# Effect of Additives on the Cloud Point Temperature of 2-Hydroxy-3-isopropoxypropyl Starch Solutions

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ⓈSupporting Information

ABSTRACT: Temperature-responsive polymers with a lower critical solution temperature (LCST) have attracted much attention in biomedical and biotechnological fields. It is important to tune their cloud point temperature (T_c) in a broad temperature range as desired by the applications. In this study, new thermo-responsive 2-hydroxy-3-isopropoxypropyl starches (HIPS) was synthesized using Hylon V starch as raw material and isopropyl glycidyl ether as hydrophobic reagent. The phase transition behavior of HIPS and their T_c were determined by spectrophotometry. The effects of several conditions on the T_c of the HIPS were also investigated, which indicated that varying the molar substitution (MS) of HIPS can adjust T_c in a broad temperature range from 69 to 28 °C by changing the hydrophobic–hydrophilic balance of starch. The phase transition became fast and the T_c decreased with increasing polymer concentration. The effect of a series of sodium salts on the T_c of aqueous HIPS solutions was reported and the effectiveness of ions follows a trend, known as Hofmeister series. Several organic solvents were selected and the organic additives with small molecular weight can also regulate the T_c of HIPS in a certain range by changing the polymer–water interactions.
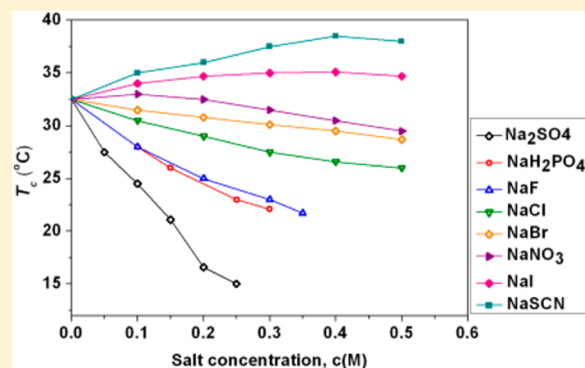
1. INTRODUCTION

Temperature-responsive polymers with a lower critical solution temperature (LCST) are of great importance for application as stimulus-sensitive biomaterials and have attracted much attention. Temperature-responsive polymers have inverse temperature-dependent solubility, which means that the polymers dissolve in the aqueous solution below their cloud point temperature (T_c) and exhibit a phase separation above their T_c.[1,2] Many applications of temperature-sensitive polymers have been reported in biomedical and biotechnological fields such as drug delivery and the separation of different kinds of compounds.[3,4] The diversity of these applications requires the temperature-responsive polymers with sharp, fast, and fully reversible phase transitions and their T_c in a broad temperature range, which depends on the polymer's structure and compositions.[5,6] Unfortunately, these conditions are only partially met by the above cases. For example, the linear poly(N-isopropylacrylamide), whose T_c is about 32 °C, shows a very sharp transition when heated, but there is a broad hysteresis of about 4 °C in the cooling process.[7]

It is generally believed that the LCST behavior originated from varying inter- and intramolecular interactions upon heating.[8] Grafting hydrophobic groups on polymer chains can adjust the temperature-responsive behavior by disrupting the inter- and intramolecular hydrogen bonds of the polymers. Addition of small molecules to the polymer solutions is also a good method to change the polymer–water interactions and hence tune the LCST behaviors.[9] Recently, the effect of small

molecular additives, for the widely discussed temperature-responsive PNIPAM, such as salts and organic additives on the LCST behavior of PNIPAM have been extensively investigated. Most of the salts are found to reduce the T_c because ions in solution can affect the hydrophobic–hydrophilic transition of the polymers. The effect of ions on T_c obeys the so-called Hofmeister series.[10,11] The effectiveness of the anions to decrease the T_c follows the order: CO_3^{2-} > SO_4^{2-} > $S_2O_3^{2-}$ > $H_2PO_4^-$ > F^- > Cl^- > Br^- ≈ NO_3^- > I^- > ClO_4^- > SCN^-. The ions on the left of Br^- decrease the T_c and are referred to as kosmotropes, while the species on the right of Br^- initially increase the T_c at lower salt concentration, then decrease at larger salt concentration and are known as chaotropes.[12] In addition, the effects of organic additives on T_c are full of variety. For instance, it is known that PNIPAM exhibits cononsolvency in methanol–water mixtures. That is, the T_c of aqueous PNIPAM solutions shifts to lower temperature when methanol is added. The temperature drop is the largest from 31.5 °C down to −7.5 °C at a volume fraction of methanol of 0.55.[13] The study also shows that PNIPAM has an upper critical solution temperature (UCST) in many mixtures of water and organic additives including ethanol, propanol, and dimethyl sulfoxide (DMSO) at higher organic solvent concentrations.[14,15] These phenomena resulted from competition in

Scheme 1. Synthesis Pathway of the Thermo-Responsive HIPS
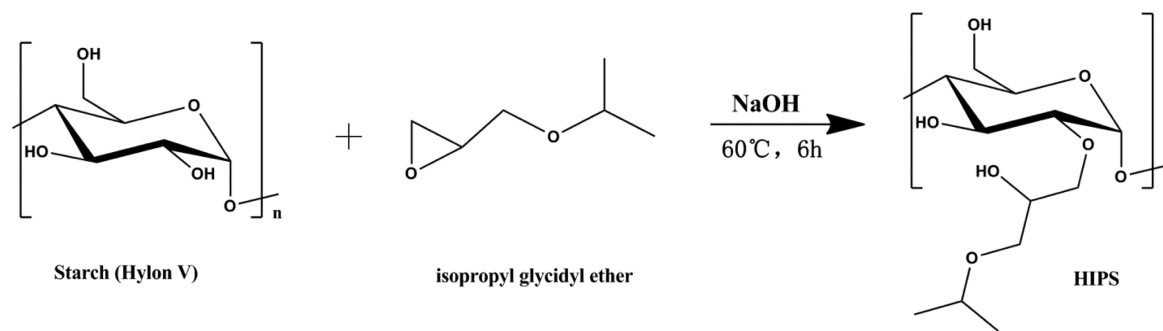
forming polymer—water hydrogen bonds and water—organic additive hydrogen bonds because of addition of organic additives.[16] The effect of solvent on the T_c of temperature-responsive polymers may serve as a methodology for the application of temperature-responsive compounds based on polysaccharide.

Starch, in particular, is a material which occupies a prominent position in the group of natural polymers. It and its derivatives have emerged among the most promising smart biomaterials due to their biodegradability and biocompatibility. Even though starch is insoluble in cold water, modification of starch by grafting an appropriate amount of hydrophobic groups on starch chains can generate water-soluble polymers by disrupting the inter- and intramolecular hydrogen bonds of starches. In the previous study,[17] we synthesized temperature-responsive 2-hydroxy-3-butoxypropyl starches (HBPS) by grafting an appropriate amount of hydrophobic groups on starch chains and investigated micelles self-assembled from HIPS for drug delivery. In current work, we synthesized a new series of 2-hydroxy-3-isopropoxypropyl starches (HIPS) by using Hylon V starch as raw material and isopropyl glycidyl ether as hydrophobic reagent. Moreover, we discussed in detail the phase transition behavior of HIPS and the T_c was determined by spectrophotometry. The effects of the molar substitution and the concentration of the HIPS polymer on tuning T_c were studied. We also examined the effects of a series of sodium salts and organic solvents on tuning the T_c of HIPS. To the best of our knowledge, in the case of starch-based temperature-responsive polymer, the effects of polymer concentration, sodium salts, and organic solvents on tuning the T_c have not been reported yet. The as-synthesized temperature-responsive HIPS polymer may be applied to biomedical and biotechnological fields, and the effect of the small molecular additives on the phase transition behavior also can provide some guidance for the practical application.

2. EXPERIMENTAL SECTION

Materials. Corn Starch (Hylon V) was supplied by National Starch and Chemistry Company. Isopropyl glycidyl ether was obtained from Tokyo Chemical Industry Co. Ltd. Methanol, ethanol, isopropanol, butanol, and acetone were analytical grade; other reagents and solvents were commercially available and used without further purification.

Synthesis of HIPS. HIPS was prepared according to the reported literature.[17] Briefly, Hylon V corn starch (4 g, 24.7 mmol) was suspended in distilled water and the mixture was heated to 60 °C. Then the solution was initiated by addition of 2 g NaOH (40%, 12.5 mmol) for 1 h under stirring. A predetermined amount of isopropyl glycidyl ether (IPGE) was

added to the flask. The reaction was carried out at 60 °C for 5 h. Then the suspension was cooled and neutralized to pH 7.0 with 1 M CH$_3$COOH. The product was subsequently precipitated in acetone and washed three times. The product was purified via dialysis in deionized water for two days, and then dried in a vacuum oven at 80 °C for 5 h.

Characterization. ^{1}H NMR spectra was recorded at room temperature on a Varian INOVA 400 spectrometer. The purified HIPS were dissolved in D$_2$O as test specimens. The optical transmittance of the aqueous polymer solution was measured by a spectrophotometer (Agilent Technologies Cary 100 UV—vis, America) equipped with a temperature controller (Agilent Technologies Cary temperature controller, America). The transmittance of HIPS in aqueous solution (1%, w/w) was measured at 590 nm under heating at rate of 1 °C/min. The T_c is defined as the temperature at which the transmittance of the solution becomes 50%. Furthermore, the T_c of the HIPS-4 solutions including a series of sodium salts and organic solvents was also measured.

3. RESULTS AND DISCUSSION

Synthesis of HIPS. The general synthetic route for the preparation of HIPS is shown in Scheme 1. HIPS with different DS were prepared, and characteristics of five HIPS samples with thermosensitivity are summarized in Table 1.

Table 1. Preparation and Characterization of HIPS

Sample	IPGE[a]:AGU(—OH)[b]	MS[c]	T_c (°C)[d]	Efficiency (%)
HIPS-1	0.5	0.86	69	57.4
HIPS-2	0.75	1.33	52	59.1
HIPS-3	1	1.72	43	57.3
HIPS-4	1.5	2.38	32	52.8
HIPS-5	2	2.77	28	46.2

[a]Isopropyl glycidyl ether. [b]OH molar ratio in IPGE and AGU. [c]MS, molar substitution of IPGE determined by ^{1}H NMR. [d]Determined by Cary series UV—vis spectrophotometer.

A typical ^{1}H NMR spectrum of HIPS is shown in S1 of the Supporting Information. Peak assignment for substituent was straightforward (see Figure 1 and inset), where the triplet at 1.00 ppm belongs to the methyl group. The peaks between 3.00 and 4.00 ppm corresponded to the six protons of the anhydroglucose units (AGUs) and one proton of the —OCH(CH$_3$)$_2$ group of the substituent. The peaks at 5.1—5.65 ppm were assigned to the anomeric proton (H1) of HIPS and the clear broadening of H1's peak for HIPS is due to the substitution at O-2 position. The downfield shift indicates successful etherification. The molar substitution (MS) was
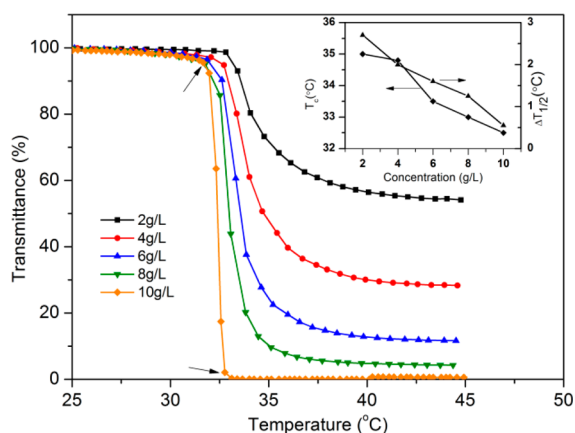
Figure 1. Influence of temperature on the light transmittance of different concentrations of HIPS-4 in deionized water (inset: effect of the concentration of HIPS-4 (MS = 2.38) in deionized water on the T_c).

defined as the molar ratio of isopropyl glycidyl ether substituent to AGU of the starch molecules. ^{1}H NMR was used for the calculation of MS according to eq 1:

$$MS = \frac{\left(\frac{I_{CH3}}{6}\right)}{I_{H1}}$$

where I_{CH3} is the integral for the methyl group peak at 1 ppm, while I_{H1} is the integral for the anomeric proton (H1) of HIPS between 5.10 and 5.65 ppm.

Effect of Aqueous Solutions Concentration of HIPS on the Phase Transition Behavior. The concentration dependence of the phase transition behavior was investigated in the range of 2−10 g/L of HIPS-4 aqueous solutions whose T_c was approximately 32.5 °C, close to the human body temperature, and the results were plotted in Figure 1. It was obvious that the lower the polymer concentration, the higher the T_c and the broader the phase transition. The T_c totally decreased by almost 2.5 °C with increasing polymer concentration from 2 to 10 g/L. For comparison, $\Delta T_{1/2}$ was used to show the sharpness of phase transition because sharp phase transition was a very important property for thermoresponsive polymers employed

as smart materials, and the $\Delta T_{1/2}$ was half the value of the temperature difference between the final and initial break points in the transmittance versus temperature curves.[18] As we can see, when the concentration of the HIPS-4 was 2 g/L, the phase transition was quite broad and the $\Delta T_{1/2}$ was about 2.7 °C. When the polymer concentration increased to 10 g/L, the phase transition became sharper and the $\Delta T_{1/2}$ value was 0.55 °C. This may be related to an aggregation kinetic effect: the lower the polymer concentration, the longer the time needed for the formation of aggregates.

Effect of MS on the T_c. Figure 2a displayed the effect of molar substitution (MS) of HIPS on phase transition behavior. It was observed that the HIPS polymer solution suddenly changes from a transparent homogeneous state into a uniform milky state when it is heated to a specific temperature referred to as the cloud point (T_c). The plots of T_c values against MS (Figure 2b) indicated that the T_c decreased with increasing MS. In addition, an increase of MS from 0.86 to 2.77 resulted in a decrease in the T_c from 69 to 28 °C. It revealed that the LCSTs of HIPS could be controlled by varying the MS value. It is worth noting that the HIPS with MS from 0.86 to 2.77 have good thermoresponsivity, the HIPS with MS < 0.86 are water-soluble, and HIPS with MS > 2.77 are difficult to synthesize. The different T_c of the five HIPS samples reflect the differences in hydrophilicity. With the increase of MS, the number of hydrophobic isopropyl groups on HIPS increased and the inter- and intramolecular hydrogen bonds of the starch backbone were disrupted. This indicated that the hydrophobic groups and the MS play a vital role in the thermoresponsivity and the T_c of starch derivatives.[17]

Effect of Added Sodium Salt on the T_c of HIPS. Recently, much effort has been focused on better understanding of the phase transition behavior and the parameters affecting the cloud point temperature such as the presence of salts and organic solvents. The turbidity curves for 10 g/L HIPS-4 solutions containing a series of 8 sodium salts are presented in Figure S2 of the Supporting Information. In all cases, the light transmittance falls sharply in a narrow temperature range until approaching zero, implying that the incident light is mostly scattered by the HIPS's aggregates formed due to the phase separation. Figure 3 shows the effect of the salts on the T_c of aqueous HIPS-4 solutions, which
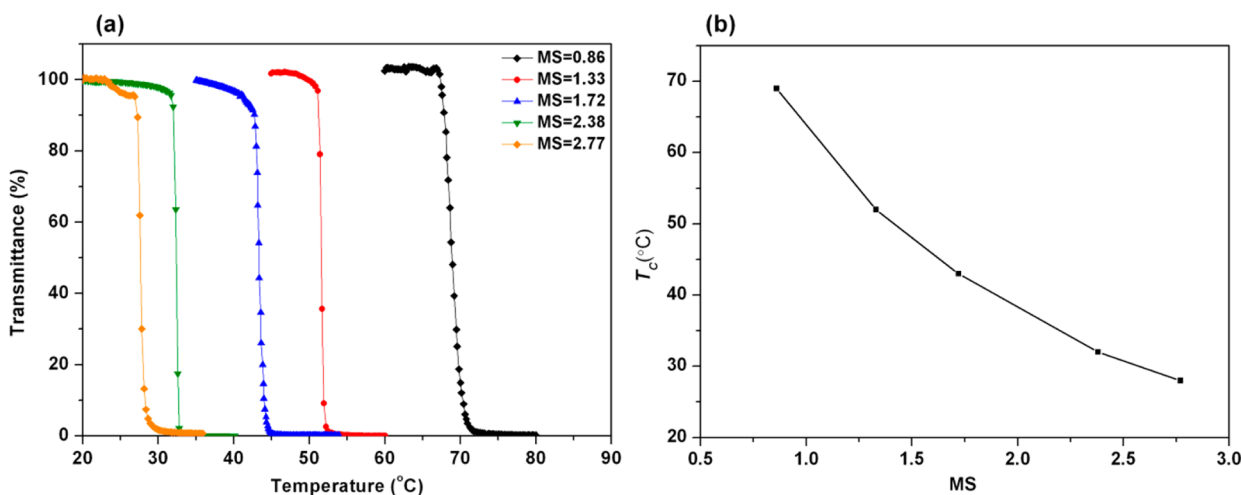
Figure 2. (a) Transmittance changes for 10 g/L aqueous solutions of HIPS 1−5 with different MS. (b) Effect of MS on the T_c of HIPS aqueous solution in distilled water.
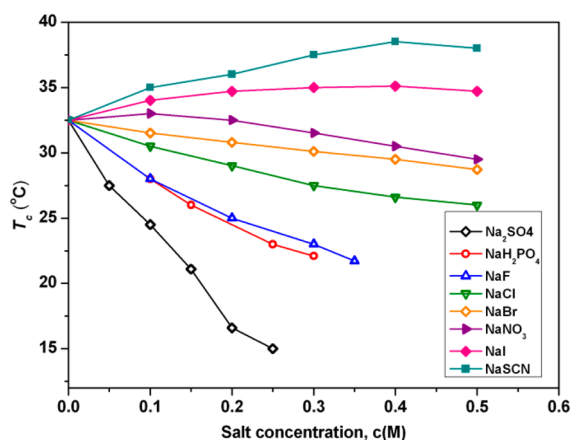
Figure 3. Change of the T_c of 10 g/L aqueous HIPS-4 solutions with the concentration of various sodium salts including five kosmotropic anions (open symbols) and three chaotropic anions (filled symbols).

clearly indicates that the T_c decreases with increasing concentrations of kosmotropic anions and following the order SO_4^{2-} > $H_2PO_4^-$ > F^- > Cl^- > Br^- (i.e., the so-called Hofmeister series of anions). Similar results were obtained for aqueous PNIPAM[10−12] and poly(2-ethyl-2-oxazoline)[19] solutions. For example, when the salt concentration was 0.20 M, the presence of Na_2SO_4 promoted a continuous decrease in T_c from 32.5 °C for HIPS-4 in pure water to around 16.5 °C, while the same concentration of NaBr promoted a decrease of only 1.7 °C. Similar to aqueous PNIPAM[10−12] and poly(2-ethyl-2oxazoline)[19] solutions, the decrease of T_c with salt concentration can be interpreted in terms of dehydration of the HIPS and surface tension of aqueous HIPS solutions. Kosmotropic salts have a stronger interaction with water molecules than the interaction between polymer−water molecules. Thus, some of the original hydrogen bonds between polymer and water are destroyed by the salt, and some hydrate water molecules are expelled from the polymer chain. This resulted in the decrease of polymer solubility in water, and hence decrease of T_c of aqueous polymer solutions. As we know, the hydration strength of the anions decreases in the order SO_4^{2-} > $H_2PO_4^-$ > F^- > Cl^- > Br^-. Therefore, the effectiveness of the anions in the series for reducing the T_c decreases from left to right. According to surface tension mechanism, surface tension of salt solutions is also known to increase with salt concentration, which will result in more hydrophobic aggregates of polymer in a salted polymer solution than a salt-free one. Therefore, the cloud point of a salted sample appears at a lower temperature.

For chaotropic anions, it was observed that the T_c initially increases at lower salt concentration, then decreases at larger salt concentration. It can be seen from Figure 3 that T_c increased in the range of 32.5−38.5 °C when the NaSCN concentration increased to 0.4 M, while the T_c decreased to 38 °C at 0.5 M. At constant salt concentration, the observed shift in T_c was in the following order: SCN^- > I^- > NO_3^-. For the NO_3^- anion, it caused T_c to peak at $c \sim 0.10$ M and decrease beyond it, which shows more negative slopes (steeper decrease of T_c with c) compared to those for the I^- and SCN^- anions at $c \sim 0.40$ M. This phenomenon was different from that discussed above for the kosmotropic anions. This can be explained as follows: for chaotropic anions (NO_3^-, I^-, SCN^-), the direct binding of anions to polymer chains was the dominant mechanism.[11,20] The anions may directly bind to the polymer

chains by the hydroxy dipole and increase the solubility of the polymer and cause T_c to increase with salt concentration toward a plateau value. However, at larger salt concentrations, H-bonding interaction between polymer and water dominates and T_c goes over a peak and decreases. So we can summarize that the addition of sodium salt to the polymer solutions can tune the T_c of HIPS. It is much easier to achieve than by the method of varying MS of the HIPS.

Effect of Organic Solvent Concentration on the T_c of HIPS. Figure S3 of the Supporting Information illustrates the turbidity curves for 10 g/L HIPS-4 solutions with different concentrations of acetone, methanol, ethanol, isopropanol, and butanol. Obviously, the phase transition became broader with increasing organic additive concentration.

The corresponding T_c values were plotted in Figure 4. It can be observed that the addition of methanol promotes a
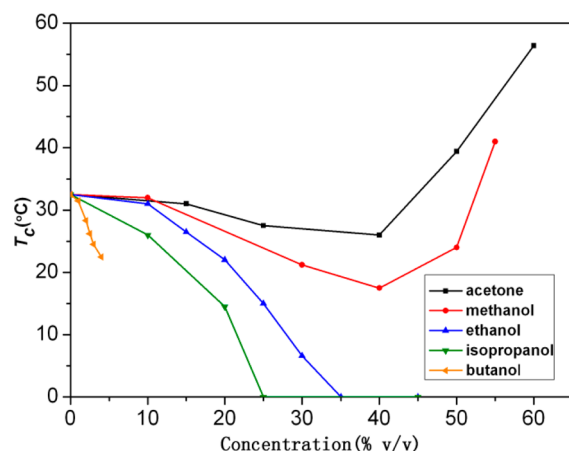
Figure 4. Comparison between cloud point temperature of HIPS-4 in water−alcohol and water−acetone solutions.

continuous decrease in T_c from 32.5 °C for HIPS-4 in pure water to around 17.5 °C for HIPS-4 in the aqueous solution with the concentration of methanol $c_v \approx 40\%$ v/v. Likewise it can be observed that HIPS-4−water−acetone system exhibits a minimum T_c at 26 °C for $c_v \approx 40\%$ v/v of acetone. In both cases, additional amounts of cononsolvent increase T_c, so that the T_c disappears at higher concentrations ($c_{acetone}$ > 60% v/v and $c_{methanol}$ > 55% v/v). Despite the similarities between both systems, the reduction promoted by acetone ceases at a lower mole fraction and it is less pronounced than in the case of methanol. The other three HIPS−water−alcohol systems all exhibited LCST behavior, but no UCST behavior was observed different from the PNIPA−water−alcohol systems. For the ethanol system, when small amounts of ethanol were added, a decrease in the T_c occurs. However, instead of a further increase in the T_c, the T_c was not observed with the addition of higher concentration of ethanol. So, for $c_v < 35\%$, phase separation occurs on increasing temperature and the T_c decreased from 32.5 to 0 °C; for $35\% < c_v < 45\%$, the polymer solution was completely turbid at any temperature; for $c_v > 45\%$, HIPS was soluble at any temperature. Similarly to the ethanol system, addition of isopropanol to HIPS-4 solution also appears to be a completely turbid phenomenon at any temperature for $25\% < c_v < 45\%$. In addition, while at $c_v = 25\%$ of ethanol, the T_c is reduced by 17.5 °C; the same amount of isopropanol promotes a decrease of nearly 32.5 °C. The fact that a more hydrophobic alcohol produces a larger decrease in T_c is related to what has

already been discussed about hydrophobic hydration. One isopropanol molecule disturbs the system much more significantly than one ethanol molecule, considering the hydrophobic volumes that need to be accommodated in the water structure.[14] On the other hand, one isopropanol molecule is hydrated by more water molecules than an ethanol molecule, so its hydration shell is destroyed by a lower concentration. Unlike the ethanol and isopropanol system, n-butanol additives only decreased the T_c of HIPS. It remarkably decreased the T_c of the polymer with increasing concentration. The T_c of the HIPS-4 polymer solution was dramatically reduced by 11 °C when the butanol concentration was only 4%. However, the T_c was not detected because of the formation of oil-in-water emulsion with increasing butanol concentration.

In general, at lower solvent concentration, all organic solvents lowered the T_c, and the effectiveness for lowering T_c was in the following order: 1-butanol > 2-propanol > ethanol > methanol > acetone. A similar phenomenon has been observed in cases of PNIPAM and poly(N-tetrahydrofurfuryl(meth)-acrylamide) in aqueous solution,[14,21] and could be attributed to the polymer dehydration caused by the formation of water/alcohol or acetone complexes.[22−24] In alcohol or acetone/water mixture, alcohol or acetone more strongly interacts with water than with a polymer, and formed water/alcohol or acetone complexes, which resulted in the reduction of either the number or the strength of polymer−water contacts and the decrease of the enthalpy of the endothermic LCST transition. As the alcohol or acetone content increases, more complexes are formed, and more water molecules involved in hydration structures of HIPS isopropyl group and backbone will mobilize to participate in the complexes. Therefore, the T_c is reduced with the increase in alcohol or acetone content. For the short chain alcohols, the number of water molecules required to form the complexes by one alcohol molecule increases with increasing hydrophobicity and size of alcohol molecules.[23] Moreover, one acetone could complex with four water molecules,[25] whereas one methanol could complex with five water molecules at lower methanol content. That is probably the reason why methanol exhibited the stronger T_c decreasing effect than acetone and a more hydrophobic alcohol produces a larger decrease in T_c.

In addition, the fact that the T_c increased with further addition of methanol and acetone, and the LCST disappears at higher concentrations ($c_{acetone} > 60\%$ v/v and $c_{methanol} > 55\%$ v/v), can also be explained by the complexation mechanism mentioned above. At higher methanol or acetone concentrations, this is sufficient to form a water/methanol or water/acetone complex with all of the water molecules present; no "free" H_2O is available to bind to polymer, but some methanol or acetone will remain free in solution. It is worth mentioning that both methanol and acetone are good solvents for HIPS-4, the excess "free" organic solvent is subsequently able to bind to and solubilize HIPS-4 allowing formation of a random coil conformation, and then the T_c increases or disappears. Likewise, both ethanol and isopropanol are also good solvents for HIPS-4; therefore HIPS-4 was soluble at any temperature at higher concentrations (>45%).

4. CONCLUSIONS

New thermoresponsive HIPS was synthesized. The phase transition became sharp and fast with the increase of polymer concentration. The T_c of HIPS in a broad temperature range from 69 to 28 °C can be adjusted by controlling the molar

substitution of HIPS. The addition of sodium salts and organic solvents also can tune the T_c of HIPS in a certain range. The effectiveness of ions on T_c follows a trend, known as Hofmeister series. Several organic solvents were selected including acetone, methanol, ethanol, isopropanol, and butanol. At lower solvent concentration, all organic solvents lowered the T_c, and the effectiveness for lowering T_c was in the following order: 1-butanol > 2-propanol > ethanol > methanol > acetone. The addition of the acetone to HIPS-4 solution initially decreased the transition temperature, and a further addition increased the transition temperature, while ethanol, 2-propanol, and butanol only decrease T_c and no UCST behavior was observed. These properties of HIPS may be useful for application of thermoresponsive compounds based on polysaccharide, and these are being studied by our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
^{1}H NMR spectra of HIPS, the measurement of the phase transition behavior of the HIPS-4 solutions containing a series of sodium salts and organic solvents. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
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