J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Fundamental Molecular Design for Precise Control of Thermoresponsiveness of Organic Polymers by Using Ternary Systems

Shogo Amemori,[†] Kenta Kokado,[†,‡] and Kazuki Sada*[,†,‡]

[†]Department of Chemical Sciences and Engineering, Graduate School of Chemical Sciences and Engineering, Hokkaido University, Kita 13, Nishi 8, Kita-ku, Sapporo 060-8628, Japan

[‡]Department of Chemistry, Graduate School of Science, Hokkaido University, Kita10, Nishi 8, Kita-ku, Sapporo 060-0810, Japan

Supporting Information

ABSTRACT: The de novo design of thermosensitive polymers in solution has been achieved by using the addition of small organic molecules (or "effectors"). Hydrogen bonding as an attractive polymer−polymer or polymer−effector interaction substantially dominates the responsivity, causing facile switching between LCST-type and UCST-type phase transitions, control of the transition temperature, and further coincidence of the two transitions. Small molecules having a high affinity for the polymer induce UCST-type phase behavior, whereas those having a low affinity for the polymer showed LCST-type phase behavior.

Thermosensitive polymers exhibiting drastic changes in polymer solubility upon heating [lower critical solution temperature (LCST)] or upon cooling [upper critical solution temperature (UCST)] have attracted continuous interest toward the design of smart materials.[1] According to the general model of LCST behavior of amphiphilic polymers such as poly(*N*-isopropylacrylamide) (PNIPAM) in water, the phase transitions are generally induced by imbalance and competition between polymer−polymer interactions and hydration of the polymer, which is substantially affected by heating or cooling.[2] Supramolecular interactions between the unit structure of the polymer chain and small molecules around the polymer such as H_2O should play a crucial role. The reverse solubility transition (i.e., UCST) originates from breaking of interactions among polymer chains by heating.[3] For example, poly(acrylic acid)[3a] or polymers containing zwitterionic groups[3b] show a UCST in water. Because of the importance of developing stimuli-responsive materials, tuning the phase transition temperatures around ambient regions (0−100 °C) has been one of the interesting topics for supramolecular and polymer chemistry. A plethora of research efforts have focused on the control of phase transitions of organic polymers, including PNIPAM, by variation of concentration, solvent, molecular weight, and copolymerization to achieve integrated control of the phase transition behavior.[4] However, the de novo design of LCST and UCST behavior still remains unclear. In this communication, we show that control of intermolecular interactions broken by heating can easily provide LCST-type and UCST-type phase transitions, wide-ranging control of their transition temperatures, and further coincidence of the two transitions using only a single polymeric component.

To realize a desirable thermoresponsivity at ambient temperature, we selected ternary systems consisting of a polymer, an "effector" (a small molecule that affects the solubility), and a solvent that meet the following criteria: (1) The polymer should contain strong hydrogen-bonding functional groups to provide a attractive interaction between the polymer chains. (2) Surrounding the polymers should be a small amount of effector, which interacts with the polymer chains through relatively weak hydrogen-bonding functional groups. (3) The solvent as a background medium must be inert toward the hydrogen bonding, meaning that it rarely interferes with the polymer−polymer or polymer−effector hydrogen bonds. In this report, we shed light on the phase transition behavior of urea polymers to which 5−10 equiv of hydrogen-bonding guest molecules as an effector have been added in aprotic nonpolar media. Moreover, chemoselective switching of the thermal behavior was accomplished by changing the strength of the hydrogen bonding of the functional group in the effector.

As a platform polymer for the ternary system, urea-modified acrylate polymer **1** was designed (Figure 1a). A urea moiety was selected as a hydrogen-bonding functional group having attractive interactions because of its remarkable ability to form one-dimensional aggregates in aprotic organic solvents.[5] The urea-modified monomer **3** was synthesized in an acceptable yield by the condensation reaction of acryloyl chloride and urea-modified alcohol **2** (Figure 1b). The structure of monomer **3** was confirmed by ^{1}H NMR and IR spectroscopy, electrospray ionization mass spectrometry, and elemental analysis. Polymer **1** was obtained via controlled radical polymerization (CRP) of monomer **3** using dithioester **4** as the chain-transfer agent (CTA).[6] The molecular weight and polydispersity index of polymer **1** were determined to be $M_n = 2.47 \times 10^4$ and $M_w/M_n = 1.92$, respectively, using size-exclusion chromatography (SEC) with poly(ethylene oxide) standards.

First, we checked the solubility of polymer **1** in various organic solvents. In aprotic solvents such as acetonitrile, tetrahydrofuran, 1,2-dichloroethane (DCE), and hexane, **1**

Received: February 20, 2012
Published: April 30, 2012

dx.doi.org/10.1021/ja301688u | *J. Am. Chem. Soc.* 2012, 134, 8344−8347

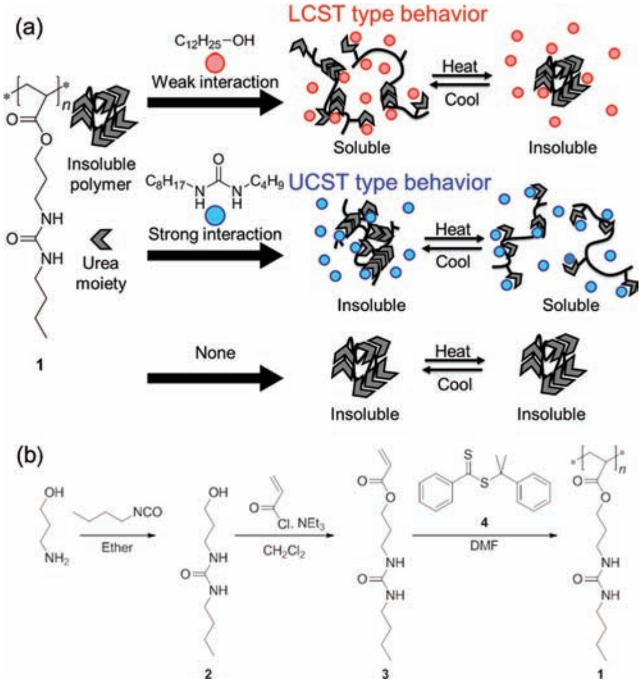


Figure 1. (a) Concept of the thermosensitive polymer with LCST-type and UCST-type behavior controlled by additives. (b) Synthetic route for urea polymer **1**.

was practically insoluble because of the strong hydrogen bonds between the urea moieties on the polymer chain. On the contrary, in methanol, ethanol, and hexanol, the polymer showed high solubility (>100 mg/mL) because these protic polar solvents can form hydrogen bonds with the urea groups and cleave the association of the polymers. This result further prompted us to investigate control of the LCST and UCST behavior of **1** in the presence of "effectors" in nonpolar media with low solubility for **1** by perturbation of the hydrogen bonds between the urea groups.

Changes in the solubility of **1** upon heating were investigated in DCE as the solvent in the presence of various small molecules such as alcohols, amides, ureas, and carboxylic acids (Table 1). As the amount of the small molecule was gradually increased, 25 mg/mL **1** (0.11 M urea units in the polymer) in DCE changed from insoluble to soluble. Moreover, at the boundary state between insoluble and soluble, thermosensitive behavior (i.e., LCST or UCST) was observed. For an example, Figure 2 shows the transmittance change of polymer **1** with 5 equiv of 1-dodecanol in DCE upon heating, and the LCST was observed at 49 °C (the clouding point was determined as the temperature with 90% transmittance). UCST-type phase separation was observed upon addition of aliphatic carboxylic acids, dialkylureas, and tetrahexylammonium bromide, as shown in Table 1. In contrast, addition of alcohols such as 1-dodecanol, pyrenebutanol, and cholesterol resulted in LCST-type phase separation. To date, few examples of LCST polymers in organic solvents have been reported[7] because of the lack of de novo design, and they were accidentally found through laborious trial and error. For a series of aliphatic amides with different alkyl-chain lengths, shorter and longer alkylamides exhibited UCST-type and LCST-type type phase separation, respectively. Furthermore, polyhydroxy compounds

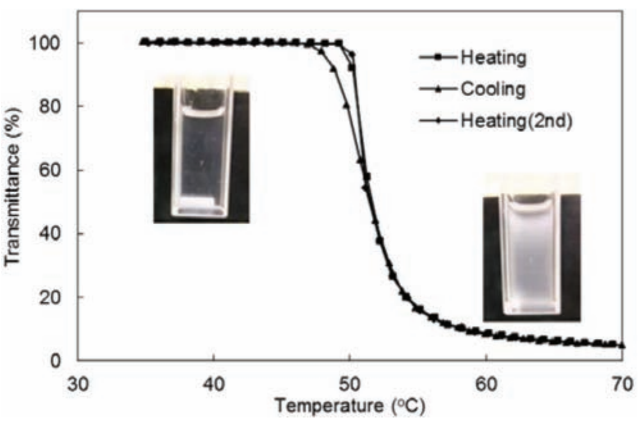
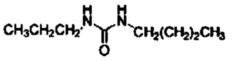
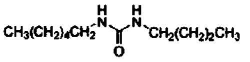
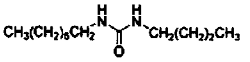
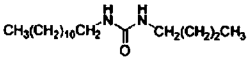
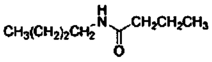
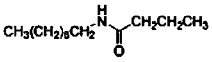
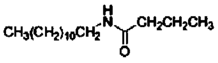
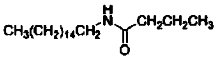
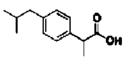
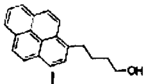
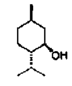
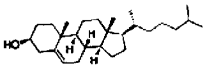
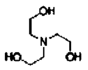


Figure 2. Transmittance of **1** (25 mg/mL, 0.11 M) as a function of temperature in the presence of 1-dodecanol (0.57 M) in DCE. The data were recorded at 700 nm at heating and cooling rates of 1 °C/min.

Table 1. Thermal Behavior of Polymer 1 [25 mg/mL (0.11 M)] in the Presence of Small Molecules in DCE (Concentrations of Small Molecules and Phase Transition Temperatures Are Given in Parentheses)

Entry	Effectors	Solubility
1	None	Insoluble
2	CH_3CN	Insoluble
3	$CH_3(CH_2)_4CH_3$	Insoluble
4	$CH_3(CH_2)_5COOH$	UCST (41 °C, 1.6 eq.)
5	$CH_3(CH_2)_7COOH$	UCST (40 °C, 1.2 eq.)
6	$CH_3(CH_2)_{11}COOH$	UCST (44 °C, 0.8 eq.)
7	$CH_3(CH_2)_{15}COOH$	UCST (40 °C, 0.6 eq.)
8	$CH_3(CH_2)_5OH$	LCST (46 °C, 6.5 eq.)
9	$CH_3(CH_2)_7OH$	LCST (43 °C, 5.9 eq.)
10	$CH_3(CH_2)_{11}OH$	LCST (43 °C, 5.2 eq.)
11	 $CH_3CH_2CH_2NHC(O)NHCH_2(CH_2)_2CH_3$	UCST (32 °C, 5.8 eq.)
12	 $CH_3(CH_2)_4CH_2NHC(O)NHCH_2(CH_2)_2CH_3$	UCST (44 °C, 3.5 eq.)
13	 $CH_3(CH_2)_6CH_2NHC(O)NHCH_2(CH_2)_2CH_3$	UCST (37 °C, 3.1 eq.)
14	 $CH_3(CH_2)_{10}CH_2NHC(O)NHCH_2(CH_2)_2CH_3$	UCST (41 °C, 2.4 eq.)
15	 $CH_3(CH_2)_2CH_2NHC(O)CH_2CH_2CH_3$	UCST (33 °C, 8.5 eq.)
16	 $CH_3(CH_2)_8CH_2NHC(O)CH_2CH_2CH_3$	UCST (63 °C, 6.3 eq.)
17	 $CH_3(CH_2)_{10}CH_2NHC(O)CH_2CH_2CH_3$	LCST (51 °C, 5.9 eq.)
18	 $CH_3(CH_2)_{14}CH_2NHC(O)CH_2CH_2CH_3$	LCST (47 °C, 5.9 eq.)
19	Br^- $N^+(n\text{-hexyl})_4$	UCST (28 °C, 0.1 eq.)
20		UCST (39 °C, 0.6 eq.)
21		LCST (55 °C, 4.7 eq.)
22		LCST (50 °C, 9.5 eq.)
23		LCST (57 °C, 4.7 eq.)
24		UCST (51 °C, 3.2 eq.)
25		UCST (76 °C, 2.8 eq.)

such as neopentyl glycol and triethanolamine exhibited UCST-type phase separation, indicating that increasing the number of hydroxyl groups changed the phase separation behavior from LCST-type to UCST-type. These results presumably indicate that the strength of the hydrogen bonding between the urea groups and the effectors plays a key role in controlling the thermosensitivity. Effectors that could interact strongly with the urea groups tended to induce UCST-type phase separation, and weakly interacting effectors induced LCST-type behavior.

To estimate the strength of the interactions between the effectors and urea moieties, ^{1}H NMR spectra of monomer **3** were measured in DCE-d_4 with effectors such as tetrahexylammonium bromide, 1-dodecanoic acid, *N*-butylpropylamide, and *N*-octylpropylamide for UCST-type behavior and *N*-dodecylpropylamide, *N*-hexadecylpropylamide, and 1-dodecanol for LCST-type behavior (Figure S1 in the Supporting Information). In all cases, with increasing amounts of the effector, the urea N−H signal shifted to lower magnetic field, but the shift values for each effector widely differed. To obtain a deeper understanding, the association constants (K_a) for the **3**/effector pairs were determined using Benesi−Hildebrand plots of $1/\Delta\delta_{obs}$ versus $1/[E]_0$, where $\Delta\delta_{obs}$ is the variation of chemical shift and $[E]_0$ is initial concentration of the effector (Table S1 in the Supporting Information). Larger K_a values (>50 M^{-1}) were observed in the presence of tetrabutylammonium bromide and 1-dodecanoic acid, which induced UCST behavior. On the other hand, 1-dodecanol showed a smaller K_a (<1M^{-1}) and induced LCST behavior. In the case of dialkyl-substituted amides, which showed intermediate K_a values (1−3 M^{-1}), the thermal behavior depended on the alkyl-chain length. Probably, the balance between hydrophobicity and hydrophilicity are valuable in determining the thermosensitivity of an effector with an intermediate K_a value. On the basis of these findings, we envision the following mechanism: When the polymer−effector interactions are weaker than the polymer−polymer interactions (e.g., for alcohols and amides with short alkyl chains), heating preferentially breaks the polymer−effector interactions, and the polymer shows insolubility. When the effector interacts with polymer strongly enough (e.g., for ureas, carboxylic acids, and halides), the interactions among the polymers are cleaved by heating, and the polymer shows UCST behavior.

To develop a desirable thermoresponsive system, we adopted a quaternary system using two kinds of effectors, one inducing LCST behavior and the other UCST behavior. The solubility of polymer **1** was investigated in the presence of 1-dodecanol (LCST-type) and *N,N'*-butyloctylurea (UCST type) in DCE. As a result, as the relative amount of *N,N'*-butyloctylurea was increased, UCST-type phase separation was easily observed, and LCST-type phase separation was caused by increasing of relative amount of 1-dodecanol. Amazingly, when appropriate amounts of 1-dodecanol and *N,N'*-butyloctylurea were used, both LCST-type and UCST-type phase separation were achieved in one sample (Figure 3). Furthermore, the system exhibited clear reproducibility upon cooling and additional heating, indicating that the certain balance of hydrogen bonding between **1** and the two additives should be responsible for the result. To provide an in-depth understanding for the quaternary system, a systematic study was carried out for samples including a broad range of concentrations of *N,N'*-butyloctylurea and 1-dodecanol. The distribution of the solubility of **1** shown in Figure 4 distinctly reflects a trend of LCST-type, UCST-type, and LCST+UCST-type phase transitions in the quaternary system. Additionally, the transition temperatures in the LCST+UCST regime were easily controlled over wide ranges (LCST, 35 → 66 °C; UCST, 24 → 9 °C) by slightly varying the amounts of the two effectors (1-dodecanol, 0.34 → 0.37 M; *N,N'*-butyloctylurea, 0.090 → 0.098 M) (Figure 5; also see Figure S2 and Table S2). It is well-known that inducing both LCST and UCST behavior at ambient temperature is difficult.[4f,g] Nevertheless, these data suggest that our fundamental molecular design is applicable to the coincidence of the two transitions.

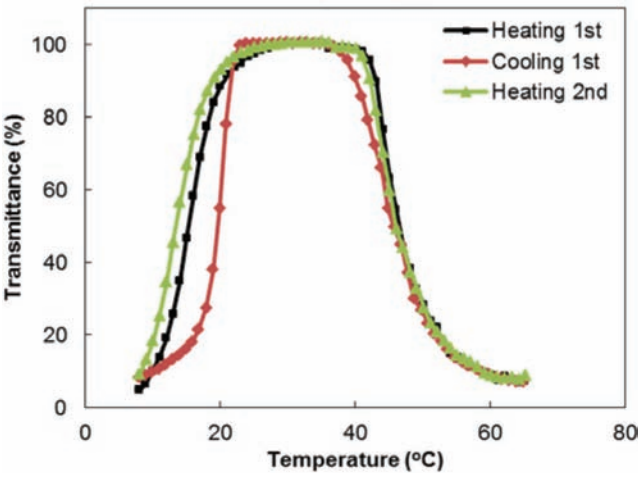


Figure 3. Transmittance of **1** (25 mg/mL) as a function of temperature in the presence of 1-dodecanol (0.39 M) and *N,N'*-butyloctylurea (0.10 M) in DCE. The data were recorded at 700 nm at heating and cooling rates of 1 °C/min.

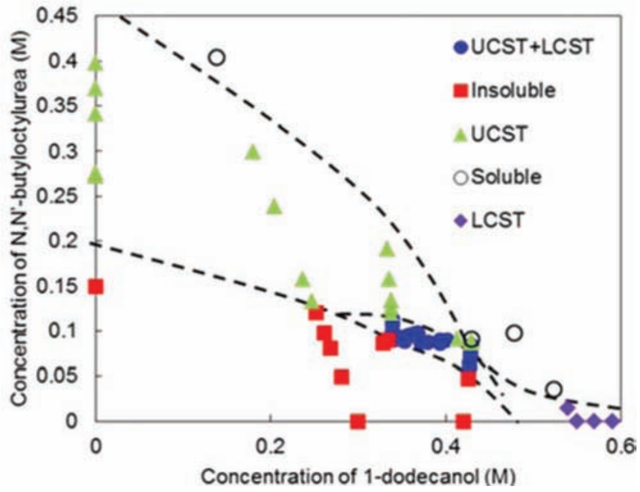


Figure 4. Distribution of solubility of **1** in the presence of 1-dodecanol and *N,N'*-butyloctylurea between 5 and 80 °C. The dashed lines represent the assumed boundaries between types of thermoresponsivity.

In conclusion, we have demonstrated a simple example of a fundamental molecular design for precise control of thermoresponsiveness by employing the single polymer **1** in DCE with the addition of effectors that are competitive with the polymer−polymer interactions. The hydrogen-bonding ability of the effector substantially governs the responsivity of **1**, resulting in facile switching between LCST-type and UCST-type phase transitions and also in their additivity (i.e., their coincidence). More generally, effectors having high affinities for

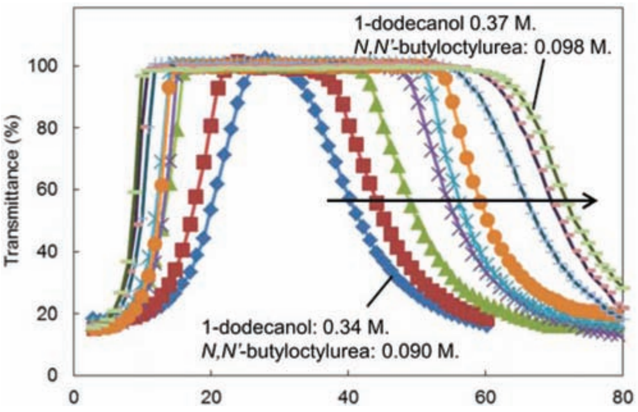


Figure 5. Temperature dependence of the transmittance of polymer **1** (25 mg/mL) upon addition of various concentrations of two kinds of small molecules in DCE (scan rate 1 °C/min).

polymers induce UCST-type phase behavior because of breaking of the interactions between polymers, whereas those having low affinities cannot interact with the polymers at high temperature, resulting in LCST-type phase behavior. In addition, we have pointed out the additivity (i.e., the coincidence) of UCST-type and LCST-type transitions. Further work on the design of smart thermosensitive systems through the use of various interactions is currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

sadatcm@mail.sci.hokudai.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the MEXT Global COE Program “Catalysis as the Basis for the Innovation in Materials Science” and a Grant-in-Aid for Scientific Research (23350048).

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