

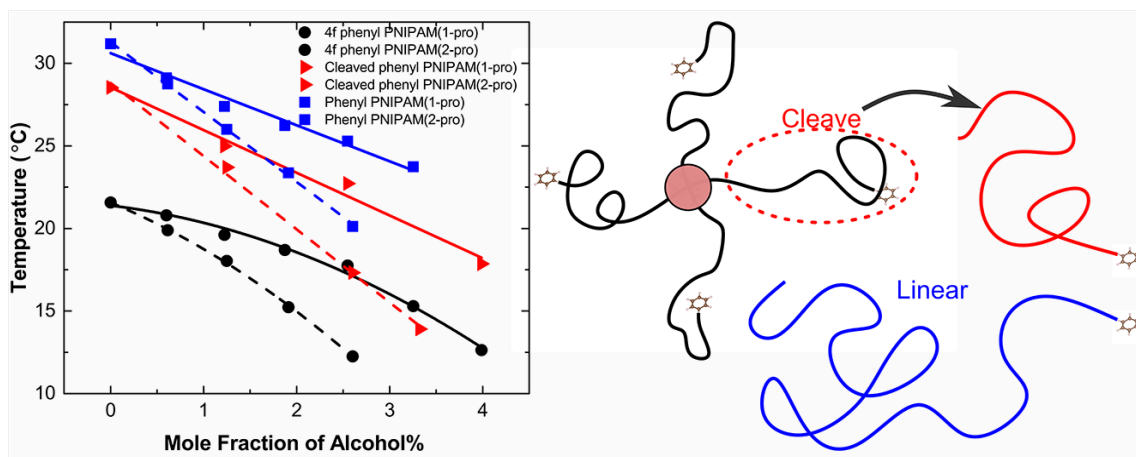
Isomeric and Structural Effects in Polymer Cononsolvent Systems

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Graphical Abstract



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Abstract

Thermoresponsive poly (N-isopropylacrylamide) (PNIPAM) has many analogs that exhibit cononsolvency behavior in mixtures of water and an alcohol. Cononsolvency is characterized by a combination of good solvents for a polymer that results in decreased solubility. In this work, the cononsolvency behavior of linear PNIPAM, four-arm (4f) star PNIPAM, and linear poly(N-n-propylacrylamide) (PNnPAM), with terminal groups that vary in hydrophobicity, were investigated in mixtures of water and propanol. Polymers were synthesized by RAFT polymerization and subsequently functionalized with one pot aminolysis/ thiol-ene chemistry. Turbidimetry measurements and dynamic light scattering (DLS) were used to study the cononsolvency behavior by determining the critical solution temperature (T_c). The measurements show that the size and shape of the hydrophobic region of both the solvent and n-alkyl acrylamide monomer affect T_c and the phase transition behavior. The findings suggest methods to impart multiresponsiveness to soft material systems.

1. Introduction

Thermoresponsive polymers, most notably poly (N-isopropylacrylamide) (PNIPAM), have been widely studied for a variety of applications.[1, 2] Aqueous solutions of PNIPAM and similar polymers, such as poly(N-n-propylacrylamide) (PNnPAM), exhibit a lower critical solution temperature (LCST). The polymers undergo a coil-to-globule transition at the LCST, above which the solubility of the polymer is drastically reduced[3]. The LCST behavior of PNIPAM in aqueous solutions results from the amphiphilic nature of the monomer. Hydrophobic isopropyl groups of PNIPAM are hydrated below the LCST and hydrophilic amide groups of PNIPAM form hydrogen bonds with water molecules, which are destabilized with increasing temperature.

Numerous studies have been performed to investigate the phase transition of PNIPAM and its analogs, focusing on factors such as terminal groups, architecture, co-monomer, tacticity, molecular weight, grafting density and addition of cosolvent.[4-9] The addition of some cosolvents to aqueous PNIPAM solutions can decrease the solvation of PNIPAM and promote reduction of the LCST[10, 11]. Polymers can exhibit unintuitive behaviors in solvent mixtures. Most water-soluble polymers show cosolvency behavior, in which solvent mixtures enhance the solvation of polymer. Poly (ethylene oxide) (PEO) exhibits cosolvency; it dissolves better in mixtures of water and ethanol than in either solvent alone[12]. In contrast, a mixture of two good solvents for a polymer, which cannot dissolve the same polymer within intermediate solvent-cosolvent mixing ratios, is referred to as cononsolvency. The somewhat paradoxical behavior was first reported for polystyrene in a cyclohexane/DMF mixture[13]. A number of polymers, including poly(ether imide), poly(n-propylacrylamide), poly (vinylpyrrolidone), and poly(vinyl caprolactam) exhibit cononsolvency in certain solvent combinations[14-16]. PNIPAM is perhaps the most studied polymer with cononsolvency behavior due to its thermoresponsiveness in aqueous solutions. The origin of the cononsolvency behavior of PNIPAM has been investigated using a variety of experimental, theoretical and computer simulation methods, with most of these studies focused on mixtures of water and methanol[10, 17-19]. Experimental methods include turbidimetry, light scattering, neutron scattering, microcalorimetry[9, 11, 20]. Theoretical studies generally concentrate on Flory-Huggins type analysis[21, 22] or cooperative/preferential hydrogen bonding[18, 23]. The cooperative hydration theory put forth by Okada and Tanaka proposed that the initial hydrogen bond formed between amide-water promotes further polymer-water hydrogen bond formation. There have been other studies trying to understand cononsolvency behavior by the combination of multiple χ parameters and complex formation between water and alcohol[11,

20, 24]. Recent work has attempted to understand cononsolvency by means of atomistic molecular dynamics (MD) simulations of short PNIPAM chains ($N = 40$, $M_n \approx 5$ kg/mol). [17, 25, 26] Computational calorimetry has found that cononsolvency may be the result of competition between water and alcohol molecules that prefer to bind to different regions of the NIPAM monomer. Analysis has found that methanol prefers to interact with the isopropyl group of the monomer, while water interacts with the secondary amine.[26] The result is a decrease in the interaction energies between the polymer and surrounding solvent environment. Assuming minimal entropic contributions, a decrease in the interaction energies will lead to a decrease in the LCST.[27]

Several groups have investigated the effect of terminal group or co-monomers on the LCST of linear PNIPAM, which show the potential ways to tune the LCST of PNIPAM and its copolymers. Generally, hydrophobic terminal groups lead to lower values of the LCST and hydrophilic groups increase the LCST by altering the polymer-polymer and polymer-solvent interactions[8, 28]. Qiu et al. studied the effects of molecular weight and end group on the phase transition behavior of aqueous PNIPAM[28]. They prepared PNIPAM from a bifunctionalized chain transfer agent and further modified the end groups, which resulted in PNIPAM with the same functionality on each chain end. By comparing the T_c of these polymers measured by DSC and turbidimetry, they observed that hydrophilic terminal groups, such as hydroxyl, increase the T_c while hydrophobic groups, such as n-hexyl, decrease T_c . The magnitude of this effect is inversely related to the molecular weight for both conditions. Interestingly, the hydrophobicity of n-butyl group has no effect on the T_c of PNIPAM, and it is independent of the molecular weight. Similarly, Nakayama et al.[29] reported thermoresponsive polymeric micelles made from PNIPAM-b-poly

(n-butyl methacrylate) (PBMA) exhibited the same LCST as a PNIPAM homopolymer, which was unrelated to the hydrophobic PBMA block length.

The substituent group on the N-alkyl acrylamide, such as an isopropyl or cyclopropyl group, strongly influences the thermoresponsive behavior of poly(N-alkylacrylamides). [4, 14, 30, 31] Inomata et al. investigated phase transitions in gels composed of either PNnPAM, PNIPAM, or poly(N-cyclopropylacrylamide) (PNCpAM). They observed that the n-propyl group of PNnPAM leads to a sharp and discontinuous volume transition compared to PNIPAM[30]. Studies have also shown n-clustering is stronger for aqueous PNnPAM solutions than for polymers like PNIPAM.[31] Scherzinger et al. investigated the cononsolvency behavior of secondary and tertiary poly (acrylamides) in water/methanol mixtures. They found that tertiary poly(alkylacrylamides), like poly (N, N-diethyl acrylamide), show a less cooperative phase transition than secondary poly(alkylacrylamides), such as PNIPAM or PNnPAM. The degree of substitution plays large part in determining the polymer/solvent interaction parameter, and therefore, the characteristics of the volume transition.

Winnik et al.[6] studied the effect of chain architecture on the phase transition of PNIPAM. They characterized star and cyclic PNIPAM phase transitions in aqueous solution by turbidimetry, dynamic light scattering, and microcalorimetry. They reported that the star architecture depressed the cloud point temperature (T_c), while the cyclic architecture increased T_c . To interpret the star polymer behavior, the authors proposed a vertical phase separation model, incorporating the local chain density and arm molecular weight effect on the calorimetry and light scattering data. Kakuchi et al.[32] investigated thermoresponsive properties of four-arm star PNIPAM that had either a covalent or non-covalent core by measuring T_c in aqueous solutions. They concluded that the hydrophobic covalent core structure decreased T_c , while the hydrophilic non-covalent core had no

explicit effect on the phase behavior due to an opposing terminal group influence. Similarly, Plummer et al.[33] investigated the solution properties of star and linear PNIPAM synthesized by RAFT terminated with a benzyl group. They characterized the solution properties of both architectures by pulsed field gradient NMR and dynamic light scattering. They observed that the benzyl group interacts with the PNIPAM, and is correlated to the polymer phase transition. The LCST is elevated with increasing molecular weight for star PNIPAM, while depressed for linear PNIPAM. These results together suggest that the benzyl end group had a negligible effect on the LCST, and only the core (or perhaps a combination of the core and benzyl group) results in depression of the LCST of PNIPAM aqueous solution.

In the case of thermoresponsive polymeric micelles, Nakayama et al. observed that a phenyl terminated micelle corona, made from PNIPAM and poly (dimethyl acrylamide), leads to a drastic decrease of LCST, and that the LCST increases as the hydrophilic corona block becomes longer.[29, 34] This effect was not observed if the phenyl group was replaced by a hydroxyl group. Uniform micelles prepared from a mixture of hydroxyl and phenyl terminated polymers led to a cooperative phase transition due to the densely packed polymer brush conditions. Shan et al. investigated phase transition behavior of the PNIPAM grafted gold nanoparticles[35]. They observed the collapse of the grafted chains at two distinct temperatures, resulting from regions of high and low monomer density. This effect may be due to *n*-clustering, and demonstrates how the local arrangement of chains may be an important consideration in utilizing polymer thermoresponsiveness.

In this work, we prepare four-arm star PNIPAM (4f-PNIPAM), linear PNIPAM, and linear P_NIPAM, with different terminal groups ranging from hydrophilic to hydrophobic, using RAFT polymerization and thiol-ene chemistry. The molar mass of these polymers are similar to rule out

its effect on phase behavior. The investigation of phase behavior in water/1-propanol and water/isopropanol mixtures is carried out by turbidimetry measurements and dynamic light scattering (DLS). Propanol is selected as a co-solvent due to its chemical similarity to the monomers of PNIPAM and PNPAM. We report new results concerning the effects of polymer architecture, polymer isometry, and alcohol structure on the cononsolvency phase diagram. In addition, by systematically varying the terminal groups on 4f-PNIPAM, we uncover the factors leading to the depression of the LCST in some star PNIPAM systems.

2. Experimental Section

Materials. Unless noted, all chemical reagents were purchased from Sigma Aldrich at the highest available purity. The 2-(Dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT) chain transfer agent was purchased from STREM. A mixture of 3:2 toluene/hexane was used to recrystallize N-isopropylacrylamide (NIPAM), which was then dried under vacuum prior to use. Linear phenyl PNIPAM, 4f phenyl PNIPAM, ethyl PNIPAM and ethyl PNPAM were prepared by reversible addition-fragmentation chain transfer polymerization (RAFT). 4f ethyl acrylate (EA) PNIPAM, 4f hydroxyethyl acrylate (HEA) PNIPAM, EA PNIPAM and HEA PNIPAM were prepared from a one pot aminolysis/Michael addition modification from RAFT synthesized precursors. Pentaerythritotetrakis (3-(S-benzyltrithiocarbonyl) propionate) (PTBTP), 2-Ethylsulfanyltrithiocarbonylsulfanyl-2-methylpropionic Acid (EDMAT), 3-Benzylsulfanyltrithiocarbonylsulfanylpropionic acid (BSPA) and N-n-propylacrylamide (NPAM) was synthesized as previously reported [4, 36] [37]. ¹H NMR spectra for PTBTP, EDMAT, NPAM, and BSPA are contained in Figures S1-S4 in the Supporting Information.

Polymerization of NnPAM and NIPAM by RAFT

NIPAM and NnPAM were polymerized by reversible addition–fragmentation chain transfer (RAFT) polymerization. PTBTP, BSPA, 4f DDMAT, DDMAT and EDMAT were used as chain transfer agents (CTA) for 4f phenyl PNIPAM, phenyl PNIPAM, 4f dodecyl PNIPAM, dodecyl PNIPAM and ethyl PNIPAM respectively. A generalized synthesis procedure for 20,000 g/mol ethyl PNIPAM was reported previously[4].

One Pot Aminolysis/Michael Addition End Group Transformation

The reaction was performed according to the previous reported procedure with slight modifications.[38] To prepare 4f hydroxyethyl acrylate (HEA) PNIPAM, 400 mg of 4f dodecyl PNIPAM precursor was dissolved in DMF in 3 mL tetrahydrofuran (THF). Butyl amine was added in a ratio [amine]: [trithiocarbonate] = 10:1, along with a small amount of reducing agent TECP in the solution. The solution was degassed for 30 min, and further stirred for 2 hours at room temperature under nitrogen atmosphere. HEA was added at a ratio [HEA]: [thiol] = 15:1 and the reaction allowed to proceed for 10 hours. The 4f HEA PNIPAM was then purified 3 times by precipitation in ethyl ether to obtain a white powder. The successful modification was further confirmed by SEC-MALS[38] (Figures S6-S9, Supporting Information)

Size and Molar Mass Characterization

Molecular weight and dispersity for all polymers were measured by SEC-MALS (Wyatt Dawn Heleos II). Differential indices of refraction (dn/dc) were measured with a Wyatt Optilab T-rEX. DMF was used as the mobile phase, with 0.05 mol/L LiBr added to improve the separation. The

differential indices of refraction were determined as $dn/dc = 0.0655 \pm 0.0006$ mL/g for linear PNIPAM, 0.0683 mL/g for 4f PNIPAM and 0.0712 ± 0.0008 mL/g for PNnPAM at 25 °C as reported in our previous research[4, 36]. Due to molar mass differences and conformational changes, dn/dc was determined separately for phenyl PNIPAM, cleaved phenyl PNIPAM and 4f HEA PNIPAM: 0.0716 ± 0.0015 mL/g, 0.0751 ± 0.0013 mL/g and 0.0613 ± 0.0007 mL/g, respectively. (Figure S10-S12, Supporting Information). The SEC-MALS chromatograms of all PNIPAM investigated in this study are summarized in Figure S13.

Turbidimetry Measurement

The cloud point of each polymer (0.5 wt%) was determined by monitoring the optical transmission as a function of temperature through a standard 10 mm path length cuvette. The temperature was increased by 0.1 °C/min during heating, and the cloud point was taken to be the temperature at which the transmission through the cuvette dropped by 10%.

Dynamic light scattering (DLS)

DLS and measurements were performed on a Möbiuζ (Wyatt Technology Corporation), under controlled temperature. The sample temperature was increased by 0.1 °C/min over the desired temperature range. At each temperature, a delay time of 2 minutes was used to ensure that the sample viscosity was equilibrated before the measurements were taken. Polymer solutions were filtered with 0.2 μm filters before the measurements. Data collection and analysis were carried out using the DYNAMICS software package (Wyatt Technology Corporation).

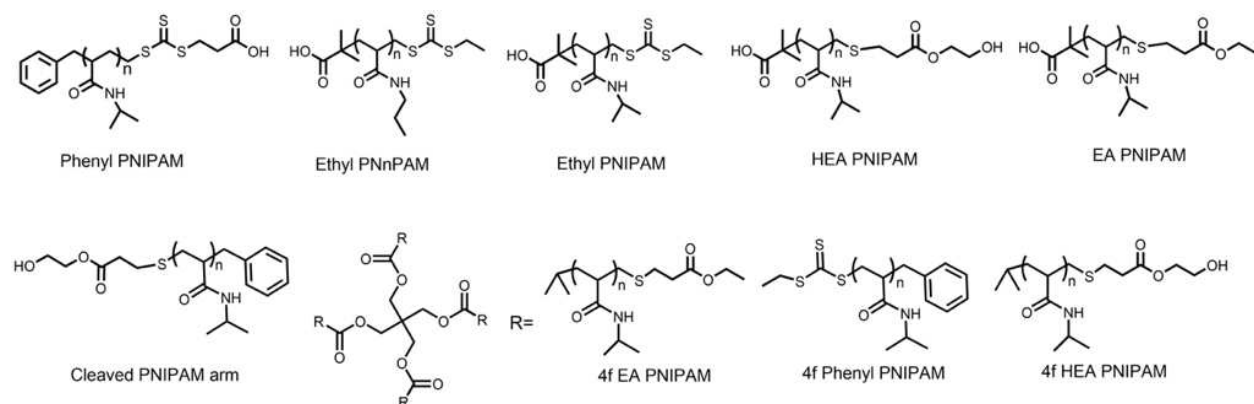


Figure 1. Chemical structures of the PNIPAM polymers investigated.

Table 1. Poly (N-alkylacrylamide) characteristics from SEC-MALS and DLS measurements.

Sample ID	T_c ^a	M_n (kg/mol)	$\bar{D}$	α group	ω group
Ethyl PNIPAM	30.3 ^b	19.7	1.04	Carboxyl	Ethyl
Ethyl PNNPAM	18.7 ^b	20.3	1.08	Carboxyl	Ethyl
Cleaved phenyl PNIPAM	28.5 ^b	8.0	1.09	Phenyl	Hydroxyl
HEA PNIPAM	33.7 ^b	25.9	1.06	Carboxyl	Hydroxyl
EA PNIPAM	34.6 ^b	23.1	1.08	Carboxyl	Ethyl
Phenyl PNIPAM	31.2 ^b	25.7	1.07	Phenyl	Carboxyl
4f phenyl PNIPAM ¹	21.6 ^b	21.3	1.07	Phenyl	Core
4f phenyl PNIPAM ²	29.5 ^b	73.5	1.09	Phenyl	Core
4f HEA PNIPAM	30.5 ^c	23.3	1.03	Core	Hydroxyl
4f EA PNIPAM	30.2 ^c	19.1	1.03	Core	Ethyl

(a) T_c of aqueous solution (b) Measured by turbidimetry (c) Measured by DLS

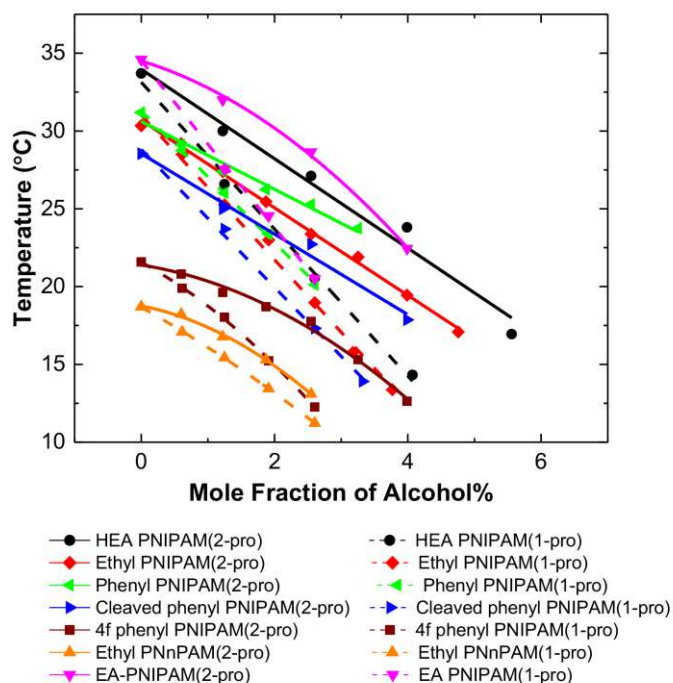


Figure 2. Dependence of phase transition temperature on 1-propanol and 2-propanol mole fraction of all PNIPAM investigated by turbidimetry measurement (markers for experimental data, solid and dashed lines are to guide the eye and represent 1-propanol and 2-propanol, solutions respectively).

3. Results and Discussion

3.1 Effect of Terminal Group

In order to incorporate different terminal groups with varying hydrophobicity, we prepared PNIPAM precursors including dodecyl-terminated 4f-PNIPAM and dodecyl-terminated linear PNIPAM, as we reported previously[4, 36]. We performed one pot aminolysis/Michael addition modification with 2-Hydroxyethyl acrylate (HEA) and ethyl acrylate (EA) to achieve 4f EA-PNIPAM, 4f HEA-PNIPAM, EA-PNIPAM and HEA PNIPAM. Linear phenyl PNIPAM is obtained by aminolysis of 4f phenyl PNIPAM. The chemical characteristics of all polymers are summarized in figure 1 and table 1.

Figure 2 compares T_c as a function of the mole fraction of 1-propanol (1-pro) /2-propanol (2-pro) in water/alcohol mixtures for PNIPAM with different terminal groups. By comparing the cononsolvency phase diagrams for all linear PNIPAM polymers, we observe that T_c decreases as the hydrophilicity of the terminal groups decreases, decreasing as carboxyl > hydroxyl > phenyl $\approx$ ethyl. One exception to this general trend is observed for EA PNIPAM, which has a slightly higher T_c than HEA PNIPAM – although we note that the critical temperatures of these two polymers are within 1 °C of each other, indicating their similarity.

Figure 3 contains the cononsolvency phase diagram of linear phenyl PNIPAM and ethyl PNIPAM. Both of these polymers contain a carboxyl terminal group, and have similar molecular weights. The linear phenyl PNIPAM and ethyl PNIPAM have a phenyl or ethyl group on the opposite chain end of the carboxyl, respectively. The T_c of linear phenyl PNIPAM is slightly higher than the ethyl PNIPAM across the composition of the solvent mixture. Surprisingly, the phenyl group has a similar effect on the phase behavior as ethyl group. The ethyl group is considered as

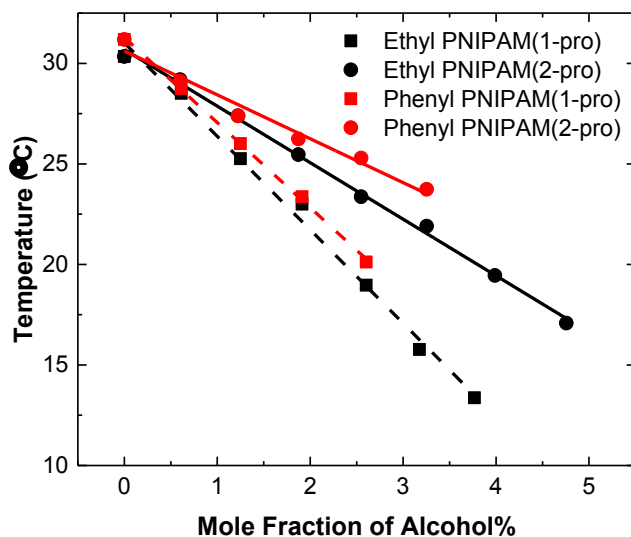


Figure 3. Phase transition temperatures of ethyl PNIPAM and phenyl PNIPAM in water/1-propanol, water/2-propanol solutions. Lines to guide the eye.

hydrophilic or neutral, since it is shorter than the n-butyl group which was previously observed to have no effect on T_c . The trithiocarbonyl adjacent to the ethyl group likely increases the polymer/water interactions, which is in accordance with results of Qiu et al[28].

Figure 4 shows the cononsolvency phase diagram of EA PNIPAM and ethyl PNIPAM. The difference between these two polymers is an ester ethyl and trithiocarbonyl ethyl group on one end of the chains, respectively. EA PNIPAM has a higher T_c compared to ethyl PNIPAM due to the ester group which can form hydrogen bonds with water, and the removal of trithiocarbonyl group increases the flexibility of EA PNIPAM chain. Chung et al. reported that the effect of hydrophobic terminal group on the phase behavior temperature is enlarged when it is located on flexible chain termini[39, 40].

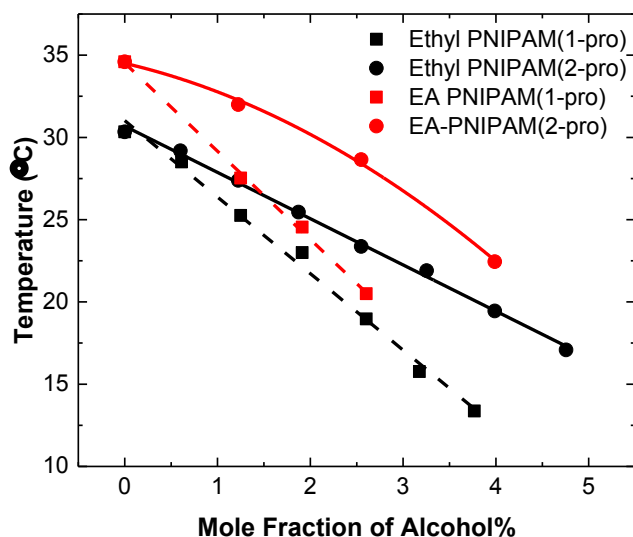


Figure 4. Phase transition temperatures of ethyl PNIPAM and EA PNIPAM in water/1-propanol, water/2-propanol solution. Lines are guides to the eye.

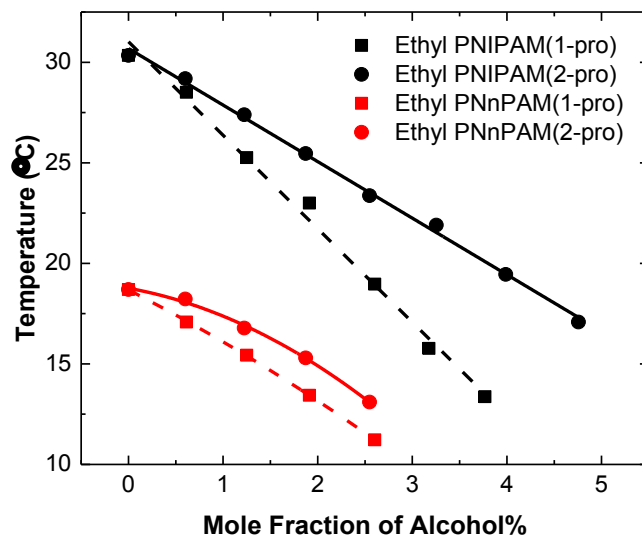


Figure 5. Phase transition temperatures of ethyl PNIPAM and ethyl PNnPAM in water/1-propanol, water/2-propanol solutions. Lines are guides to the eye.

3.2 Effect of Polymer and Alcohol Isometry

Shown in figure 5 is T_c as a function of mole fraction of alcohol for ethyl PNIPAM and PNnPAM.

The trends demonstrate that in either 2-propanol or 1-propanol, the phase transition temperature of PNnPAM has a smaller dependence on alcohol mole fraction compared to PNIPAM. In addition, for identical amounts of 1-propanol, PNIPAM shows a larger decrease in T_c than PNnPAM with increasing concentration. The difference in T_c between 1-propanol/water and 2-propanol/water is smaller for ethyl PNnPAM compared to ethyl PNIPAM. Since ethyl PNnPAM and ethyl PNIPAM have similar molecular weight and identical terminal groups (*cf.*, table 1 and figure 1), the difference between these two polymers resides only in the hydrophobic group, which is n-propyl for PNnPAM and isopropyl for PNIPAM. The distinction of the hydrophobic hydration process between these two differently shaped substituents leads to the variation in the cononsolvency phase diagram between the two polymers.

The cooperative hydration mechanism put forth by Okada and Tanaka has been previously applied to explain the phase behavior of PNIPAM and its expression of cononsolvency[18, 23, 41]. This mechanism suggests that there is a correlation in hydrogen bonds formation between neighboring bound water molecules due to the hydrophobic isopropyl groups. The rearrangement of the isopropyl group allows a second water molecule to form a hydrogen bond with an amide group on the chain. According to this theory, there are multiple consecutive sequences of bound water molecules along the backbone and they dehydrate uniformly when heating to the LCST, leading to a sharp collapse of the chain. As previously discussed, the *n*-propyl group is more hydrophobic and rigid compared to the isopropyl group on the NIPAM monomer, so it is reasonable to conclude that PNNPAM hydration may be less cooperative than PNIPAM, and that PNNPAM has a large number of shorter sequences of bound water along the chain. However, in light of more recent studies of cononsolvency, we hypothesize that the trends observed in figure 5 arise from other mechanisms. At the coil-to-globule transition, $T_c = \Delta H/\Delta S$. Graziano *et al.* have suggested that ΔS for the coil-to-globule transition does not vary significantly as small amounts of alcohol are introduced into the system.[25, 26] Their calculations, which have been substantiated by a large number of MD simulations, show that ΔH decreases as alcohol is added to the system, due to changes in the interactions between the polymer and solvent environment from geometric frustration.[27] The result of this is a decrease in T_c as ΔH decreases. The origin of the geometric frustration is the amphiphilic nature of the monomer: alcohol interacts with the hydrophobic *n*-propyl/isopropyl group while water interacts with the secondary amine. Because of the different shapes of the *n*-propyl acrylamide and isopropyl acrylamide monomers, it is reasonable that the monomer shape affects the geometric frustration, and results in a different value of ΔH as a function of alcohol content. Thus, not only is T_c different for the two isomers, but the temperature

dependence also changes. Furthermore, on the basis of this theory, it is reasonable to assume that small changes, such as to the terminal group, may further alter ΔH leading to changes in the observed critical temperature.

Bischofberger et al.[42] investigated the cononsolvency behavior of PNIPAM in water/alcohol mixtures. They observed that the solvent composition at which the excess mixing enthalpy of the water/alcohol mixtures is minimal corresponds to the lowest LCST achieved by adding cosolvent, in line with the explanation above. Based on this observation, they concluded that the energetics of water related to hydrophobic hydration is a key parameter in controlling the phase behavior of PNIPAM and other amphiphilic polymers. Hydrophobic hydration depends on the hydrophobicity of the solutes, which, in turn, is related to the shape and size of the hydrophobic entity, and temperature[43]. A spherical hydrophobic group is easier for water molecules to form a hydration shell around than linear counterparts are, since water molecules can arrange in a cage structure that causes less distortion of hydrogen bonds network in water. We recently studied poly(N-cyclopropylacrylamide) (PNCAPAM) in water. It exhibits a much higher LCST ($T_c \approx 53^\circ\text{C}$) due to its spherical cyclopropyl group, which has a smaller surface area, requires less water molecules, and creates the least amount of distortion of water hydrogen bonds network for hydrophobic hydration[4, 44]. In addition, previous studies by others have shown that tert-butanol is miscible with water at any composition, while other butyl alcohols can only partially dissolve in water due to the same phenomenon[45]. Figure 2 shows the phase transition temperature of all polymers as a function of mole fraction of 1-propanol and 2-propanol. In all cases, 1-propanol leads to a larger T_c reduction relative to 2-propanol at same mole fraction. The 1-propanol and 2-propanol combine with water molecules to form the hydration shell around the hydrophobic 1-propyl and isopropyl substituents, respectively. The more spherical isopropyl group requires less

water molecules for hydrophobic hydration, which leads to a lesser extent of depressing T_c compared to 1-propanol. For the same reason, PNnPAM requires a higher percentage of water

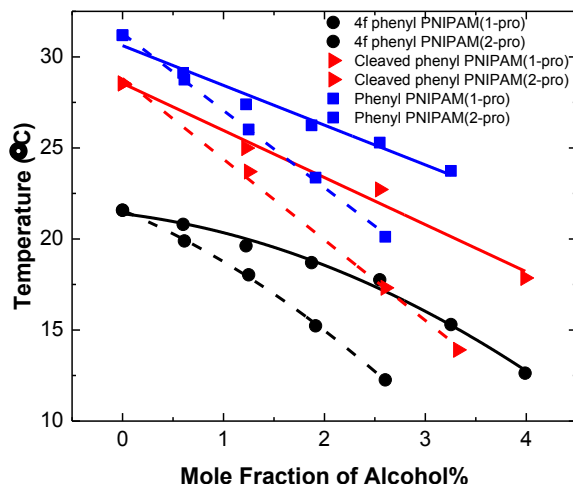


Figure 6. Phase transition temperatures of 4f phenyl PNIPAM, phenyl PNIPAM and cleaved phenyl PNIPAM in water/1-propanol, water/2-propanol solutions. Lines are guides to the eye.

molecules to hydrate the 1-propyl substituent group on the backbone than the isopropyl group of PNIPAM. As a result, there are less water molecules available to hydrate the 1-propanol and 2-propanol. This may also explain the smaller difference of T_c at same solvent composition between 1-propanol/water and 2-propanol/water, and the lower magnitude of alcohol concentration dependence of T_c for ethyl PNnPAM compared to ethyl PNIPAM.

3.3 Effect of Polymer Architecture

Figure 6 plots T_c as a function of mole fraction of 1-propanol and 2-propanol for star-branched 4f phenyl PNIPAM¹, linear phenyl PNIPAM and cleaved phenyl PNIPAM. The 4f phenyl PNIPAM¹ star polymer has a much lower T_c compared to its linear counterparts at all compositions tested. The T_c of 4f phenyl PNIPAM increased with increasing molecular weight (Figure S14, Table1),

and it is in accordance with previous results[33, 34]. Whittaker et al. investigated the T_c of 4f phenyl PNIPAM with different molar masses as well as their cleaved linear counterparts by PFG-NMR. They observed the T_c of 4f phenyl PNIPAM shifted drastically to lower temperatures, and the effect was diminished when the degree of polymerization was over 70 for the arm of the star PNIPAM[33]. They ascribed the effect to the hydrophobic core, or the combination of hydrophobic core and phenyl terminal group. The linear PNIPAM they obtained by cleaving the arms was terminated with a thiol group, meaning it was able to form disulfide bonds in solution. The possible formation of disulfide bonds could prevent the thiol terminated PNIPAM from self-assembling into micelles, which they observed with PEG-NMR. Our recent work using small-angle neutron scattering (SANS) also confirmed that the same linear PNIPAM, with thiol and phenyl functionality, does not form micelles[36].

The presence or formation of micelles can be an important consideration in determining the effect that polymer architecture has on cononsolvency. Micelles are in some ways analogous to star polymers, in that they have both a core and corona region. Nakayama et al. investigated terminal group effects on thermoresponsive micelles with PNIPAM and poly (dimethyl acrylamide) as the corona and poly (benzyl methacrylate) (PBzMA) as the hydrophobic core[34]. They found that the micelle corona, if terminated with a phenyl group, drastically lowered the LCST. At the same time, they observed that the LCST increased as the hydrophilic corona chains became longer and the hydrophobic PBzMA core size was kept fixed. There was no observed change in the LCST, and no molecular weight dependence, for hydroxyl terminated micelles with the same composition. The authors proposed that the outermost surface phenyl groups promote the dehydration process of the thermoresponsive corona, and the close-packed polymer-grafted interfaces enhance the clustering effect due to locally concentrated hydrophobic phenyl groups on the micelle surface.

There is strong clustering/association for our 4f HEA and 4f EA-PNIPAM and we cannot detect transmission decreasing with our turbidimetry measurement, making it difficult to analyze these samples further by this technique. Strong intra- or inter-polymer interaction is also confirmed by

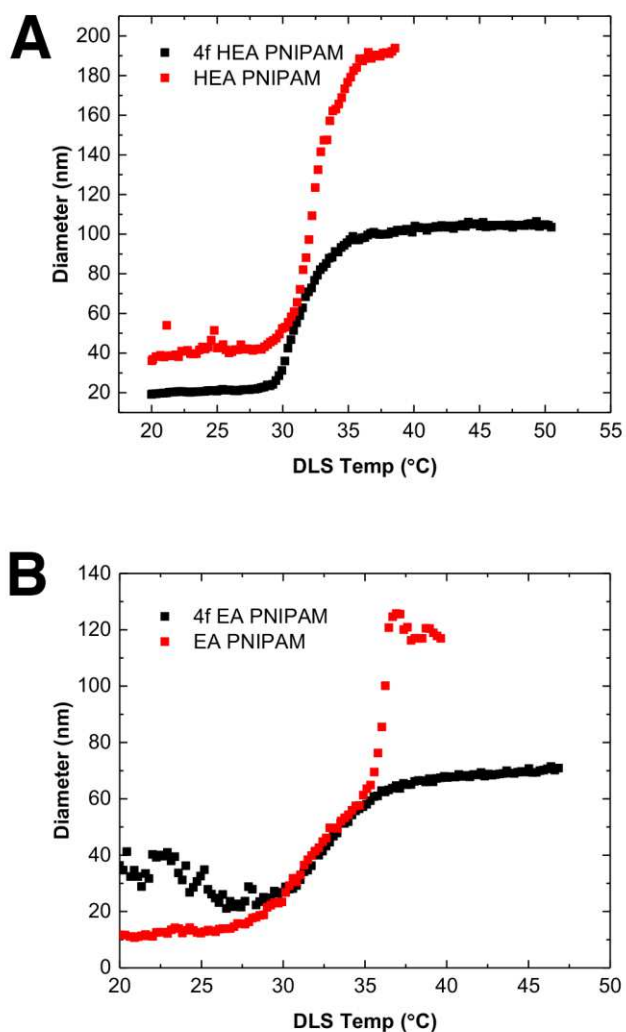


Figure 7. Hydrodynamic diameter of (a) 4f HEA PNIPAM and HEA PNIPAM (b) 4f EA PNIPAM and EA PNIPAM as a function of DLS temperature in water.

SEC-MALS results for 4f EA and 4f HEA PNIPAM by the presence of a shoulder peak, which 4f phenyl PNIPAM does not show (Figure S15-S16). We observed that after over 10 hours of intense

sonication, the shoulder peak of 4f HEA PNIPAM disappears and the molar mass is in agreement with the 4f dodecyl PNIPAM precursor prior to modifications. The shoulder peak is not due to aggregation of the polymers since it appears in both the light scattering and concentration (RI) detectors. Typical aggregation only shows a peak in the light scattering signal, but not in the RI signal.

Because turbidimetry did not show a decrease in transmission for the 4f EA and 4f HEA PNIPAM polymers, we turned to dynamic light scattering (DLS) measurements to gain additional insight into the behavior of star PNIPAM polymers in cononsolvent mixtures. We performed a DLS temperature scan to detect T_c , which we define as the temperature at which the hydrodynamic diameter (D_h) begins to increase dramatically. Figure 7 shows D_h as a function of DLS temperature for (a) HEA PNIPAM and 4f HEA PNIPAM and (b) EA PNIPAM and 4f EA PNIPAM. We observe that the values of T_c for 4f EA-PNIPAM and 4f HEA-PNIPAM are not depressed and are similar to their linear counterparts. Our results also show that the ethyl group from 4f EA PNIPAM is relatively neutral compared to hydroxyl group. Its effect on T_c is similar to the phenyl group as previously discussed for the ethyl PNIPAM and linear phenyl PNIPAM polymers. For the phenyl group, its effect on the phase transition behavior may arise from not only hydrophobicity, but also steric repulsion. D_h as a function of DLS temperature for linear phenyl PNIPAM, cleaved linear phenyl PNIPAM and 4f phenyl PNIPAM¹ is shown in Figure 8. All phenyl terminated PNIPAM polymers show a much larger D_h when heated above their LCST, and display a unique phase transition behavior compared to the HEA and EA polymers. In the case of the phenyl terminated polymers, D_h increases drastically to a peak value, and then decreases to a stable value as temperature increases. The 4f phenyl polymer exhibits a sharper increase in D_h compared to linear phenyl PNIPAM and cleaved linear counterparts. The phenyl group decreases the cooperativity of

hydration and promotes the dehydration, as the temperature increases.[29, 34] The star conformation, which increases the local hydrophobic phenyl group concentration, further enhances the clustering effect and subsequent dehydration of the chains. This observation is substantiated by the fact that the 4f phenyl PNIPAM² sample, which has a higher molecular weight, does not form aggregates as large as the lower molecular weight polymer (*i.e.*, 4f phenyl PNIPAM¹). Figure 9 plots D_h as a function of DLS temperature for 4f phenyl PNIPAM¹ at 0.5 wt%, and 4f phenyl PNIPAM² at 0.5 wt%, and 4f phenyl PNIPAM² at 0.5 and 1.0 wt%. We observe two main features in this figure. First, the size of 4f phenyl PNIPAM² aggregates is proportional to the concentration (blue and red points), but T_c does not vary with concentration for the values we measured. This finding is in agreement with the results of Plummer et al.[33] Second, 4f phenyl PNIPAM¹ forms larger cluster/aggregates than 4f phenyl PNIPAM² after heating above T_c . Because 4f phenyl PNIPAM¹ has shorter arms than 4f phenyl PNIPAM², the shorter arms adopt a smaller size which enables the terminal phenyl groups to interact more readily with the hydrophobic core of the star. This behavior can be observed in Figure 8, as well. The cleaved linear phenyl PNIPAM chains (red points) have a much lower molecular weight compared to linear phenyl PNIPAM (black points, *cf.* Table 1) such that, under the same concentration (0.5 wt%), the cleaved linear phenyl PNIPAM sample contains a higher mole concentration of phenyl groups. The interaction of these groups leads to larger aggregates upon heating. The cleaved arms also contain a hydroxyl group on the opposite chain end, which is less hydrophilic than the carboxyl group of linear phenyl PNIPAM, and thus have a lower T_c than the linear phenyl PNIPAM chains, but a higher T_c than the star polymer. This result is in agreement with our turbidimetry results (Figure 2), and the sizes measured are in reasonable agreement with our previous study of 4f phenyl PNIPAM which found a large R_g of around 661 ± 5 nm upon aggregation, as measured by MALS[36]. Taken together,

from these observations we conclude that the depression of T_c for 4f phenyl PNIPAM comes from the *combination* of the core shell structure and the phenyl terminal group for lower molecular weight star polymers. This effect vanishes as the molecular weight of the arms increases.

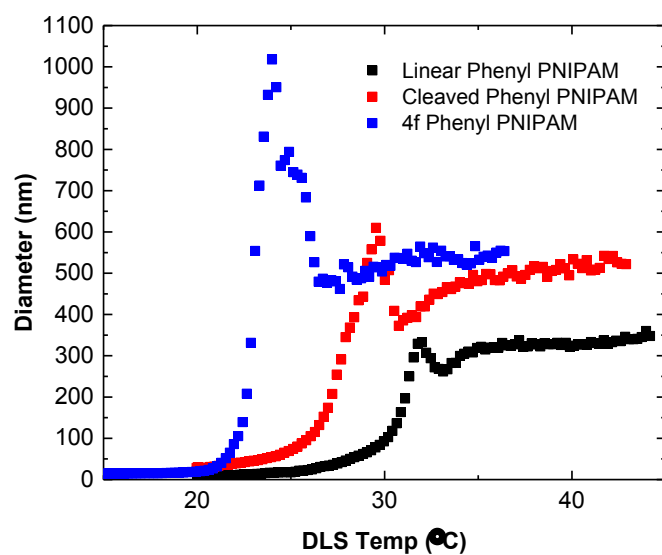


Figure 8. Hydrodynamic diameter of 4f phenyl PNIPAM, linear phenyl PNIPAM and cleaved phenyl PNIPAM as a function of DLS temperature in water.

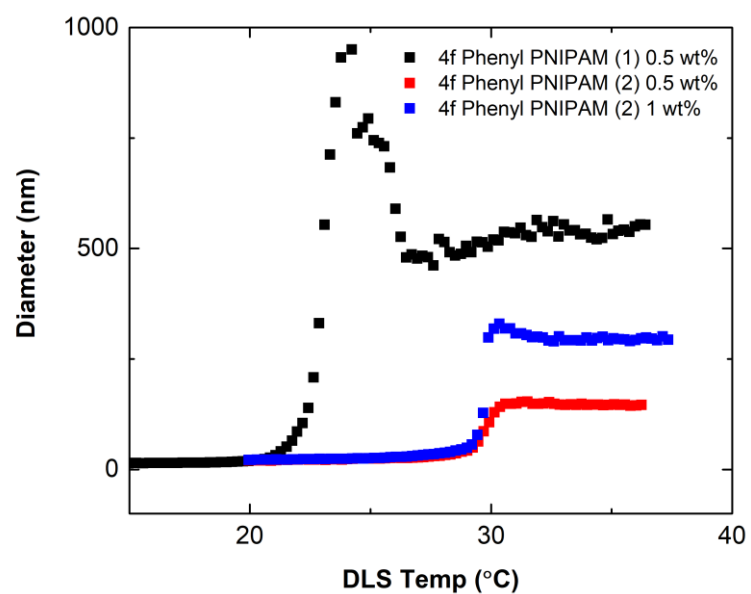


Figure 9. Hydrodynamic diameter of 4f phenyl PNIPAM, 4f phenyl PNIPAM (b) as a function of DLS temperature in water.

Recent studies by Kyriakos *et al.* and Zaccone *et al.* provide a mechanistic understanding of the effect of polymer architecture on cononsolvency. [46, 47] Kyriakos and colleagues used time-resolved small-angle neutron scattering (TR-SANS) to study the structure of polystyrene-*b*-PNIPAM micelles in D₂O, D₂O/methanol, and D₂O/ethanol mixtures, finding that as alcohol is added, the repulsive interaction potential between globules decreases due to a disruption of hydrophilic regions on the globules. Zaccone *et al.* combined DLS measurements with a theoretical argument to conclude that for PS-*b*-PNIPAM micelles, hydrophobic attraction leads to aggregation of micelles. For our results in Figure 8, a lack of propanol may lead to the sharper increase of D_h for the star architecture versus the linear architecture, since PNIPAM chains are concentrated near the core of the star polymer and hydrophobic attraction between star polymers may be strong. Finally, a common feature observed in all DLS measurements in Figures 8-9, and partially visible in Figure 7b, is an overshoot in the measurement of the hydrodynamic size of the polymers as the temperature approaches T_c . Szydowski *et al.* observed a similar behavior in DLS and SANS measurements of polystyrene/methylcyclohexane solutions, finding that the both the scattering intensity and estimates of polymer size diverged exponentially at the critical temperature. [48] Thus, this feature is not associated with PNIPAM cononsolvency, but may yield a more accurate value for the critical solution temperature in our systems than turbidimetry.

4. Summary

In this work, we successfully prepared linear and star PNIPAM with different terminal groups by RAFT polymerization and one pot aminolysis/Michael addition modification. This approach allowed us to systematically investigate the effect of terminal group and polymer architecture on PNIPAM cononsolvency in water/propanol mixtures. The phase transition temperatures (T_c) in binary mixtures of water/1-propanol and water/2-propanol were measured using turbidimetry and

DLS as a function of alcohol content in the solvent mixtures. The effects of different terminal groups on T_c are compared ranked as carboxyl > hydroxyl > phenyl $\approx$ ethyl. The effect of polymer isometry studied between ethyl-terminated PNNPAM and PNIPAM indicates that hydrophobic hydration plays a critical role in determining T_c . The n-propyl group of PNNPAM decreases the hydration cooperativity and a larger number of shorter hydration chains are formed along the backbone below the LCST, which promotes the dehydration – leading to a lower T_c and a sharper phase transition compared to PNIPAM. The spherical, hydrophobic isopropyl group on the NIPAM monomer requires less water molecules for hydrophobic hydration and cause less distortion of the water network, which is likely why 2-propanol results in a lower T_c . This effect is less pronounced for PNNPAM and star PNIPAM compared to linear PNIPAM. These results are also in line with a theory and calculations by Graziano and others which attributes changes in T_c to changing interaction strengths between polymers and surrounding solvent as alcohol is added.[26, 27] The physical origin of this behavior is geometric frustration in the solvent molecules as they interact with different portions of the monomer. By varying the terminal groups and molecular weight of 4f star PNIPAM, we determined that the reduction in LCST observed by several studies for phenyl-terminated arms is the result of both the terminal group and chemistry of the core of the star polymer. The reduction in LCST vanishes at high arm molecular weights, and for terminal groups other than phenyl. The effect of phenyl group comes from its hydrophobicity as well as steric repulsion. The longer hydrophilic arm creates a more extended chain conformation, reducing the star PNIPAM local chain concentration and reducing the interaction between the phenyl groups with the hydrophobic core of the star polymer. These observations provide new insight into the factors affecting PNIPAM cononsolvency, and will lead to a greater ability to utilize cononsolvency in responsive material systems in the future.

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