution polymerization: i.e. , MA (1.225 g), CVE (1.332 g), AIBN (0.006 g), and MEK (5 g) were added into a 50 mL three-neck flask equipped with a condenser and an inlet of nitrogen gas. The polymerization solution was stirred for 2 hours at the 70 °C. The resultant polymer was precipitated in diethyl ether and dried under vacuum at 100 °C for at least 8 hours. In order for polymerization of lower molecular weight polymer, MA (1.225 g), CVE (1.332 g), AIBN (0.01 g), and THF (10 g) were also reacted in the same system at 60 °C for 6 hours.

Gel permeation chromatograph (GPC)

Molecular weight of the prepared copolymer were determined by GPC using 2 columns of TSKgel GMH_{XL} and one column of TSKgel G2000H_{XL} connected to integrated HLC-8020 system (TOSOH) at a 1.0 mL/min flow rate of THF. Polystyrene standards were used for molecular weight calibration.

FT-IR measurement

Infrared spectrum of copolymer was recorded in a Nicolet AVATAR 320S FT-IR spectrophotometer in KBr pellet.

Sample preparation of polymer solution

Certain amount of polymer was dissolved in the mixed solvent of THF and hexane. The composition of the used solvents was different from one to another. The sample was sealed and kept in a refrigerator at about 3 °C overnight before the measurements were done.

Static light scattering (SLS) measurement

Thermoresponsive phase behavior of the polymer solution was characterized by the scattered light intensity (I_s) at different temperatures at a fixed angle of 90°. I_s was measured by a laboratory-made apparatus equipped with an ALV/SO-SIPD detector using He-Ne laser (the wavelength $\lambda_0 = 633$ nm) [32]. Sample solutions were optically purified by a Millipore filter of nominal pore size of 1.0 μm and transferred into optical tube. The heating and cooling rate of the system was about 0.2 °C/min. I_s of the polymer solution was measured immediately as the temperature of the system reached the desired temperature.

^1H NMR measurement

About 0.088 g polymer was dissolved in 0.52g THF- d_8 in a NMR tube with an outer diameter of 5 mm, and ^1H NMR spectra in THF- d_8 at different temperature were measured using BRUKER AVANCE 600 (600 MHz) spectrometer. Weight percentage of polymer in THF- d_8 was about 15wt%. After ^1H NMR spectra at different temperatures in THF- d_8 , about 0.02 g polymer (to keep the same polymer concentration) and 0.105g hexane was added into the former polymer solution, and ^1H NMR spectra at different temperatures were also measured in the mixed solvent. The weight percentage of polymer was about 15wt% in mixed THF- d_8 /hexane solvent, and the weight percentage of THF- d_8 in the mixed solvent

was about 83.2wt%. Scanning times was 128 and receiver gain was kept constant in all NMR measuring experiments.

Results and discussion

Synthesis and chemical composition of copolymers

The GPC graph of synthesized copolymer is shown in Fig. 1. P(CVE-MA)-H, with a weight-averaged molecular weight (M_w) of 66,000 g/mol, was synthesized in MEK (Fig. 1a), and another copolymer P(CVE-MA)-L with M_w of 6,000 g/mol was prepared in THF (Fig. 1b). P(CVE-MA)-H owns a broad molecular weight distribution and the ratio of M_w and number-averaged molecular weight (M_n) was 3.14, while P(CVE-MA)-L owns M_w/M_n of 1.89.

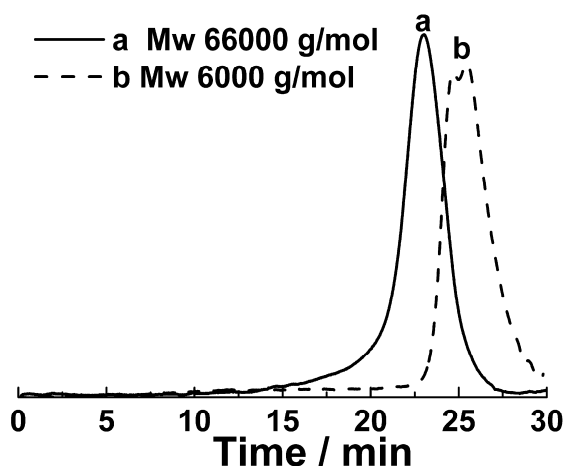


Fig. 1 GPC graph of prepared polymers.

The FT-IR [spectrum](#) of P(CVE-MA)-H is shown in Fig. 2. Peaks at 1850 and 1780 cm^{-1} correspond to the asymmetric and symmetric C=O stretch. Peaks at 1225 and 927 cm^{-1} are due to ring stretching vibrations of a saturated cyclic five-membered anhydride. Peaks at 1110, 736 and 665 cm^{-1} are the characteristic adsorption of groups of 2-chloroethyl vinyl ether repeating unit. It is concluded that the resultant polymer is a copolymer of maleic anhydride and 2-chloroethyl vinyl ether. The spectra of ^1H NMR and ^{13}C NMR of copolymer have been reported in former report and it could be concluded that the overall molar ratio of

maleic anhydride and 2-chloroethyl vinyl ether is 1:1 and the resultant copolymer should be an alternating copolymer [21].

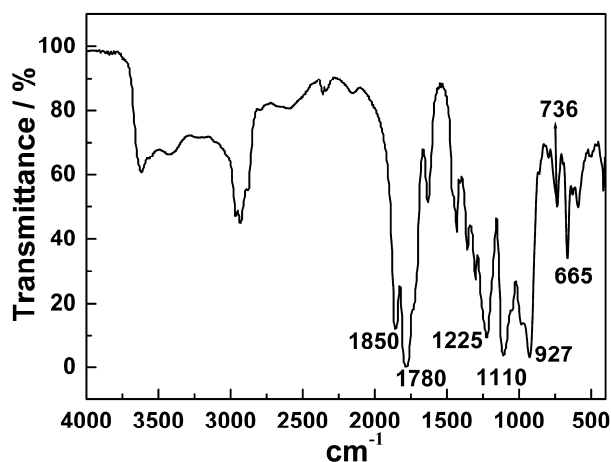


Fig. 2 FT-IR spectrum of P(CVE-MA)-H.

LCST-type phase behavior of polymer solution

The solution of P(CVE-MA) in the mixed solvent of THF/hexane can exhibit reversible thermoresponsive behavior. In SLS measurements, I_s of polymer solution increased substantially above a certain critical temperature (Fig. 3). Visually, the polymer solution would become turbid as the temperature increased to a certain temperature, means phase separation occurred at higher temperature region. The turbid system can recover to the original state of clear polymer solution as the temperature became lower than the critical temperature, and this kind of process was reversible. The temperature at which the polymer solution becomes turbid depends on the polymer concentration in the solution at a certain solvent composition. Especially at lower polymer concentrations, the temperature at which I_s increased sharply was lower than the temperature at which the polymer solution became turbid visually [21]. Here, the former temperature is considered as the cloud point (T_{cp}) of the polymer solution. T_{cp} is defined from the curve of I_s versus temperature, i.e., the temperature at the intersection point of the tangent of two part curves with different increase ratio, as indicated by point A in Fig.3.

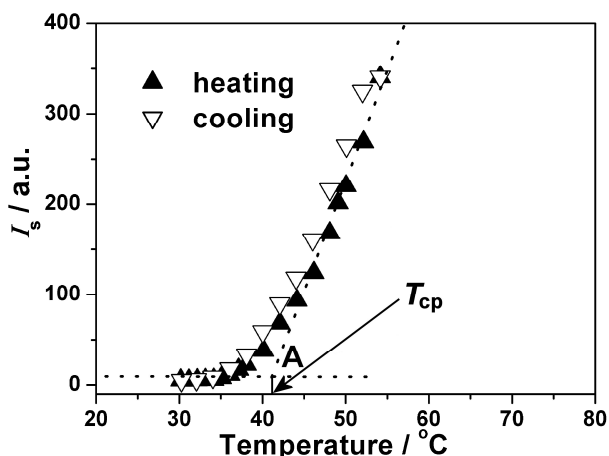


Fig. 3 Temperature dependence of I_s for P(CVE-MA)-H solution in the mixed solvent of THF and hexane. The weight percentage of THF in the mixed solvent is 83 wt%, and concentration of P(CVE-MA)-H is 0.4 wt%.

Effect of polymer concentration and solvent composition on T_{cp}

P(CVE-MA) solution can occur phase separation at desired temperature by tuning the solvent composition of mixed solvent of THF and hexane. First we investigated the [thermoreponsive](#) behavior of P(CVE-MA)-H ($M_w = 66,000$ g/mol). As the polymer concentration was above 0.1 wt% and the weight percentage of THF in the mixed solvent was enough low (usually, < 79 wt%), T_{cp} of polymer solution was below 0 °C (observed by naked eyes in refrigerator). As the weight percentage of THF was far high (usually, > 88 wt%) and polymer concentration was below 2 wt%, the polymer solution maintained clear state below boiling point of THF and hexane. So in order to characterize thermoresponsive behavior, the weight percentage of THF in mixed solvent ranged from 81 to 85 wt% in this paper. Temperature dependence of I_s of polymer solutions in different solvent compositions is shown in Fig. 4. It can be seen from Fig. 4 that I_s increases abruptly at a certain T_{cp} , which indicates thermoresponsive behavior of polymer solution.

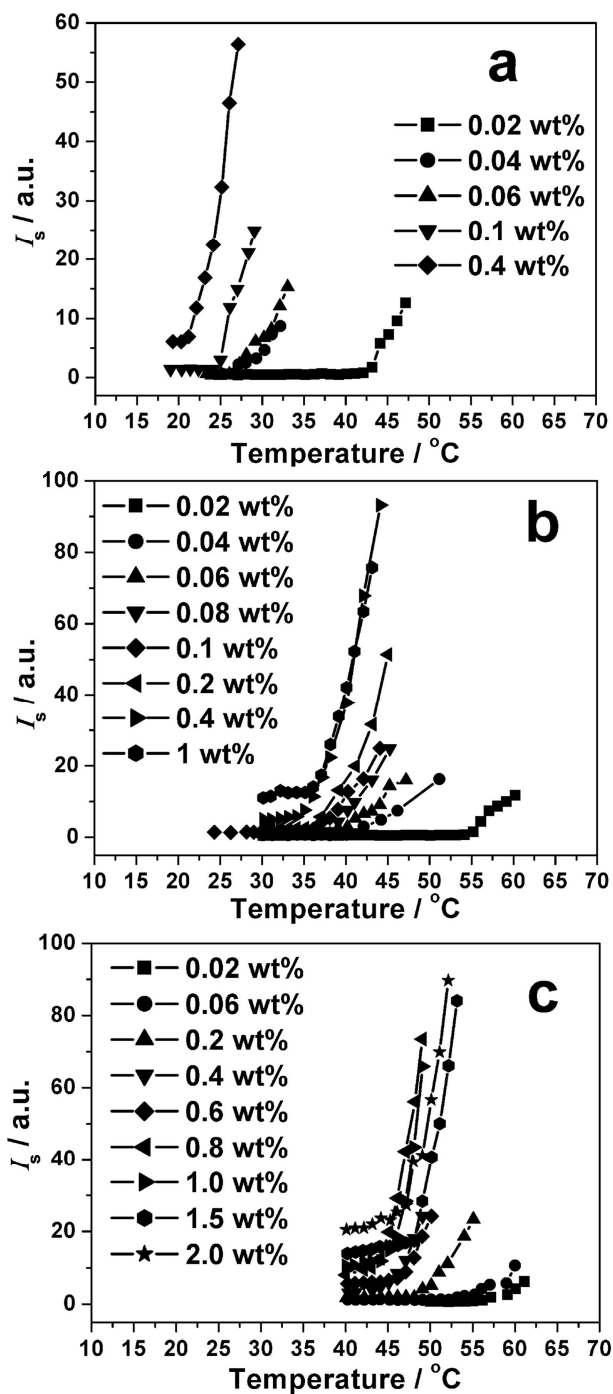


Fig. 4 Temperature dependence of I_s of P(CVE-MA)-H solutions at different weight percentage of THF (a) 81 wt%, (b) 83 wt%, and (c) 85 wt%. The weight percentage of polymer in solution is indicated in the graph.

As shown in Fig. 4 the increasing behavior of I_s with temperature depends on polymer concentration. At higher concentrations, I_s increased much more abruptly and its temperature dependence after phase separation was much steeper than those of lower polymer concentration.

It can be seen from Fig. 4 that T_{cp} of polymer solution is relied on polymer concentration and solvent compositions to a certain extent. T_{cp} as a function of polymer concentration can be obtained from Fig. 4 and plotted in Fig. 5. It can be seen from Fig. 5 that P(CVE-MA)-H presents LCST-type phase behavior in the mixed solvent of THF/hexane with proper weight percentage of THF. In low concentration region, T_{cp} decreased as the increase in polymer concentration, and then approached to a certain constant value. This phenomenon is often observed in various LCST-type thermoresponsive polymer solution [33-36] and also observed in P(CVE-MA)/n-butyl acetate solutions in our previous paper [37]. THF is a good solvent for P(CVE-MA) and hexane is nonsolvent, so with increase in THF in the mixed solvent, the homogeneous one-phase region below the T_{cp} curve in Fig. 5 became wider. Similar result was also observed in mixed [aqueous](#) solution of poly(*N*-isopropyl acrylamide) [22].

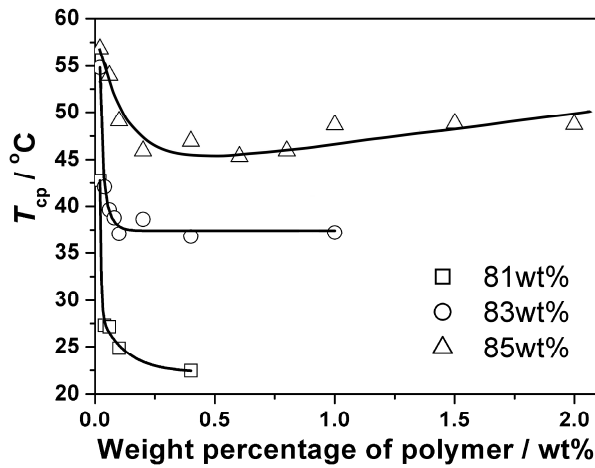


Fig. 5 T_{cp} of polymer solution at different polymer concentrations for P(CVE-MA)-H. The weight percentage of THF in mixed solvent is indicated in the graph.

Thermoresponsive behavior of P(CVE-MA)-L with lower M_w (6,000 g/mol) was also investigated in the mixed solvent of THF and hexane as shown in Fig. 6. In the mixed solvent with THF weight percentage of 81 wt%, LCST-type thermoresponsive behavior was observed at the polymer concentration ranging from 1 wt% to 10 wt%, and T_{cp} decreased with increase of polymer concentration (Fig. 6a). When the THF weight percentage was 83 wt%, the abrupt increase in I_s was not [observed](#) at the polymer concentration of 1 wt%, and LCST-type thermoresponsive behavior was [recognized](#) above 1.5 wt% (Fig. 6b). By further

increase in THF weight percentage to 85 wt% (Fig. 6c), there was no thermoresponsive behavior even at high polymer concentrations of 10 wt%.

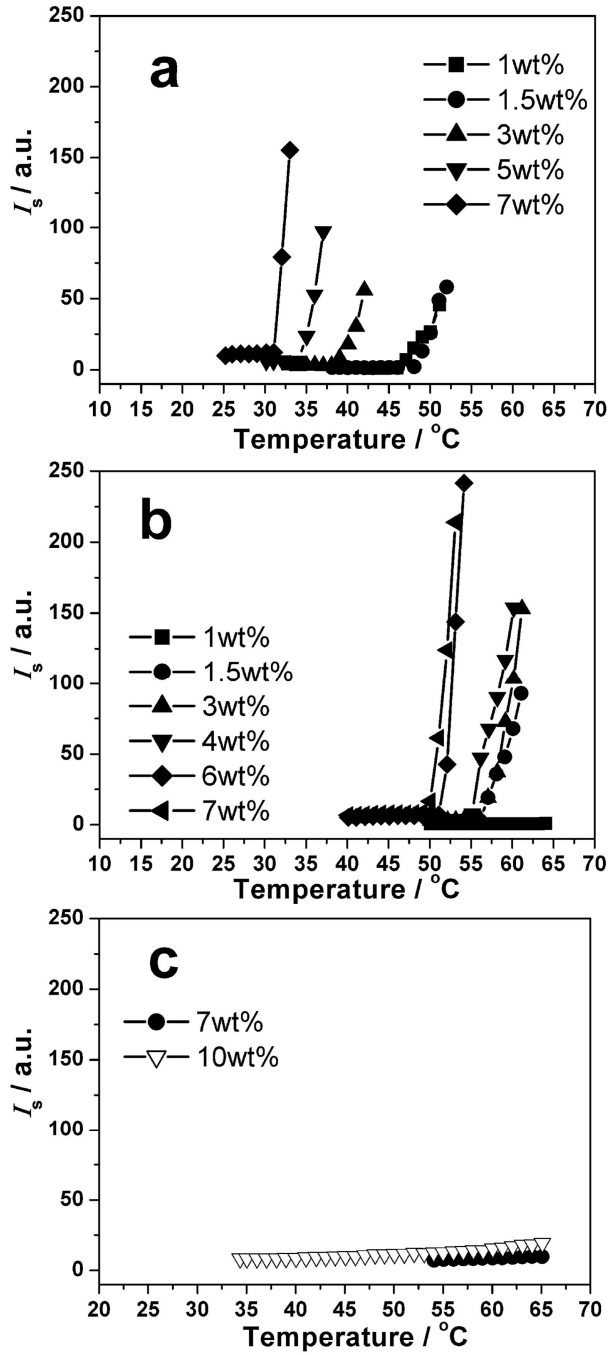


Fig. 6 Temperature dependence of I_s of P(CVE-MA)-L solutions at different weight percentage of THF (a) 81 wt%, (b) 83 wt%, and (c) 85 wt%. The weight percentage of polymer in solution is indicated in the graph.

T_{cp} as the function of polymer concentration for P(CVE-MA)-L is shown in Fig. 7. It can be seen that polymer concentration owns less influence on T_{cp} in solutions with higher THF weight percentage. As similarly observed in Fig. 5, T_{cp}

line for 83 wt% THF solution located at high temperature region than those for 81 wt% THF solution.

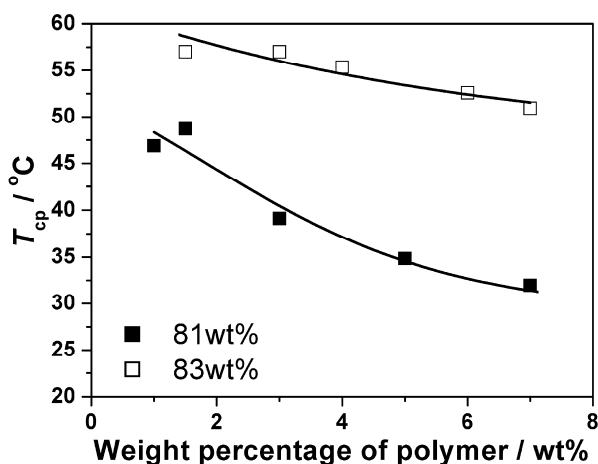


Fig. 7 T_{cp} of polymer solution at different polymer concentrations for P(CVE-MA)-L. The weight percentage of THF is indicated in the graph.

From comparison between Fig.5 and Fig.7, it can be concluded that T_{cp} of P(CVE-MA)-H solution is lower than that of P(CVE-MA)-L solution under same solvent conditions. Similar results was also observed in P(CVE-MA)/*n*-butyl acetate system [37].

NMR spectra of polymer solution

NMR spectroscopy can be used for studying thermoresponsive phase behavior of polymer solution and can help to understand the phase transition in molecular level [38-43]. High resolution ^1H NMR spectra of different protons of P(CVE-MA)-H in pure THF- d_8 measured at different temperature and their assignments are shown in Fig. 8a. In pure THF- d_8 all the protons of the polymer revealed a fine spectrum. The spectrum was almost identical in the range of 25 °C – 60 °C, indicates the almost same chemical environment for all protons within this temperature region.

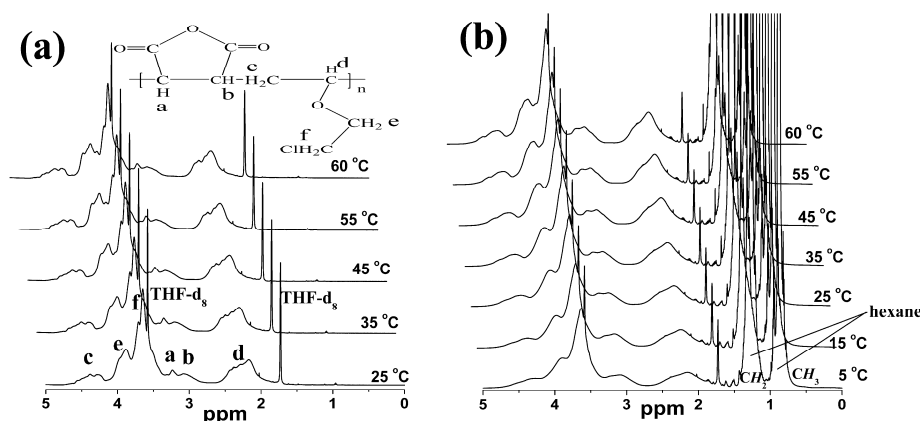


Fig. 8 ^1H NMR spectra of P(CVE-MA) at different temperatures. (a) In pure THF- d_8 , and (b) in THF- d_8 /hexane mixed solvent.

^1H NMR spectra of P(CVE-MA)-H in mixed THF- d_8 /hexane solvent measured at different temperatures are shown in Fig. 8b. It should be noted that no phase separation happened visually below 25 °C, and the solution in NMR tube became turbid above 35 °C. Comparing to the ^1H NMR spectrum in pure THF- d_8 , line shape for polymer protons broadened and splitting of the resonance disappeared. This indicates that the mobility of polymer chains was restricted with addition of hexane. We can also point out that the spectrum became sharper with the increase of temperature, which is in contrast to the spectrum in pure THF- d_8 , suggesting that the chemical environment or mobility of the polymer chain are strongly influenced by temperature in solution around T_{cp} . However, any discontinuous changes in the spectra at 25 °C and 35 °C, between which the phase separation occurred, could not be recognized. In usual LCST or UCST systems, NMR signals will be broadened and decreased in intensity by the phase separation because of the decrease in mobility of the polymer chain. Therefore, the results in Fig 8b seems strange because the peak intensity continued to increase even after the phase separation occurred above 35 °C.

One possible explanation of the above results is as follows. For P(CVE-MA), THF is good solvent and hexane is non-solvent. So in the THF/hexane mixed solvent, the polymer should be solvated by more THF molecules than hexane, presumably because of some specific interaction between THF and polymer. As the result, the solution can be recognized as the system of THF-solvated polymers dissolved in THF/hexane. If the amount of the solvated THF will be reduced with increasing temperature, the mixed solvent THF/hexane will

become worse for the solvated polymer, and the polymer start to aggregate resulting into phase separated state. Even after the phase separation into polymer-rich and polymer-poor phases, chain mobility in the former phase will be enough high because of the solvated THF, that is why any changes in ^1H NMR spectrum was not recognized by the phase separation and only the peak sharpening with increasing temperature was observed.

In order to inspect the above speculation, further researches for understanding this LCST behavior in molecular level much more deeply and accurately, such as vibrational spectroscopies, should be necessary, and will be conducted in future.

Conclusion

Alternating copolymer P(CVE-MA) with higher or lower molecular weight exhibited LCST-type phase behavior in mixed THF/hexane solvent. Cloud point of copolymer solution can be tuned by changing the solvent composition of mixed solvent or copolymer concentrations. Higher molecular weight polymer revealed lower T_{cp} than lower molecular weight polymer. As the weight percentage of THF increased in mixed THF/hexane solvent, T_{cp} was increased and effect of polymer concentration on T_{cp} became smaller. ^1H NMR spectra suggested that addition of hexane into polymer solution in THF may create proper medium condition in which temperature change can induce variation of polymer chain's environment or mobility largely. However, any discontinuous changes in NMR signals around T_{cp} could not be observed.

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Figure legends

Fig. 1 GPC graph of prepared polymers.

Fig. 2 FT-IR spectrum of P(CVE-MA)-H.

Fig. 3 Temperature dependence of I_s for P(CVE-MA)-H solution in the mixed solvent of THF and hexane. The weight percentage of THF in the mixed solvent is 83 wt%, and concentration of P(CVE-MA)-H is 0.4 wt%.

Fig. 4 Temperature dependence of I_s of P(CVE-MA)-H solutions at different weight percentage of THF (a) 81 wt%, (b) 83 wt%, and (c) 85 wt%. The weight percentage of polymer in solution is indicated in the graph.

Fig. 5 T_{cp} of polymer solution at different polymer concentrations for P(CVE-MA)-H. The weight percentage of THF in mixed solvent is indicated in the graph.

Fig. 6 Temperature dependence of I_s of P(CVE-MA)-L solutions at different weight percentage of THF (a) 81 wt%, (b) 83 wt%, and (c) 85 wt%. The weight percentage of polymer in solution is indicated in the graph.

Fig. 7 T_{cp} of polymer solution at different polymer concentrations for P(CVE-MA)-L. The weight percentage of THF is indicated in the graph.

Fig. 8 ^1H NMR spectra of P(CVE-MA) at different temperatures. (a) In pure THF- d_8 , and (b) in THF- d_8 /hexane mixed solvent.