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Rational Design of Dual Chemo- and Thermo-responsive Phase Separation of Poly(4-hydroxystyrene) in Non-aqueous Media

Kota HASHIMOTO¹, Natsuki INABA¹, Keitaro MATSUOKA^{1,2*}, and Kazuki SADA^{1,2*}

¹ Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan.

² Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan.

*Corresponding author, E-mail: sadatcm@sci.hokudai.ac.jp, ma2oka@sci.hokudai.ac.jp

Abstract

Dual stimuli-responsiveness in non-aqueous media could allow various molecular designs using a system that is not compatible with aqueous media. However, the difficulty in controlling the desolvation of the polymer chains in non-aqueous media for lower critical solution temperature (LCST)-type phase separation at ambient temperature has hindered the attainment of dual stimuli-responsiveness based on chemical stimuli. In this study, we rationally designed dual chemo- and thermo-responsive phase separations of poly(4-hydroxystyrene) in non-aqueous media. The LCST-type thermo-responsiveness of poly(4-hydroxystyrene) in 1,4-dioxane/toluene was considerably altered by the addition of small amounts of hydrogen-bonding molecules as chemical stimuli. Secondary amines or molecules containing two hydrogen-bonding functional groups formed stronger hydrogen bonds with the polymer chains than 1,4-dioxane, which altered the solvation state and induced the UCST-type thermo-responsiveness or insolubility of PHS. This dual stimuli-responsive system could serve as a chemical sensor to detect the presence of acids.

Main Text

Stimuli-responsive polymers undergo significant solubility changes in solution due to alterations in the polymer conformation triggered by external stimuli¹⁻⁷. Among them, lower critical solution temperature (LCST)-type thermo-responsive polymers exhibit reversible solubility changes upon heating and cooling to cause the polymer aggregation above a specific temperature called the cloud point (T_{cp}) and the polymer dissolution below this temperature, respectively⁸⁻¹¹. Recently, dual stimuli-responsive polymers based on LCST-type thermo-responsive polymers in aqueous media¹²⁻¹⁵ have gained attention as smart materials for molecular sensors^{16,17}, membrane channels¹⁸, drug delivery systems^{19,20}, and vesicle size control^{21,22}. These polymers incorporate additional functional groups, such as azobenzene and spiropyran structures, that respond to light stimuli or chemical stimuli, such as pH and host-guest interactions²³⁻²⁸. Light or chemical stimuli induce changes in the polymer conformation and polarity, consequently altering the hydration of the polymer chain and the cloud point of thermo-responsiveness. In these applications, a controlled amount of a second stimuli-responsive moiety needs to be incorporated into the original thermo-responsive polymer through copolymerization or end-group modification. Moreover, with this strategy, the operating medium is

limited to water because of the easy accessibility of the LCST-type thermo-responsive polymers in water. Therefore, due to these processes, the complexity of the polymer structure is increased, and the creation of multiple-responsive polymers for each stimulus independently is more challenging because of the difficulty in incorporating many stimuli-responsive moieties.

Compared with aqueous media, non-aqueous media provides greater potential for achieving dual stimuli-responsiveness since various functional groups that are incompatible with aqueous media can be utilized in non-aqueous media²⁹⁻³⁷. For example, Sato and coworkers demonstrated the photo- and LCST-type thermo-responsive phase separation of poly(7-methacryloyloxycoumarin) in chloroform²⁹⁻³¹. Similarly, Watanabe and coworkers reported dual photo-responsiveness and LCST-type thermo-responsiveness of various homo- and copolymers in an ionic liquid bearing azobenzene units³⁵⁻³⁷. Nevertheless, dual stimuli-responsiveness has been limited to light as the sole external stimulus owing to the difficulty in controlling the desolvation of the polymer chains in non-aqueous media for LCST-type phase separation at ambient temperatures³⁸⁻⁴¹. Herein, we present a rational and novel design for dual chemo- and LCST-type thermo-responsiveness in non-aqueous media using poly(4-hydroxystyrene) (PHS) as a commercially available polymer without any synthetic modifications of the polymer chain (Figure 1a). The thermo-responsiveness of PHS was significantly altered by the addition of a small amount of hydrogen bonding molecules, such as amines and nitrogen-containing heterocyclic compounds, as external chemical stimuli. This designed dual stimuli-responsive system was then applied as a chemo-sensor to detect the presence of acids.

As one of the rational supramolecular designs in non-aqueous media, we previously proposed LCST-type thermo-responsive polymers by controlling the hydrogen bonds between the polymer chains and solvents⁴². This design consists of three components: a polymer with hydrogen-bonding functional groups, a hydrogen-bonding good solvent, and a non-polar poor solvent. Under the appropriate solvent mixing ratio, the polymer could dissolve in the binary solvent mixture at ambient temperature because of solvation by the hydrogen bonds. Upon heating, thermal cleavage of the hydrogen bonds between the polymer chain and the good solvent triggers the aggregation of the polymer chains, leading to LCST-type phase separation. Additionally, we reported LCST-type phase separation in poor solvents using a pseudo-solvating molecule known as an effector, instead of a good solvent⁴³⁻⁴⁸. Even in poor solvents, the polymer chain could maintain an extended coil state by the solvation of a small number of effectors to the polymer chain. Therefore, we envisioned that the addition of an effector as a fourth component to a ternary polymer solution exhibiting LCST-type phase separation could achieve dual chemo- and thermo-responsiveness in organic media (Figure 1b). Dual responsiveness could be useful for adjusting the coil–globule transition of the polymer chain according to the chemical species, their amount, and the temperature. These chemo-responsive controls of LCST-type phase separation have often been reported for nonionic amphiphilic polymers to control hydration and hydrophobic aggregation of the polymer chain in water.

Materials and methods

Poly(4-hydroxystyrene) (PHS) (average M_w : ~25,000) was purchased from Sigma–Aldrich (aldrich/436224). All other reagents were commercially available and used as received unless otherwise noted.

A solubility test of PHS (75 mg) in 1,4-dioxane/toluene = 6.1:3.9 (3 mL)⁴² with an appropriate effector (up to 25 mol% = 0.25 equivalents per hydroxyl group in the polymer unit) was performed by mixing a suitable amount of the effector and polymer solutions and storing them at low temperature (0 °C), room temperature (ca. 25 °C) and elevated temperature (ca. 100 °C).

The evaluation of chemical sensor system was performed by sequentially adding piperazine (1.1 mg, 1 mol%), TFA (0.9 μ L, 1 mol%), piperazine (4.2 mg, 4 mol%), and TFA (3.7 μ L, 4 mol%).

Transmittance measurements at 800 nm were recorded on a Jasco V-750 spectrophotometer with a Jasco ETC-505T temperature controller, and the temperature scan rate was 1.5 °C/min. The cloud point (T_{cp}) was determined to be the temperature at which the %transmittance was equal to 90% in the heating process for LCST-type phase separation using UV-vis spectroscopy.

Results and discussion

We hypothesized that if the effector forms stronger hydrogen bonds with the polymer chains than good solvents, the addition of a small amount of hydrogen-bonding effector would induce a drastic change in solvation, thereby altering thermo-responsiveness. In accordance with our previous study⁴², we decided to use 1,4-dioxane, which has only a hydrogen-bonding acceptor and forms weak hydrogen bonds with PHS in mixed organic solvents. A ternary polymer solution consisting of PHS in 1,4-dioxane/toluene at a ratio of 6.1: 3.9 (25 mg/mL) was selected as the standard condition. This constant molar ratio was regulated to produce the LCST-type phase separation at the cloud point ($T_c = 78$ °C). The effector was added to the ternary polymer solution up to 25 mole percent (mol%) per hydroxy group in the polymer chain. Next, we investigated the solubility changes of PHS at low temperatures (ca. 4 °C), room temperature (ca. 25 °C), and elevated temperatures (ca. 100 °C). First, we tested a series of basic amines as effectors since PHS possesses a weakly acidic phenolic OH group (Table 1, S1-S3). The addition of 20 mol% cyclohexylamine resulted in the loss of the LCST-type thermo-responsiveness, causing a higher solubility of PHS at elevated temperatures, while the other primary amines had a limited effect on the LCST-type thermo-responsiveness of PHS. Due to the small increase in T_c , the addition of primary amines slightly increased the solubility by forming hydrogen bonds with PHS. In contrast, the addition of 15 mol% diethylamine decreased the T_{cp} of LCST-type phase separation and induced the upper critical solution temperature (UCST)-type phase separation. Cyclic secondary amines (2-10 mol%), such as pyrrolidine, piperidine, and morpholine, were more effective at changing the thermo-responsive behavior. However, the addition of secondary dialkylamines with relatively large substituents (dibutylamine and *N*-methylcyclohexylamine) did not considerably affect the thermo-responsive behavior. Some tertiary amines with large alkyl groups could function as pseudo-non-polar poor solvents causing a decrease in the cloud point, producing a decrease in the solubility of PHS. Compared with the addition of monoamines, the addition of a small amount of

diamine (1–6 mol%) significantly influenced the thermo-responsiveness of PHS. *N,N,N,N*-Tetramethyl-1,3-diaminopropane resulted in both UCST-type and LCST-type phase separation at ambient temperatures. Piperazine and trans-1,2-cyclohexanediamine rendered PHS insoluble at only 1 mol%. These diamines reduced the solubility of PHS in 1,4-dioxane/toluene, irrespective of the number of amino group substituents. We then investigated the influence of nitrogen-containing heterocyclic compounds to expand the variety of effectors with other types of functional groups (Tables 2, S4, S5). Interestingly, the addition of 25 mol% pyridine did not affect the LCST-type phase separation of PHS; however, with the addition of only 4 mol% 4-dimethylaminopyridine (DMAP), PHS became insoluble. Similarly, with the addition of only 1 mol% 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), PHS became insoluble. The addition of either imidazole or 1-methylimidazole, regardless of the presence of the N-H group, caused the UCST-type and LCST-type phase separation of PHS; these results indicated that effector molecules with two hydrogen-bonding functional groups played a pivotal role in modulating its LCST-type thermo-responsiveness.

Therefore, small secondary amines and bifunctional amines could serve as strong effectors and drastically change the solubility of PHS to be completely insoluble or just insoluble at lower temperatures, such as during UCST phase separation. However, both the class of amines, such as primary, secondary, and tertiary amines, and the size of the substituent alkyl groups were varied. The correlation between the molecular structure and the activity of effectors is not fully understood. To further understand this phenomenon, we compared the acid dissociation constants (pK_a) of phenol and various amines in acetonitrile^{49,50}. As the monomeric model compound PHS, 4-methylphenol ($pK_a = 27.45$)⁵⁰ has a significantly larger pK_a than those of various aliphatic amines ($pK_a = 18\sim 20$)⁴⁹ and heterocycles such as pyridine ($pK_a = 12.53$)⁴⁹, imidazole ($pK_a = 15.07$)⁴⁹, and DBU ($pK_a = 24.31$)⁴⁹. Therefore, the acid–base reaction between the phenol group in the polymer chain and the nitrogen–base effector is not expected to proceed in acetonitrile. Moreover, the dielectric constant of the medium (1,4-dioxane ($\epsilon = 2.2$)/toluene ($\epsilon = 2.3$) = 6.1/3.9) is extremely low at ~ 2 , the formation of ion pairs should presumably be suppressed, and the addition of a small amount of the effector would not increase the solvent polarity. Therefore, hydrogen bonds and other weak interactions likely play a key role in solvation of the polymer chains. The high activity of the cyclic aliphatic secondary amines is likely caused by the formation of the cyclic hydrogen bond network that was observed in the 1:1 complexes of phenol and amines in the crystalline state, as shown in Figure S3^{51,52}. Thus, the cross-linking of the polymer chain potentially causes the decrease in the solubility. Similar cross-linking may occur with the addition of bifunctional amines.

To further validate this hypothesis, we examined the effects of various alcohols as hydrogen-bonding effectors. Here, the addition of primary alcohols such as 1-butanol, 1-hexanol, and 1-octanol had minimal effects on the LCST-type thermo-responsiveness of PHS; however, the addition of ethylene glycol caused a decrease in the T_{cp} of LCST-type phase separation and insolubility at a concentration of 2.5 mol%. Glycerin also reduced the solubility of PHS and induced UCST-type phase separation. The presence of two or three hydroxyl groups in these alcohols likely facilitated cross-linking of the

polymer chains through the intermolecular hydrogen bonds, thereby reducing the solubility of PHS in 1,4-dioxane/toluene.

The sensitivity of the effectors in influencing the LCST-type phase separation of PHS was evaluated via temperature-dependent transmittance measurements. In the absence of effectors, LCST-type phase separation of PHS occurred at 78 °C. Notably, upon the addition of morpholine (2–10 mol%), a decrease in the T_{cp} of LCST-type phase separation was observed, along with the appearance of UCST-type phase separation in the region of lower temperature (Figure 2a). The T_{cp} decreased linearly with increasing effector amounts (Figure 2b). Similarly, the addition of DMAP resulted in a linear reduction in T_{cp} with each 1 mol% increase (Figure 2c,d). Based on these findings, the addition of these effectors clearly leads to a quantitative decrease in the solubility of PHS. Since a slightly excess amount of 1,4-dioxane (31 equivalent to the hydroxy group of PHS) was present in the ternary polymer solution, these effectors strongly interacted with the polymer chain to alter the solvation state, which destabilized the weak hydrogen bonds between the hydroxy group of PHS and 1,4-dioxane, thereby facilitating desolvation of the polymer chain.

As previously mentioned, the addition of a small amount of basic effectors significantly reduced the solubility of PHS in 1,4-dioxane/toluene. Hence, we hypothesized that these quaternary polymer solutions could serve as a kind of chemo-sensor system to detect acids (Figure 3). Although many reports on the development of pH-responsive polymers as chemical sensors exist, the pH-responsive functional groups needed to be introduced into the polymer chains^{53,54}. Our chemo-sensor system consisted of commercially available PHS and simple small molecules without any synthetic modifications. In the absence of suitable acids, the polymer solution with the basic effector remained turbid, whereas its presence rendered the polymer soluble owing to the decrease in the concentration of the basic effector from the acid–base reaction between the basic effector and the acidic additive; this causes the polymer solution to become transparent. As discussed earlier, the OH group of PHS does not have sufficient acidity; here, the key design is the removal of the basic effector from the system by the acid-base reaction and no interference from the salt formed by the reaction of the basic effector and the acidic additive on the solubility of the polymer chain. Therefore, the presence of acids need to be visualized based on the appearance of the solution. To assess its reversible sensing capability, we conducted visual detection of trifluoroacetic acid (TFA, $pK_a=10.6$ in acetonitrile⁵⁵) using piperazine ($pK_a=18.89$ in acetonitrile⁴⁹) as a basic effector. Initially, upon the addition of 1 mol% piperazine to the PHS ternary polymer solutions, the solution rapidly became turbid at room temperature (Figure 4a). The addition of 1 mol% TFA (0.9 μ L of TFA/3 mL of polymer solution) subsequently rendered the polymer solution transparent. These results indicated that our chemo-sensor system was highly sensitive to TFA. This change in the appearance of the polymer solution was consistently observed upon the addition of 4 mol% piperazine followed by the subsequent addition of 4 mol% TFA, indicating that the detection limit of TFA could be modulated depending on the amount of piperazine. Since reversible temperature-dependent transmittance changes were observed both with and without piperazine and TFA, the quaternary polymer solution of PHS in 1,4-dioxane/toluene

demonstrated high sensitivity and reversibility as a chemo-sensor system (Figure 4b). After a few cycles of the alternative addition of piperazine and TFA, the salt formed by the acid–base reaction did not cause any interference with the LCST phase separation of PHS.

Conclusions

In summary, we demonstrated that the addition of hydrogen-bonding effectors as chemical stimuli induced drastic changes in the LCST-type thermo-responsiveness of PHS in 1,4-dioxane/toluene. The effectors impacted the solvation of PHS, which was mediated by hydrogen bonds between the polymer hydroxy group and 1,4-dioxane; this resulted in alterations in the solubility at ambient temperatures. Notably, basic secondary amines, such as morpholine, and molecules containing two hydrogen-bonding functional groups, such as DMAP, acted as strong effectors at only a few molar fractions (1–10 mol%); their additions led to the disappearance of LCST-type phase separation and the appearance of UCST-type separation. By constructing the intermolecular hydrogen bonds, these effectors could cross-link the polymer chains and consequently decrease the solubility of PHS. Furthermore, this quaternary polymer solution served as a chemo-sensor system for the detection of the acids through the acid–base reaction of piperazine and TFA. We anticipate that our molecular design will facilitate the development of more complex dual stimuli-responsiveness materials in non-aqueous media, with promising applications as smart materials in the future.

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Additional Information: Supplementary information is available for this paper.

Correspondence and requests for materials should be addressed to Kazuki Sada and Keitaro Matsuoka.

Figure Legends

Figure 1. Rational design of dual chemo- and LCST-type thermo-responsive phase separation of PHS in organic media. (a) Quaternary polymer solutions composed of PHS in 1,4-dioxane as a hydrogen-bonding good solvent and toluene as a non-polar poor solvent with a pseudo-solvating molecule (effector) as chemical stimuli. (b) Schematic representation of the drastic changes in the LCST-type thermo-responsiveness of ternary polymer solutions induced by the effectors.

Figure 2. (a, c) Transmittance change at 800 nm of PHS in 1,4-dioxane/toluene = 6.1:3.9 (25 mg/mL) with an appropriate amount of effector with respect to the temperature changes (scan rate: 1.5 °C/min); the solid line and the dotted line represent the heating and cooling processes, respectively. (b, d) Effects of the number of effectors (mol%) on the change in the cloud point during the heating process (90% transmission). (a, b) Morpholine 0–10 mol%, (c, d) DMAP 0–2 mol%.

Figure 3. Schematic representation of the mechanism of the chemo-sensor system for the visual detection of acids through acid–base reactions.

Figure 4. PHS quaternary polymer solution as a chemo-sensor system to detect acids. (a) Visual observations of the polymer solution after the addition of repeated amounts of piperazine and TFA. (b) Reversible temperature-dependent transmittance changes at 800 nm for PHS in 1,4-dioxane/toluene with and without piperazine and TFA (scan rate: 1.5 °C/min); the solid and dotted lines represent the heating and cooling processes, respectively. B: Base, A: Acid.

Table 1. Screening of the amines as effectors^a.

Effector	Amount (mol%)	Efficacy	Phase separation
None	-	-	LCST(78 °C)
1-Hexylamine	25	No	-
Cyclohexylamine	20	Yes	Soluble
1-Dodecylamine	25	No	-
Diethylamine	15	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
Pyrrolidine	2	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
Piperidine	6	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
Morpholine	10	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
Dibutylamine	25	No	-
<i>N</i> -Methylcyclohexylamine	25	No	-
Tris(2-ethylhexyl)amine	20	Yes	Insoluble
Tri- <i>n</i> -decylamine	20	Yes	Insoluble
<i>N,N,N',N'</i> -Tetramethyl-1,3-diaminopropane	3	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
Piperazine	1	Yes	Insoluble
trans-1,2-Cyclohexanediamine	1	Yes	Insoluble

^aConditions: PHS (75 mg) in 1,4-dioxane/toluene = 6.1:3.9 (3 mL) with appropriate amines (1–25 mol/OH in PHS) from ca. 0 °C to ca. 100 °C.

Table 2. Screening of the nitrogen-containing heterocyclic compounds and alcohols as effectors^a.

Effector	Amount (mol%)	Efficacy	Phase separation
None	-	-	LCST(78 °C)
Pyridine	25	No	-
DMAP	4	Yes	Insoluble
DBU	1	Yes	Insoluble
Imidazole	4	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
1-Methylimidazole	5	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
1-Butanol	25	No	-
1-Hexanol	25	No	-
1-Octanol	25	No	-
Ethylene glycol	2.5	Yes	Insoluble
Glycerin	10	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
Effector	Amount (mol%)	Efficacy	Phase separation
None	-	-	LCST(78 °C)
Pyridine	25	No	-
DMAP	4	Yes	Insoluble
DBU	1	Yes	Insoluble
Imidazole	4	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
1-Methylimidazole	5	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
1-Butanol	25	No	-
1-Hexanol	25	No	-
1-Octanol	25	No	-
Ethylene glycol	2.5	Yes	Insoluble
Glycerin	10	Yes	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)

^aConditions: PHS (75 mg) in 1,4-dioxane/toluene = 6.1:3.9 (3 mL) with appropriate nitrogen-containing heterocyclic compounds and alcohols (1-25 mol%/OH in PHS) from ca. 0 °C to ca. 100 °C.

**Rational Design of Dual Chemo- and Thermo-responsive Phase Separation of
Poly(4-hydroxystyrene) in Non-aqueous Media**

Kota Hashimoto¹, Natsuki Inaba¹, Keitaro Matsuoka^{1,2*}, and Kazuki Sada^{1,2*}

¹ Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan.

² Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan.

Phone: +81-11-706-3473 / Fax: +081-11-706-3474

E-mail: sadatcm@sci.hokudai.ac.jp, ma2oka@sci.hokudai.ac.jp

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1. General information

Poly(4-hydroxystyrene) (PHS) (average Mw: ~25,000) was purchased from Sigma-Aldrich ([aldrich/436224](#)). All other reagents were commercially available and used as received unless otherwise noted.

A solubility test of PHS in the mixtures of 1,4-dioxane and toluene with an appropriate effector was done by mixing the suitable amount of the effector and polymer solutions at low temperature (0 °C), room temperature (ca. 25 °C) and elevated temperature (ca. 100 °C).

Transmittance Measurements at 800 nm were recorded on a Jasco V-750 spectrophotometer with a Jasco ETC-505T temperature controller, and the temperature scan rate was 1.5 °C/min. Cloud point (T_{cp}) was determined by the Transmittance measurement using UV-vis as the temperature at which %Transmittance = 90 in the heating process for LCST-type phase separation.

2. Changes of thermo-responsiveness of PHS induced by effectors

The conditions: PHS (75 mg) in 1,4-dioxane/toluene = 6.1:3.9 (3 mL). S: soluble, I: insoluble, cool: ca. 0°C, heat: 70-100°C

Table S1. Effects of primary amines

Effector	Amount (mg)	Equiv. (mol%)	Solubility			Thermo- responsiveness
			cool	r.t.	heat	
none	-	-	S	S	I	LCST (78 °C)
Aniline	14.5	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
1-Hexylamine	15.8	25	S	S	I	LCST (90 °C < T_{cp})
<i>tert</i> -Butylamine	11.4	25	S	S	I	LCST (90 °C < T_{cp})
Benzylamine	16.7	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
Cyclohexylamine	9.3	15	S	S	I	LCST (90 °C < T_{cp})
	12.4	20	S	S	S	Soluble
	15.5	25	S	S	S	Soluble
1-Nonylamine	22.4	25	S	S	I	LCST (90 °C < T_{cp})
1-Dodecylamine	28.9	25	S	S	I	LCST (90 °C < T_{cp})

Table S2. Effects of secondary amines

Effector	Amount (mg)	Equiv. (mol%)	Solubility			Thermo- responsiveness
			cool	r.t.	heat	
Piperidine	2.7	5	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	3.2	6	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	3.7	7	I	I	I	Insoluble
Morpholine	4.3	8	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	5.4	10	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	6.5	12	I	I	I	Insoluble
Pyrrolidine	0.4	1	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	0.9	2	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	1.3	3	I	I	I	Insoluble

	4.6	10	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
Diethylamine	6.8	15	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	11.4	25	I	I	I	Insoluble
N-Ethylpropylamine	13.6	25	S	S	I	LCST (90 °C < T_{cp})
Dibutylamine	20.2	25	S	S	I	LCST (90 °C < T_{cp})
N-Methylcyclohexylamine	17.7	25	S	S	I	LCST (90 °C < T_{cp})

Table S3. Effects of tertiary amines

Effector	Amount (mg)	Equiv. (mol%)	Solubility			Thermo- responsiveness
			cool	r.t.	heat	
Triethylamine	15.8	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
Tributylamine	28.9	25	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
Tris(2-ethylhexyl)amine	22.1	10	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	33.1	15	S	I	I	LCST (0 °C < T_{cp} < r.t.)
	44.1	20	I	I	I	Insoluble
Tri- <i>n</i> -decylamine	27.3	10	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	41.0	15	S	I	I	LCST (0 °C < T_{cp} < r.t.)
	54.6	20	I	I	I	Insoluble

Table S4. Effects of diamines

Effector	Amount (mg)	Equiv. (mol%)	Solubility			Thermo- responsiveness
			cool	r.t.	heat	
<i>N,N,N',N'</i> - Tetramethyl-1,3- diaminopropane	1.6	2	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	2.4	3	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	3.3	4	I	I	I	Insoluble
Piperazine	0.5	1	I	I	I	Insoluble
	1.1	2	I	I	I	Insoluble
trans-1,2- Cyclohexane diamine	0.7	1	I	I	I	Insoluble
	1.4	2	I	I	I	Insoluble
cis-1,2- Cyclohexane diamine	0.7	1	I	I	I	Insoluble
	1.4	2	I	I	I	Insoluble

Table S5. Effects of nitrogen-containing heterocyclic compounds

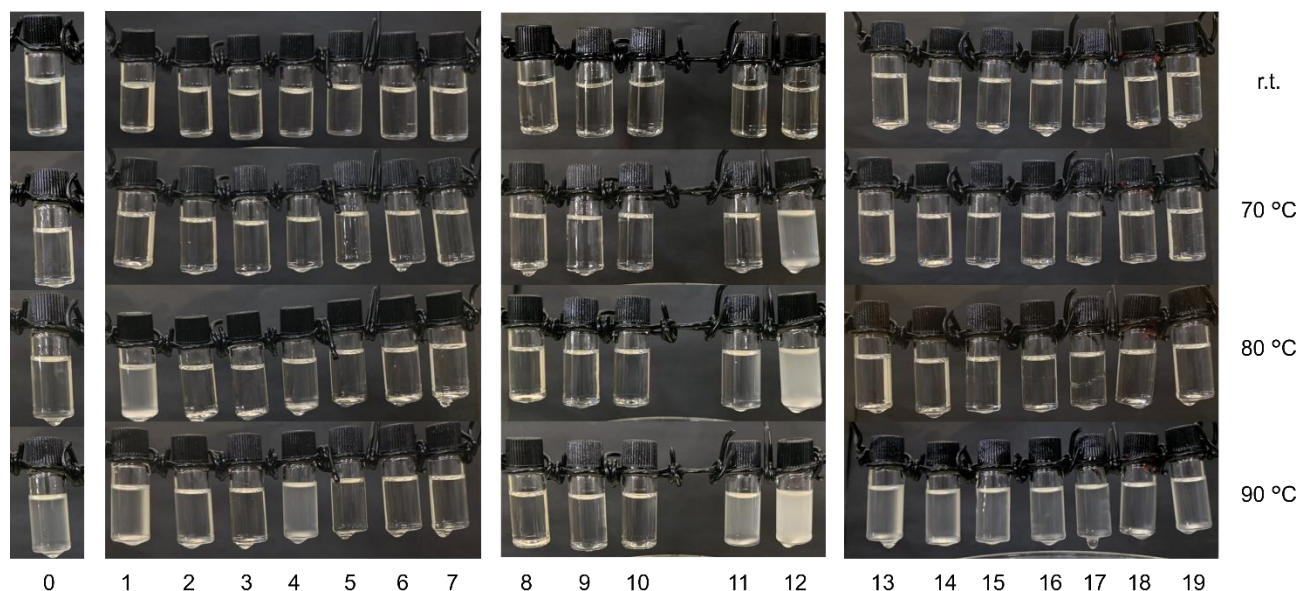
Effector	Amount (mg)	Equiv. (mol%)	Solubility			Thermo- responsiveness
			cool	r.t.	heat	
Pyridine	12.3	25	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	14.8	30	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	17.3	35	I	I	I	Insoluble
DMAP	1.5	2	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	3.0	4	I	I	I	Insoluble
DBU	0.9	1	I	I	I	Insoluble
	1.9	2	I	I	I	Insoluble
Imidazole	1.3	3	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	1.7	4	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	2.1	5	I	I	I	Insoluble
1-Methylimidazole	2.0	4	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	2.6	5	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	3.1	6	I	I	I	Insoluble

Table S6. Effects of alcohols

Effector	Amount (mg)	Equiv. (mol%)	Solubility			Thermo- responsiveness
			cool	r.t.	heat	
Methanol	5.0	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
Ethanol	7.2	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
1-Propanol	9.4	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
1-Butanol	11.6	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
<i>tert</i> -Butylalcohol	11.6	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
1-Hexanol	15.9	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
1-Octanol	20.3	25	S	S	I	LCST (80 °C < T_{cp} < 90 °C)
Ethylene glycol	0.8	2	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	1.0	2.5	I	I	I	Insoluble
	1.2	3	I	I	I	Insoluble
Glycerin	2.9	5	S	S	I	LCST (r.t. < T_{cp} < 70 °C)
	5.7	10	I	S	I	LCST (r.t. < T_{cp} < 70 °C) & UCST (0 °C < T_{cp} < r.t.)
	8.6	15	I	I	I	Insoluble

3. Visual observation of thermo-responsiveness of PHS

After the polymer solutions were immersed in an oil bath at the appropriate temperature, the appearance of the solution was observed. For polymer solution compositions; See **Table S1-S6**. LCST-type phase separation was observed from a clear solution to a turbid suspension



Lot No.	Effector
0	none
1	Aniline
2	1-Hexylamine
3	<i>tert</i> -Butylamine
4	Benzylamine
5	Cyclohexylamine
6	1-Nonylamine
7	1-Dodecylamine
8	<i>N</i> -Ethylpropylamine
9	Dibutylamine
10	<i>N</i> -Methylcyclohexyl amine

Lot No.	Effector
11	Triethylamine
12	Tributylamine
13	Methanol
14	Ethanol
15	1-Propanol
16	1-Butanol
17	<i>tert</i> -Butylalcohol
18	1-Hexanol
19	1-Octanol

4. Evaluation of thermo-responsiveness of PHS by temperature-dependent transmittance measurements

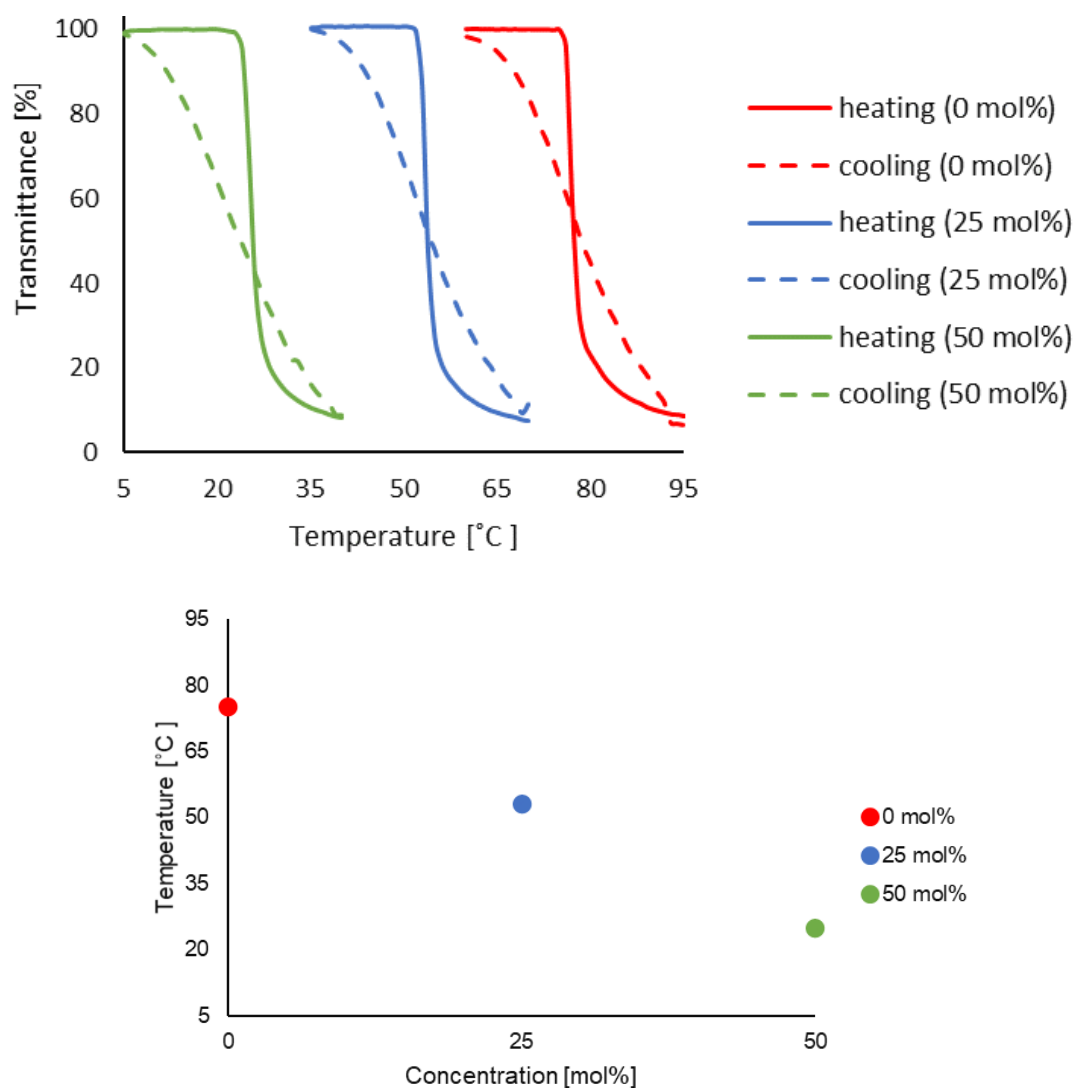


Figure S1. Transmittance change of PHS in 1,4-dioxane and toluene with tributylamine

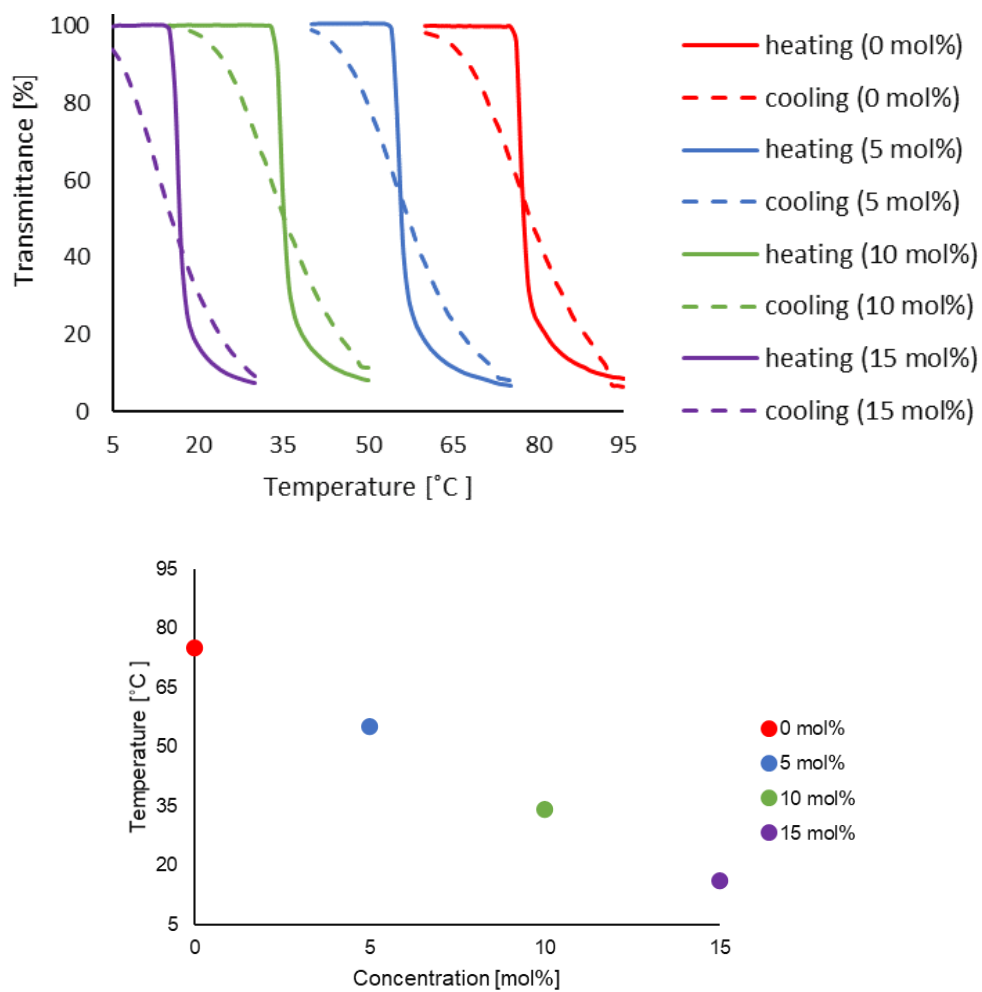


Figure S2. Transmittance change of PHS in 1,4-dioxane and toluene with tri-*n*-decylamine

5. Plausible mechanism that small secondary amines could serve as strong effectors

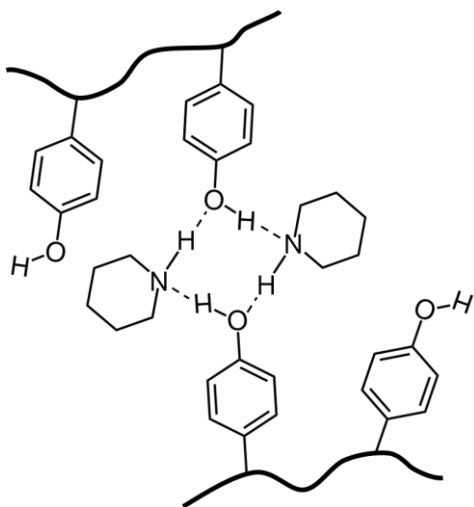
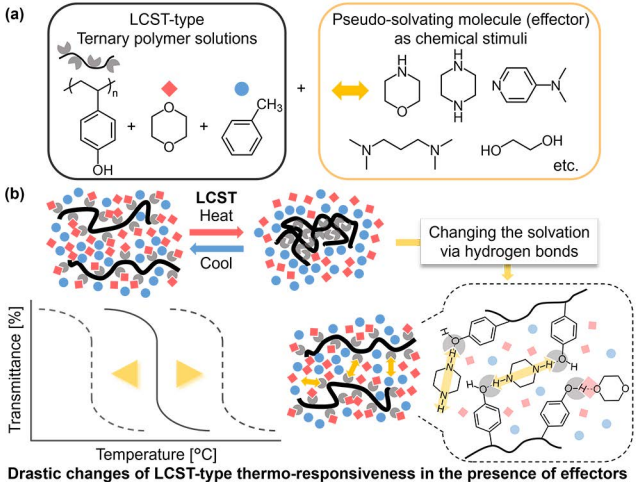
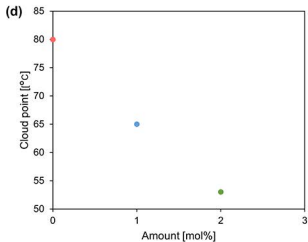
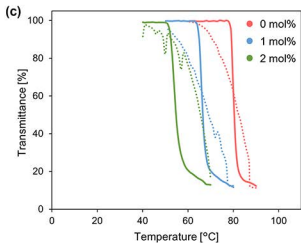
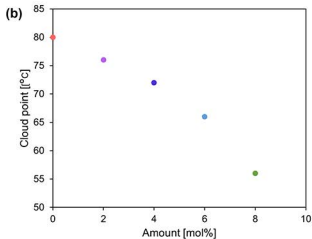
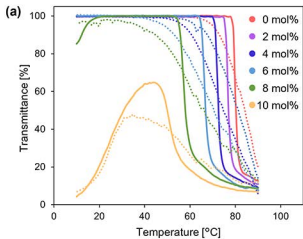
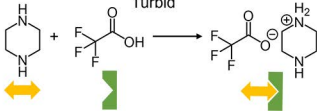
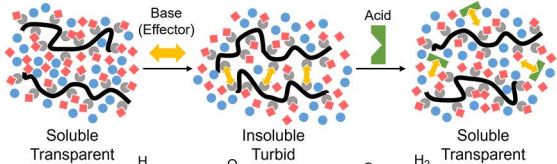
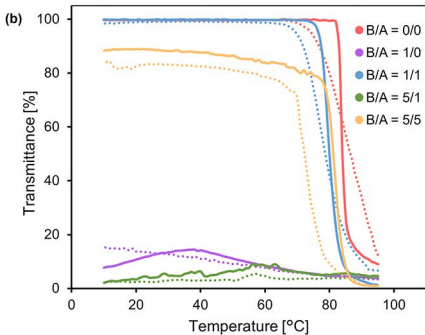
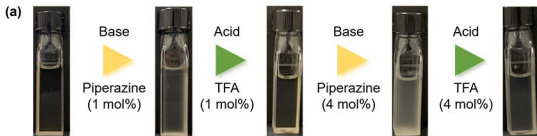


Figure S3. The formation of the cyclic hydrogen bond network formed by the 1:1 complexes of phenol and amines alters the solvation of PHS







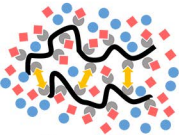


Chemically-induced

UCST

Heat

Cool



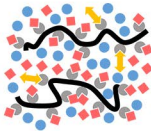
Cross-linking

Thermally-induced

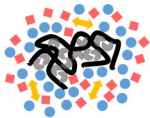
LCST

Heat

Cool



Solvated



Collapsed

Dual chemo- and thermo-responsive phase separations of poly(4-hydroxystyrene) in non-aqueous media were demonstrated. The addition of small amounts of hydrogen-bonding molecules as chemical stimuli caused a considerable change of LCST-type thermo-responsiveness of poly(4-hydroxystyrene) in 1,4-dioxane/toluene. Secondary amines or molecules containing two hydrogen-bonding functional groups could cross-link the polymer chains through the hydrogen bonds, which altered the solvation state and induced the UCST-type thermo-responsiveness or insolubility of the polymer. This dual stimuli-responsive system worked as a chemical sensor to detect the presence of acids.