Molecular Design for Thermo-Sensitive Behavior by Using Non-Covalent Bonds between Polymer and Small Molecules

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Contents

Chapter 1: General Introduction

1. 1. Introduction

In this thesis, the author focuses on the molecular design of thermo-sensitive polymers in organic solvents based on supramolecular interactions and molecular recognitions. Thermo-sensitive polymers are defined as polymers that drastically change their conformations in response to thermal stimuli, i.e., small changes in temperature. Generally, such conformational changes directly induce changes in solubility, insoluble or soluble, and when they are chemically cross-linked, they exhibit a volume change dependent on the temperatures, swelling or collapsing of the polymer gels. These macroscopic changes in the thermo-sensitive materials have been prompting us to develop intelligent or smart materials triggered by various stimuli. Indeed, various applications such as drug delivery, [1] gene therapy,[2] temperature-sensitive chromatography,[3] surface modifiers,[4] and cultivation sheets for cells[5] have been extensively reported.

Researches in applications using water-soluble thermo-sensitive polymers are numerous. However, there are few reports of applications in non-aqueous system compared with aqueous systems. This is attributed to the fact that molecular designs of thermo-sensitive polymers in the non-aqueous system, especially lower critical solution temperature (LCST)-type thermo-sensitive polymers, are difficult to design as discussed later. Here, the main issue of this thesis is to develop thermo-sensitive polymers in non-aqueous system be designing non-covalent bonds. And the author used two approaches In this chapter, the author briefly introduces and reviews the thermo-sensitive polymers including the classification and the mechanism for thermal response, and then the author discuss *de novo* approach to design thermo-sensitive polymer systems in non-aqueous system.

1.2 Thermo-Sensitive Polymer

The critical solution temperature (T_c) in the thermo-sensitive polymer is the temperature at which the phase of the polymer and solution is discontinuously changed according to their compositions. If the polymer solution has one phase below the critical solution temperature and is phase-separated above this temperature, it is generally called a lower critical solution temperature (LCST).[6] On the other hand, if the polymer solution has two phases below the critical solution temperature and becomes one phase above this temperature, it is called an upper critical solution temperature (UCST).

[6] These thermo-sensitive behaviors are generally evaluated as a cloud point by the thermal change in the transmittance or turbidity using the VIS absorption spectrum (Figure 1_1). And, generally, it is determined as the temperature with a certain transmittance around 50% or 90% that depend on the researchers. In many cases the cloud point is the common way to evaluate thermo-sensitiveness of polymer solutions due to the easiest method.

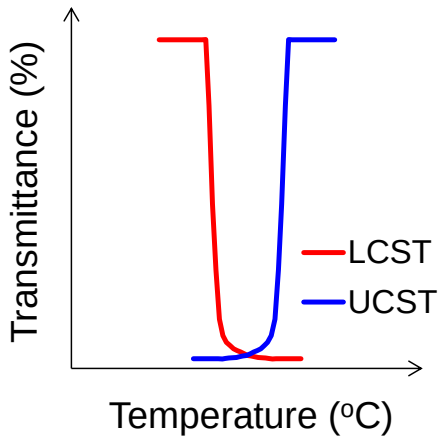


Figure 1_1. Transmittance change of LCST-type or UCST-type thermo-sensitive polymer in a solution against temperature.

The Gibbs free energy of mixing ΔG_m can be described by an equation independently derived by Staverman and Van Santen, by Huggins and by Flory (FHS model, equation 1_1)[7]:

$$\frac{\Delta G_m}{NRT} = \left(\frac{\varphi_1}{m_1}\right)\ln(\varphi_1) + \left(\frac{\varphi_2}{m_2}\right)\ln(\varphi_2) + g\varphi_1\varphi_2 \qquad \text{(equation1\_1)}$$

where ϕ_1 and ϕ_2 are the volume fraction of a solvent and polymer, respectively, m_1 and m_2 are the number of lattice sites that are occupied by a solvent and polymer, respectively, g is interaction parameter. The first two terms in equation 1_1 represent the ideal or combinatorial part of the entropy of mixing. The combinatorial entropy of mixing for polymers is based on a lattice model where an arbitrary lattice site volume is defined. In case of polymer solutions, m_2 is far greater than m_1. The FHS model shows that the combinatorial entropy of mixing is much smaller for polymers than for low molar mass compounds. Therefore, even little interaction can cause miscibility gaps and temperature- and concentration-dependence of interaction parameter g, which is the last term in equation 1_1, plays a key role for thermo-sensitiveness. For this reason, a polymer solution takes place unusual phase behaviors unlike small molecules solution.

1.3. Classification of Thermo-Sensitive Polymer and Physicochemical Basis of Phase Behavior

Extensive studies by polymer chemists revealed that a larger number of polymers have LCST or UCST behaviors in various solvents. Typical thermo-sensitive homopolymers, which contain only a single monomer unit, are roughly categorized into two types which are aqueous systems and organic solvent systems (Figure 1_2).

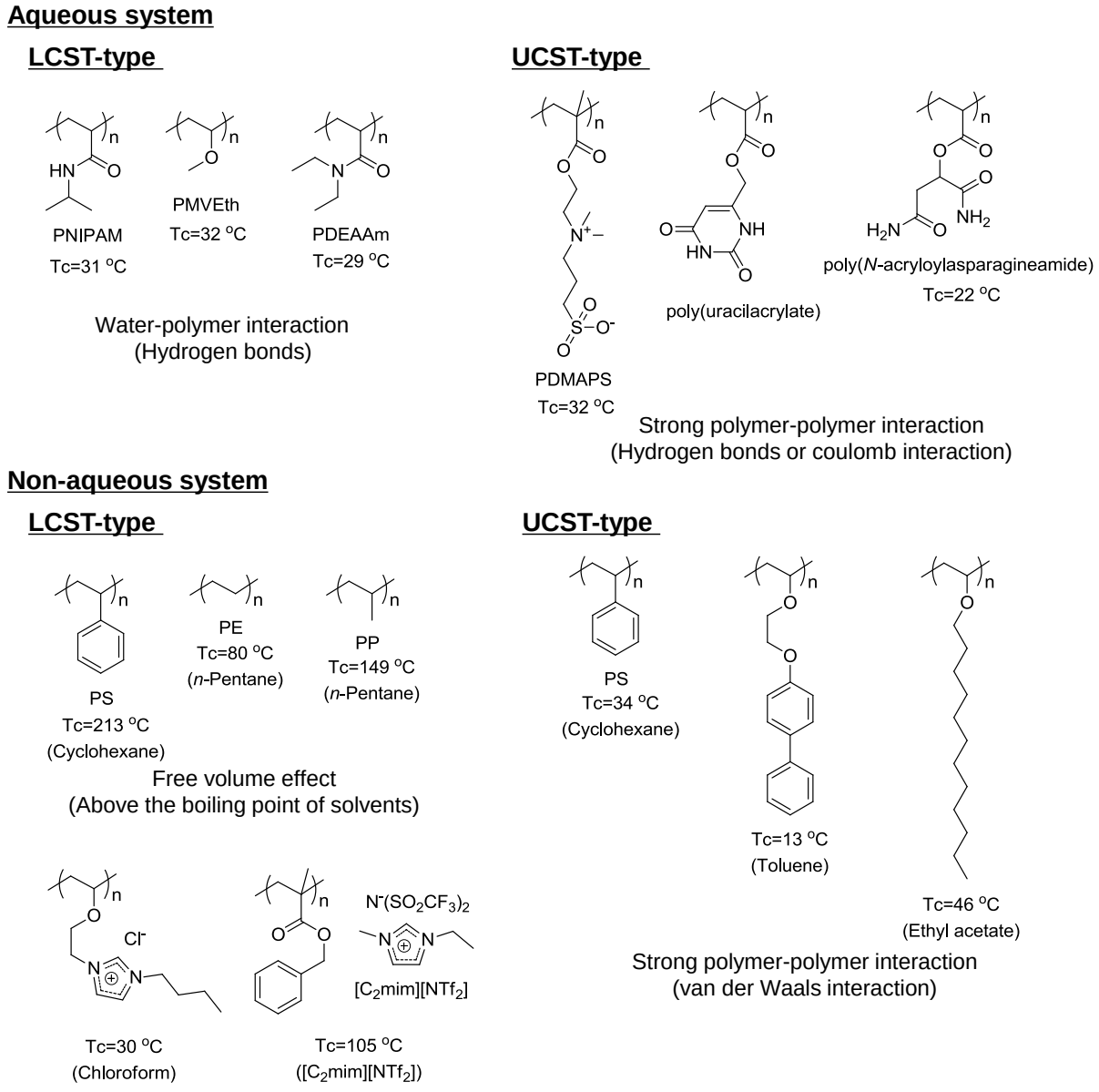


Figure 1_2. Typical thermo-sensitive homopolymers.

1.3.1. Thermo-Sensitive Behavior in Aqueous Systems

With regard to the aqueous systems, LCST-type thermo-sensitive polymers and UCST-type thermo-sensitive polymers have different structural feature and general molecular design, respectively. For example, non-ionic amphiphilic polymers such as poly(*N*-isopropylacrylamide) (PNIPAM), poly(methylvinylether) (PMVEth) and poly(*N*,*N*-diethylacrylamide) (PDEAAm) are well-known as LCST-type thermo-sensitive polymer in aqueous system.[8] On the other hands, UCST-type thermo-sensitive polymers have strong polymer-polymer interaction consisting hydrogen bond or Coulomb interaction in many cases as shown in Figure 1_2.[9]

$$\Delta G_m = \Delta H_m - T \cdot \Delta S_m \qquad \text{(equation 1\_2)}$$

Whether UCST or LCST-type phase behavior occur depends on the free enthalpy of mixing which comprises enthalpic and entropic conditions. Instead equation 1_1, for more simplified qualitative discussion of thermo-sensitiveness, a polymer dissolves in a solvent when the Gibbs free energy of mixing is negative (equation 1_2). Although in equation 1_2 shortcomings are the neglect of temperature and concentration dependence of the enthalpic and entropic terms, influence on thermo-sensitive behavior of chemical structures can qualitatively be estimated. LCST-type phase behavior in water can occur, when entropic contribution to Gibbs free energy of mixing overwhelms enthalpy of amphiphilic polymer (equation 1_2). The hydrophilic part in the amphiphilic polymer is able to interact strongly with water molecules and increase solubility in water. The hydrophobic part organizes the surrounding water molecules and then contributes negative entropy change of mixing, and hydrophobic attraction among them functions in order to minimize the entropic loss of the system. The negative total entropy change upon heating controls the system over the enthalpy of the hydrogen bonding, and the change in the Gibbs free energy of the mixing becomes positive, causing contraction of the polymer chain and, eventually, phase transition. Therefore, balance between the hydrophilic part as a solubilizing group and hydrophobic part as an aggregative group is important to LCST-type phase behaviors in water and then a change of the balance upon heating caused the phase separation by reducing amount of binding water molecules around the polymer as shown in Figure 1_3.

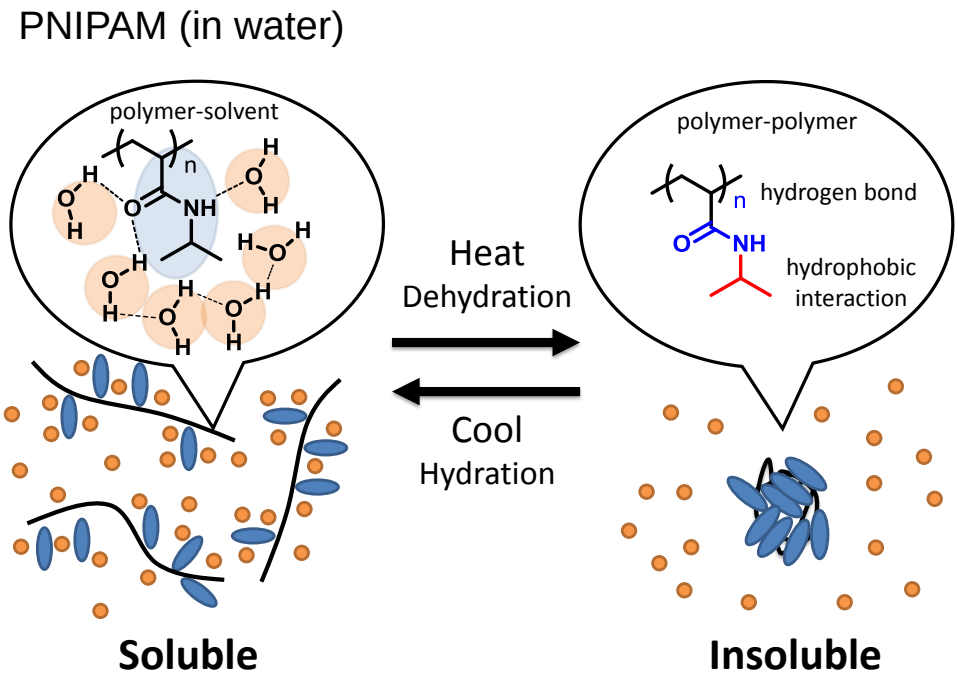


Figure 1_3. LCST behavior in aqueous system.

According to equation 1_2, the polymers with the UCST-type phase behavior should have positive ΔH_m and ΔS_m values. This suggests that the strong polymer-polymer and solvent-solvent interactions compared to polymer-solvent interactions are required for the positive ΔH_m. The hydrophobic part, which induces large negative entropic change by mixing, is less dominant on UCST-type polymers for a positive ΔS_m. Therefore, UCST-type polymers generally have hydrophilic and strong hydrogen bonding functional groups such as carboxylic acid[10], ureido[11], and uracil[12], or Coulomb interactions groups such as zwitterion.[13] As above, molecular designs of thermo-sensitive behavior in aqueous systems are very clear.

1.3.2. Thermo-Sensitive Behavior in Non-Aqueous Systems

In non-aqueous solvents, especially in non-polar solvents, UCST-type thermo-sensitive behaviors of organic polymers are relatively common. For example, it is shown using systems consisting of non-polar solvents such as cyclohexane and toluene, and non-polar polymers or polymer having crystalline or liquid crystalline moiety (Figure 1_2).[14] A relatively strong polymer-polymer interaction compared to polymer-solvent interaction is important to UCST-type phase behavior as well as in aqueous system, because breaking the interaction among polymer upon heating leads to an increase entropy of mixing and then changes the solubility of the polymer. On the other hands, generally, the combinatorial entropy of mixing is much smaller for polymers than for low molar mass compound (equation 1_1). Therefore, even little interaction can cause miscibility gaps. In

other words, it is difficult that utilizing extremely strong polymer-polymer interaction, such as electrostatic interaction and multiple hydrogen bonds, for UCST-type phase behavior of a polymer in non-polar solvents.

Although UCST-type thermo-sensitive polymer have been reported relatively, LCST-type thermo-sensitiveness is hardly observed under ambient conditions, because there are few polymer-solvent interactions in non-polar solvent which induce negative entropy change (ΔS_m) by ordered architecture (equation 1_2). Therefore LCST-type phase behaviors of polymers in non-polar solvent are regulated to a certain conditions. For example, under unusual conditions such as a high-pressure system in a sealed cell at above boiling points of the solvents, LCST-type phase behaviors have been widely reported.[15] This systems are understood based on a dissimilarity in free volume between the dense polymer solution and the expanded solvent so-called "free volume effect" (Figure 1_4). Mixing at above the boiling point of the solvents is like the condensation of a gas (solvent) into a dense medium (polymer). Associated with this effect there is an exothermic heat effect and a negative contribution to ΔS_m. Also, thermo-sensitive systems using ionic liquid as solvent and LCST-type phase behaviors of the polymer having ionic liquid moieties in organic solvents are reported as a few report.[16] In these cases, unique interactions between the ionic liquid and the polymer or the organic solvents and the ionic group of the polymer play a key role in the LCST-type phase behavior. Therefore the LCST-type phase behaviors of those aren't versatile, if at all.

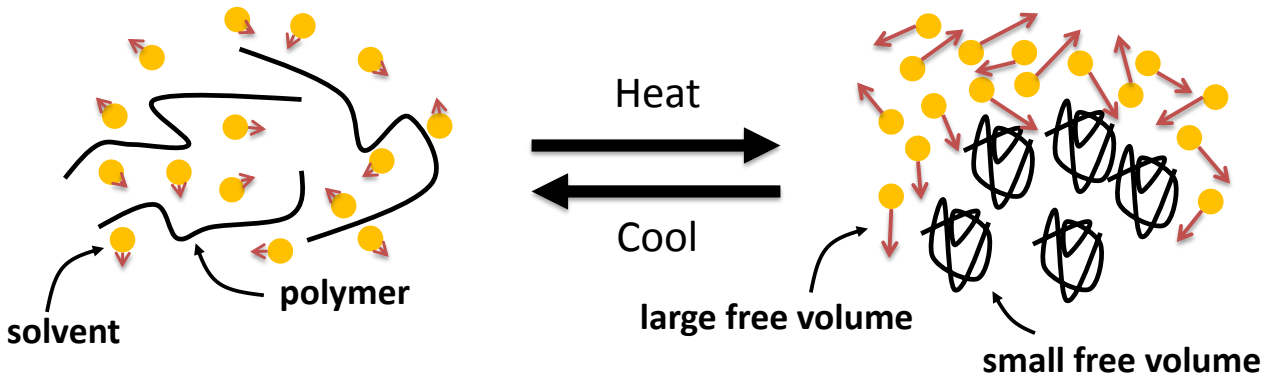


Figure 1_4. LCST behavior in organic solvent system by free volume effect.

1.4. Purpose for the Thesis

As discussed the previous section, in non-polar solvents, developing a thermo-sensitive polymer has LCST-type phase behavior at ambient condition is difficult and rational molecular design of the

polymer is demanded. This is attributed to the fact that there are few the ordering of solvent around a polymer, which produces the negative entropy changes, in non-polar solvent. Also, types of attractive groups which can be utilized for molecular design of UCST-type thermo-sensitive polymers are restricted in non-polar solvents, because non-covalent bond, such as hydrogen bond and electrostatic interaction, strongly act in them. Therefore, this thesis was aimed providing novel molecular design of thermo-sensitive system in non-polar solvent. Especially, the thesis was primarily intended to develop LCST-type thermo-sensitive system. In the next section, the author discussed controlling thermo-sensitive behavior in order to consider *de novo* design of LCST-type phase behavior with respect to supramolecular chemistry and controlling interaction between polymer and small molecules as the third component.

1.5. Control of LCST Behavior by Utilizing Non-Covalent Bond in Aqueous Systems

In aqueous system, several concepts have been developed to control thermo-sensitive behavior of polymers. In recent years, specific control of LCST-type phase behavior by using polymer-small molecules interaction was accomplished when the balance of the hydrophilicity and hydrophobicity of a polymer is changed by the interaction. Solubility of these systems mainly depends on association between the polymer and small molecules in addition to the interaction between the polymer and water molecules. Therefore, these concepts are effective for controlling of solubility of polymers in non-polar solvent in which relatively strong polymer-solvent interaction such as hydration hardly function.

In this section, the author describes researches of LCST-type phase behavior of polymers in aqueous system which are controlled and induced by utilizing non-covalent bond between polymer and small molecules. Their researches are categorized into two types. One is the researches using thermo-sensitive polymers such as PNIPAM, and the other is the researches using polymers which are insoluble in water. In the former cases, controlling LCST-type phase behavior have been widely reported and accomplished with relative ease. The LCST-type phase behaviors are attributed mainly to the dehydration of the polymer (Figure 1_5). In the latter case, LCST-type phase behaviors were induced by breaking non-covalent bond between the polymer and small molecules.

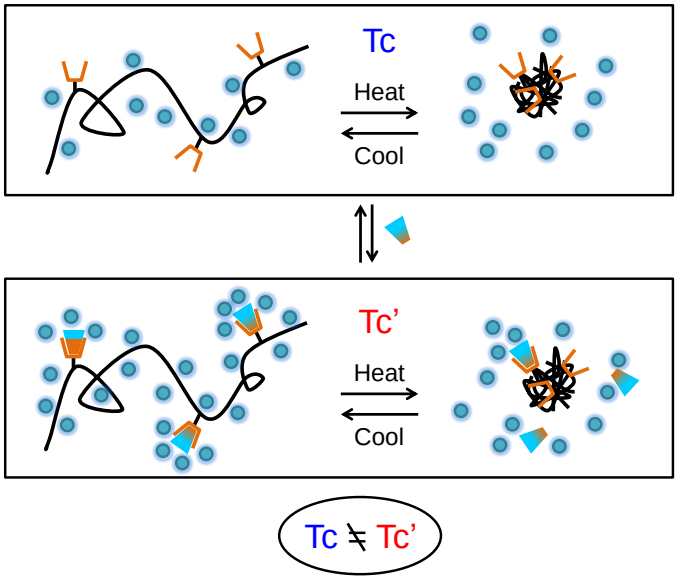


Figure 1_5. Concept of a LCST-type phase behavior controlling by host-guest interactions.

1.5.1. Control of LCST Behavior of Thermo-Sensitive Polymers

First, the author demonstrated simple examples utilizing LCST-type thermo-sensitive polymer with molecular recognition events 1) cyclodextrins and hydrophobic guests, 2) crown ethers and cations, 3) boronic acids and sugars. Subsequently, other interactions such as cucurbit[8]uril with hydrophobic guests are documented.

Cyclodextrins (CDs) are macrocyclic oligosaccharides consisting of some D-glucopyranose units (Figure 1_6). The CDs have been well-known as host molecules that increase the solubility of hydrophobic guest molecules in water by the formation of host-guest complexes.[17]

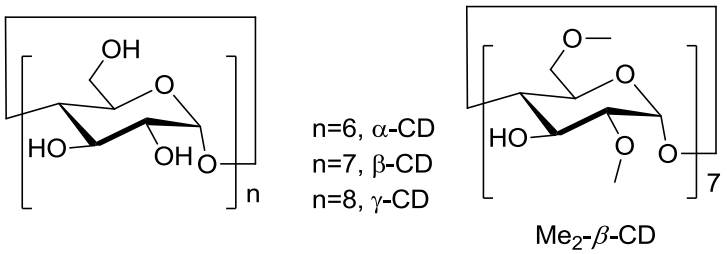


Figure 1_6. Structure of cyclodextrins (CDs)

Ritter *et al.* first reported the control of an LCST-type phase behavior of PNIPAM bearing adamantyl moieties **1.1** by the addition of Me_2-*β*-CD (Figure 1_7).[18] An aqueous solution of the polymer **1.1** showed an LCST of 17 °C. Through addition of Me_2-*β*-CDs to an aqueous solution of **1.1**, the LCST increased to around 40 °C. Moreover, potassium-1-adamantylcarboxylate **1.2** as a competitive external guest, which was expected to compete with the polymer-bounded adamantyl

groups, was added to an aqueous solution of **1.1** in the presence of Me_2-β-CD. As a result, the LCST decreased with increasing concentration of **1.2** (Figure 1_7). This results show that wrapping hydrophobic adamantyl groups with Me_2-β-CD increased the hydrophilicity of the polymer, and then increased the LCST. It is also reported that to control the LCST behavior, PNIPAM introduced hydrophobic moieties other than the adamantyl groups by addition of the CDs.[19] In all cases, the addition of CDs increased the LCST.

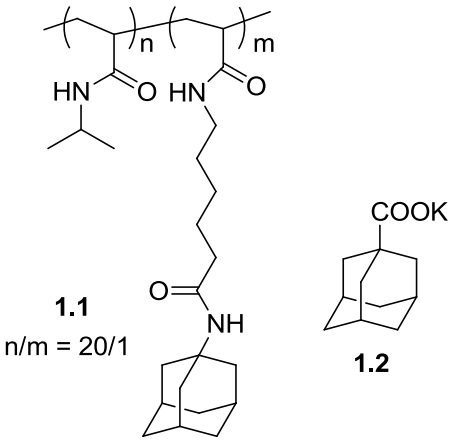


Figure 1_7. (a) Structure of PNIPAM with an adamantyl moiety and potassium-1-adamantylcarboxylate as a competitive guest.

Crown ethers are heterocycles consisting of an oxyethylene unit, and their sizes depends on the number of this repeating unit. They are well-known to selectively capture a cation into its cavity. Specific cation recognitions of the crown ethers have provided various applications such as metal cation sensors and phase transfer catalysts.[20]

In 1992, Irie *et al*. synthesized the ion-sensitive polymer poly(NIPAM-*co*-BCAm) **1.3** consisting of *N*-isopropylacrylamide units and benzo[18]-crown-6-ether units (BCAm) for the first time (Figure 1_8).[21] The polymer **1.3** showed a 31.5 ^{o}C LCST in an aqueous solution. The LCST value increased with the increasing concentration of potassium chloride. Yamaguchi *et al.* carried out a further detailed study on the correlation between the ion recognition and the LCST of PNIPAM bearing crown ethers.[22] They focused on the quantity of the complex of the crown ether receptor and ions in order to quantify the influence of the addition of ions. They used KCl, $SrCl_2$ and $BaCl_2$ as additives and PNIPAM bearing benzo[18]-crown-6-ether **1.3**. The complex formation constant (*K*) between **1.3** and the ions was evaluated using the ion mobility of the solution. Calculated from the added ion concentration and *K*, they estimated the degrees of complexation as the ratios of the quantity of benzo[18]-crown-6-ether units that form complexes in the presence of metal cations to the total quantity of the benzo[18]-crown-6-ether units. As a result, the change in

the LCST depended on the degrees of complexation, and not on the ion species. It is indicated that the hydrophilicity and LCST-type thermo-sensitivity of the polymer were precisely controlled by the addition the ion species.

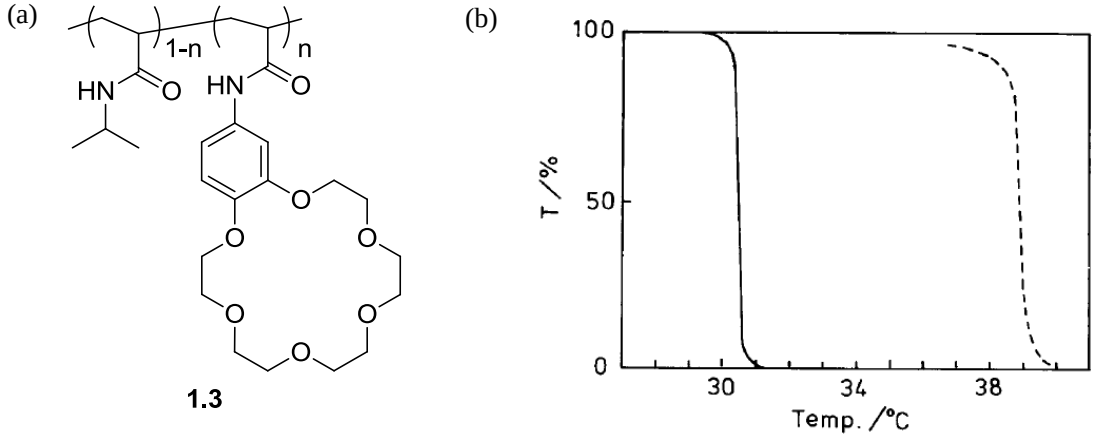


Figure 1_8. (a) PNIPAM copolymer with BCAm **1.3**. (b) Transmittance curves of **1.3** in water in the absence (solid line) and presence (dashed line) of 1.05 x 10^{-1} M potassium chloride.

The characteristic chemical nature of boronic acids is the formation of reversible covalent complexes with 1,2- or 1,3-diols such as ethylene glycol, sugars and polysaccharides(Figure 1_9). The interaction between a boronic acid and diols has been widely applied to the development of a sugar sensor, insulin delivery systems, lipase inhibitors and human immunodeficiency virus (HIV) inhibitors.[23]

In 1994, Kataoka *et al*. demonstrated the thermo-sensitive behavior of a copolymer **1.4** of *N*,*N*-dimethylacrylamide containing 15 mol% of 3-(acrylamide)phenylboronic acid with glucose (Figure 1_10).[24] They controlled the LCST by changing the concentration of glucose. In the absence of glucose, **1.4** had an LCST around 27 ^{o}C in HEPES-buffered saline (pH 7.4). In the presence of glucose, an increase in the LCST was observed and with increasing glucose concentration. Based on the pK_a of the boronic acid in the presence of glucose, they estimated the ratio of borate anions, i.e., degrees of complexation, among a hydroxylated boronic acid, the complex of the glucose and boronic acid. This provided a good correlation between the LCST of **1.4** and the degree of complexation. These results indicated that the addition of glucose increases the pK_a of boronic acids to yield the anion forms, which increased the hydrophilicity of the polymer and generated the charge for the increase in the solubility.

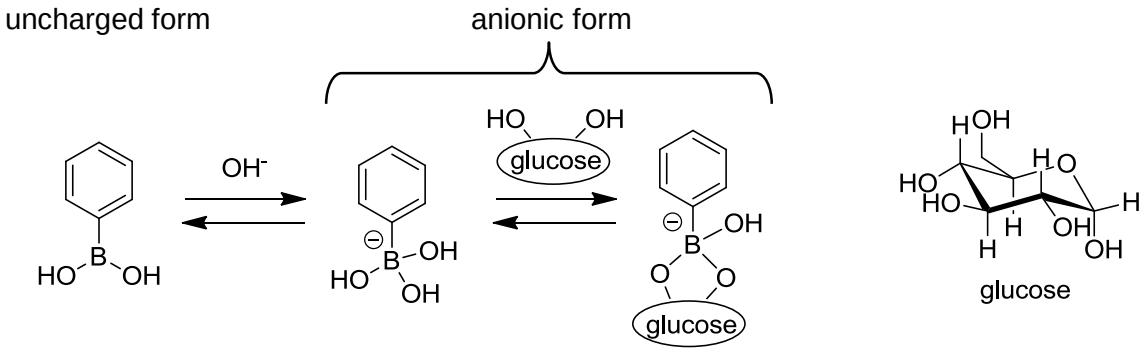


Figure 1_9. Equilibria of phenylboronic acid in aqueous solution in the presence of glucose.

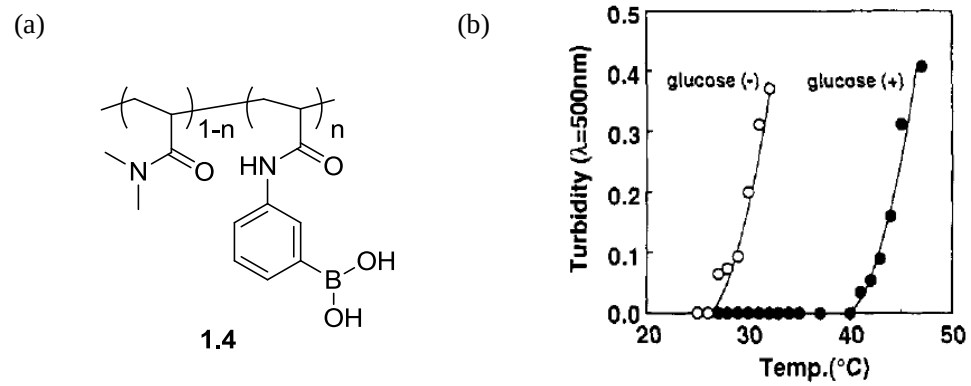


Figure 1_10. (a) Copolymer **1.4** of *N*,*N*-dimethylacrylamide containing the phenylboronic acid moiety. (b) Turbidity of **1.4** in HEPES-buffered physiological salin (pH 7.4): (○) without glucose, (●) with glucose (16.7 gL^{-1}).

Although interactions controlling the LCST of a thermo-sensitive polymer involve the three above systems, several other examples with different interactions in combination with LCST polymers have recently been reported. Scherman *et al.* showed a thermo-sensitive system containing the PNIPAM end functionalized with a dibenzofuran moiety **1.5**, cucurbit[8]uril(CB[8]) and methylviologen(M_2V) (Figure 1_11).[25] Indeed, CB[8] has been known to form a variety of strong, stable ternary complexes consisting of a complementary pair of an electron-deficient aromatic compound, such as M_2V, and an electron-rich aromatic compound, such as dibenzofuran. The LCST of the polymer lower than that of the typical PNIPAM due to the hydrophobic nature of a dibenzofuran end-functionalized. However, the addition of CB[8] and M_2V increased the hydrophilicity of the polymer due to covering the dibenzofuran and increasing the LCST. Also, pillararenes are known as a host incorporating hydrophobic guest in water. Ogoshi *et al.* demonstrated that LCST behavior of pillar[5]arenes **1.6** modified with oligoethylene oxide groups and LCST control by the addition of viologen derivatives(Figure 1_11).[26]

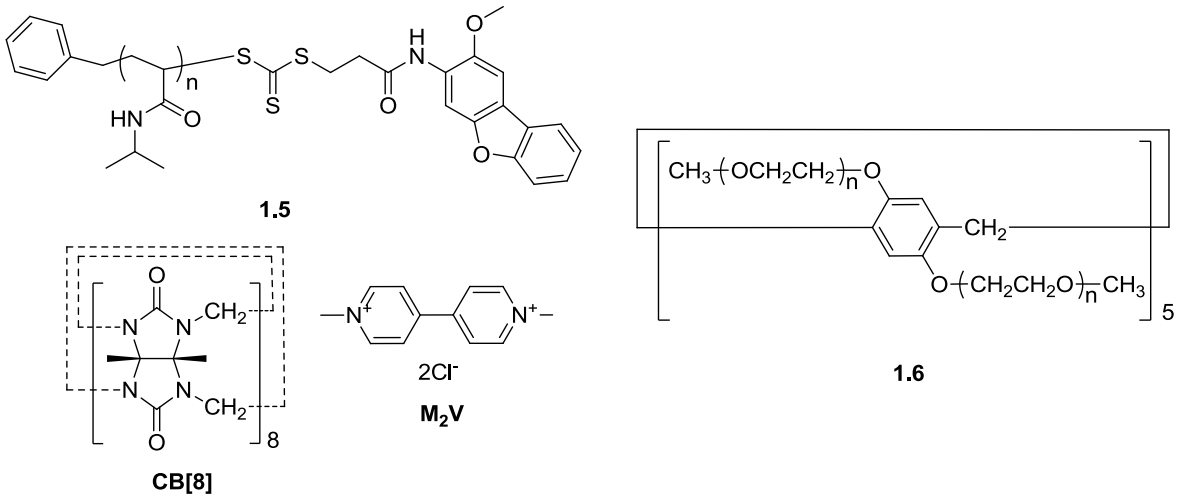


Figure 1_11. LCST systems using host-guest complexation of cucurbituril or pillararene.

In the above-mentioned cases, the polymers have originally LCST-type thermo-sensitiveness, and the hydrophilicity of that was controlled by utilizing non-covalent bonds between the polymer and small molecules, resulting in the change of LCST. And it was revealed that the quantitative relationship between the LCST-type phase behavior and the association consisting of the polymer and small molecules. However, the LCST-type phase behaviors are attributed to the breaking hydrogen bond between the polymer and water. Therefore, these strategies can't be directly applied for LCST-type phase behavior in non-polar solvents, because the phase behaviors are hardly observed in ambient condition in them.

1.5.2. Inducement of LCST Behaviors of Insoluble Polymers

Whereas controlling the LCST of thermo-sensitive polymers has been extensively reported, the *de novo* design of LCST polymer systems from insoluble homopolymers in the presence of suitable guest molecules has recently attracted considerable interest with respect to the supramolecular chemistry between them. Ritter *et al*. reported that the polymer bearing the bulky hydrophobic such as bromoisopropyl moieties showed an LCST behavior in the presence of randomly methylated *β*-cyclodextrin (RM-*β*-CD) in water for the first time. [27] The polymer was insoluble in water without any suitable guest molecules due to attractive interactions through the strong hydrophobic interaction among these hydrophobic groups. However the hydrophobic groups in the polymer chain were wrapped by the added cyclodextrin, and then the polymer-CD supramolecular complexes became water-soluble. Moreover, the dissociation of supramolecular complexes at an elevated

temperature triggered a drastic change in the solubility of the polymers resulting in the LCST-type phase behavior (Figure 1_12). To prove the postulated dissociation of the complex at temperatures higher than the clouding point, the total amount of RM-β-CD in solution was determined by ^{1}H NMR measurements after filtration of the precipitated polymer. As a result, the filtered polymer was nearly free of CD. It clearly showed that changing equilibrium between association and dissociation with temperature play a key role in the LCST-type phase behavior.

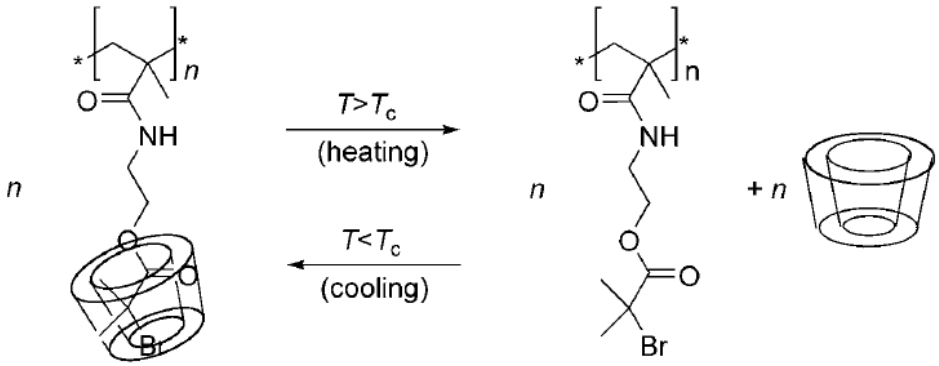


Figure 1_12. LCST behavior by temperature-dependent reversible unthreading of CD from the bulky side group during the heating procedure.

Also, the LCST-type phase behavior of the insoluble polymer, which having adamantyl group as a hydrophobic group, have been reported by Ritter and co-workers (Figure 1_13). [28] Likewise, the polymer changed to soluble in water by addition of RM-β-CD, because hydrophilicity of the polymer increased to cover adamantyl group by RM-β-CD. And dissociation of the complex consisting of adamantyl group and RM-β-CD induced aggregation of the polymer upon heating, resulting in the LCST-type phase behavior. Moreover, LCST increased with increasing concentration of the complex, because dissociation processes in highly concentrated solutions are higher in energy (Figure 1_13b).

These two researches indicated that potential to be able to induce LCST behavior of an insoluble polymer in non-polar solvent utilizing formation of a complex between the polymer and the small molecule without an interaction between polymer and solvent. However, such inducements of LCST-type phase behavior were only accomplished in aqueous system.

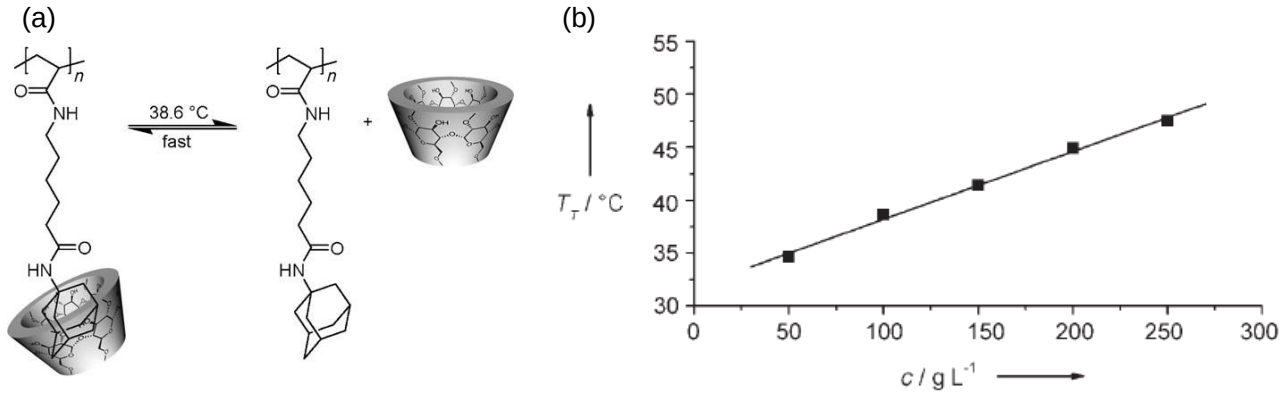


Figure 1_13. (a) LCST-type phase behavior of the polymer having adamantyl groups. (b) Cloud points plotted against the concentration of the polymer-CD complex.

1.5.3. Summary

In this section, the author demonstrated the control of the thermo-sensitivity of the LCST polymer by incorporation of molecular recognition sites in aqueous systems. In all cases, when the complexation of the recognition sites in the polymer chains with small molecules or ions increase the solubility of the polymers, the LCST moves to a higher temperature. Increasing the concentration of the small molecules increases the phase transition temperature due to enhancement of the solubility by complexation. Moreover, as shown last case (section1.5.3), the LCST systems of the insoluble polymer in water have already accomplished applying similar concept. In either case, the solubility of the polymer was dominated by association between the polymer and small molecules. In order to induced LCST-type phase behavior in non-polar solvent, these concepts could generalize down to a ternary system, which consists of a polymer, small molecule, and solvent, as shown Figure 1_14. In this system, the polymer have attractive group and is insoluble in solvent, and the small molecule have high solubility in solvent and can interact with the polymer by non-covalent bond. However, in non-polar system, a LCST-type phase behavior of such ternary system definitely designed have been not accomplished, although various molecular recognition and supramolecular system for non-covalent bonds have been reported. Therefore, the author employed the ternary system to design LCST system in non-polar solvent.

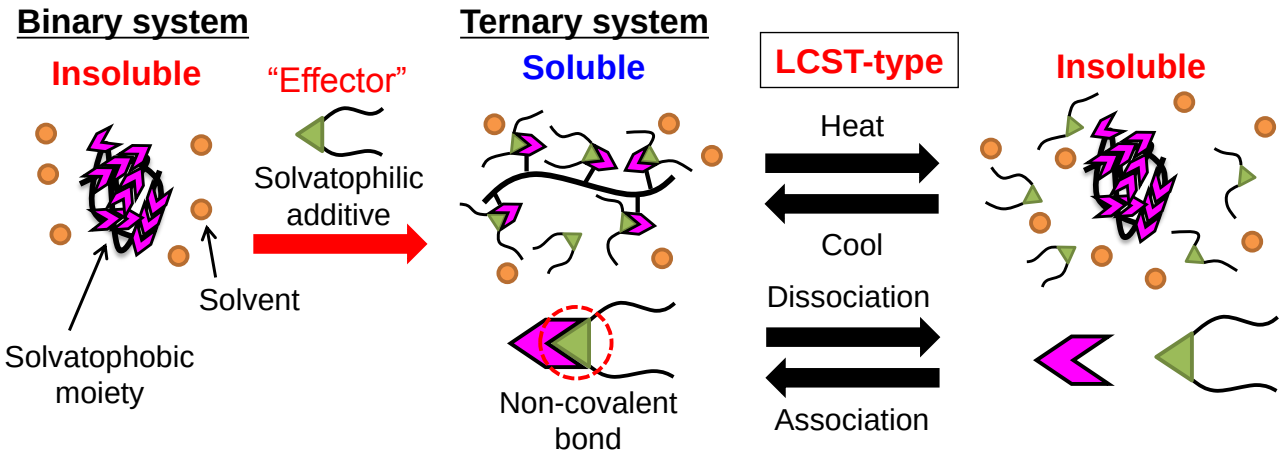


Figure 1_14. Concept for designing LCST type thermo-sensitive behavior by using host-guest interaction.

1.6. Survey of This Thesis

As pointed in the previous sections, designing and controlling LCST behavior in non-polar solvent at ambient condition are difficult and have been hardly demonstrated. Therefore, this thesis was aimed providing novel molecular design of thermo-sensitive system in non-polar solvent. Especially, the main issue of this thesis is to develop LCST-type thermo-sensitive system in non-polar solvent exploiting ternary system.

This thesis is composed of 5 chapters in total including general introduction and concluding remarks.

In Chapter 1, the purpose and the composition of this thesis are described from the background of thermo-sensitive polymer system using non-covalent bonds between the polymer and small molecules.

Chapter 2 demonstrates LCST-type phase behavior of polymer having pyrene units in the organic solvents such as 1,2-dichloroethane and toluene by adding some acceptor molecules. And the author clearly showed a relationship between thermo-sensitivity and charge transfer interaction by evaluating association degrees. Moreover cononsolvency of quaternary system was accomplished adding the competitive donors.

Chapter 3 demonstrates thermo-responsive behavior and control of the phase transition temperatures

of urea polymers by adding the hydrogen bonding guest molecules as additives in 1,2-dichloroethane. For example, UCST-type phase separation was caused by addition of *N,N'*-butyloctylurea and LCST-type phase separation was caused by addition of 1-octanol. Moreover UCST-type and LCST-type phase separation at ambient temperature was induced in quaternary system by addition of both 1-octanol and *N,N'*-butyloctylurea.

Chapter 4 describes the preparation of lipophilic polyelectrolytes bearing urea derivatives as hydrogen-bonding groups. And their thermal behaviors were investigated in the organic solvents. For example, in 1,2-dichloroethane upper critical solution temperature (UCST)-type phase separation was observed. Imbalance between electrostatic repulsion among the lipophilic ions and the attractive interaction among the urea groups resulted in the phase separation induced by heating or cooling.

In Chapter 5, the knowledge revealed in this thesis, the signification, and prospect for the future are mentioned.

1.7. Reference

1) Bajpai, A. K.; Shukla, S. K.; Bhanu, S.; Kankane, S. *Prog. Polym. Sci.* **2008**, *33*, 1088-1118. Oh, J. K.; Drumright, R.; Siegwart, D. J.; Matyjaszewski, K. *Prog. Polym. Sci.* **2008**, *33*, 448-477.

2) Jeong, J. H.; Kim, S. W.; Park, T. G. *Prog. Polym. Sci.* **2007**, *32*, 1239-1274.

3) Kikuchi, A.; Okano, T. *Prog. Polym. Sci.* **2002**, *27*, 1165-1193. Kanazawa, H.; Okano, T. *J. Chromatogr. A* **2011**, *1218*, 8738-8747.

4) Lee, H.-I.; Pietrasik, J.; Sheiko, S. S.; Matyjaszewski, K. *Prog. Polym. Sci.* **2010**, *35*, 24-44.

5) Brun-Graeppi, A. K.; Richard, C.; Bessodes, M.; Scherman, D.; Merten, O. W. *Prog. Polym. Sci.* **2010**, *35*, 1311-1324.

6) Koningsveld, R.; Stockmayer, W. H.; Nies, E. *Polymer Phase Diagrams*, Oxford University Press, Oxford, **2001**.

7) a) Staverman, A. J.; van Santen, J. H. *Recl. Trav. Chim. Pays-Bas* **1941**, *60*, 76. b) Staverman, A. J. *Recl. Trav. Chim. Pays-Bas* **1941**, *60*, 640. c) Huggins, M. L. *J. Chem. Phys.* **1941**, *9*, 440. d) Huggins, M. L. *Ann. N. Y. Acad. Sci.* **1942**, *43*, 1. e) Flory, P. J. *J. Chem. Phys.* **1941**, *9*, 660. f) Flory, P. J. *J. Chem. Phys.* **1942**, *10*, 51.

8) Aseyev, V.; Tenhu, H.; Winnik, F. M. *Adv. Polym. Sci.* **2011**, *242*, 29-89. Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163-249.

9) Seuring, J.; Agarwal, S. *Macromol. Rapid Commun.* **2012**, *33*, 1898-1920. Seuring, J.; Agarwal, S. *ACS Macro. Lett.* 2013, 2, 597-600.

10) Flory, P. J.; Osterheld, J. E. *J. Phys. Chem.* **1954**, *58*, 653-661.

11) Shimada, N.; Ino, H.; Maie, K.; Nakayama, M.; Kano, A.; Maruyama, A. *Biomacromolecules* **2011**, *12*, 3418-3422.

12) Aoki, T.; Nakamura, K.; Sanui, K.; Kikuchi, A.; Okano, T.; Sakurai, Y.; Ogata, N. *Polym. J.* **1999**, *31*, 1185-1188.

13) Schulz, D. N.; Peiffer, D. G.; Agarwal, P. K.; Larabee, J.; Kaladas, J. J.; Soni, L.; Handwerker, B.; Garner, R. T. *Polymer* **1986**, *27*, 1734-1742.

14) Seno, K.; Date, A.; Kanaoka, S.; Aoshima, S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 4392-4406.

15) a) Cowie, J. M. G.; Maconnachie, A.; Ranson, R. J. *Macromolecules* **1971**, *4*, 57-61. b) Burchard, W. *Polymer* **1969**, *10*, 467-475.

16) a) Seno, K.; Kanaoka, S.; Aoshima, S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5724-5733. b) Ueki, T.; Watanabe, M. *Langmuir* **2007**, *23*, 988-990.

17) a) Rekharsky, M. V.; Inoue, Y. *Chem. Rev*. **1998**, *98*, 1875-1917. b) Uemura, T.; Moro, T.; Komiyama, J.; Iijima, T. *Macromolecules* **1979**, *12*, 737-739. c) Harada, A.; Adachi, H.; Kawaguchi, Y.; Kamachi, M. *Macromolecules* **1997**, *30*, 5181-5182. d) Hashidzme, A.; Harada, A. *Polym. Chem.* **2011**, *2*, 2146-2154.
18) Ritter, H.; Sadowski, O.; Tepper, E. *Angew. Chem. Int. Ed*. **2003**, *42*, 3171-3173. Corrigendum: Ritter, H.; Sadowski, O.; Tepper, E. *Angew. Chem. Int. Ed*. **2005**, *44*, 6090-6099.
19) a) Gingter, S.; van Sloun, C.; Ritter, H. *Polym. Int.* **2012**, *61*, 1234-1237. b) Ogoshi, T.; Masuda, K.; Yamagishi, T.; Nakamoto, Y. *Macromolecules* **2009**, *42*, 8003-8005.
20) Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev*. **2004**, *104*, 2723-2750.
21) Irie, M.; Misumi, Y.; Tanaka, T. *Polymer* **1993**, *34*, 4531-4535.
22) Ito, T.; Sato, Y.; Yamaguchi, T.; Nakao, S. *Macromolecules* **2004**, *37*, 3407-3414.
23) a) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Nature* **1995**, *374*, 345-347. b) Ravaine, V.; Ancla, C.; Catargi, B. *J. Controlled Release* **2008**, *132*, 2-11. c) Cambre, J. N.; Sumerlin, B. S. *Polymer* **2011**, *52*, 4631-4643.
24) Kataoka, K.; Miyazaki, H.; Okano, T.; Sakurai, Y. *Macromolecules* **1994**, *27*, 1061-1062.
25) Rauwald, U.; Barrio, J. D.; Loh, X. J.; Scherman, O. A. *Chem. Commun*. **2011**, *47*, 6000-6002.
26) Ogoshi, T.; Shiga, R.; Yamagishi, T. *J. Am. Chem. Soc.* **2012**, *134*, 4577-4580.
27) Kretschmann, O.; Steffens, C.; Ritter, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 2708-2711.
28) Schmitz, S.; Ritter, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 5658-5661.

Chapter 2: Thermo-Sensitive Behavior of Donor Polymer Having Pyrene Units in the Presence of Acceptor Molecules

2.1. Introduction

Charge-transfer (CT) interaction is one of intermolecular attractive force between π-electron-rich (donor molecules) and π-electron-deficient species (acceptor molecules). The high specificity of CT interactions usually provides the alternative arrangement, and the resulting CT complex shows a characteristic absorption band in the visible region; this absorption band provides information on their association as supramolecular complexes.[1-4] Therefore, CT interaction is one of the most powerful tools the designing of supramolecular complexes, and used as fundamental materials such as organic crystalline materials with superconductivity or conductivity,[1] low-molecular-weight organic gelators,[2] preorganized building blocks for rotaxane,[3] and supramolecular polymers.[4]

In many cases, the attractive interaction in them is not so steady, and CT complexes can be collapsed readily by heating. The weak binding prompted the author to apply CT interaction for designing LCST-type thermo-sensitive polymer in the organic solvents, which show drastic solubility change of the polymer solution from miscibility to immiscibility with increasing temperature in water generally[5]. Moreover the prominent CT band in the UV/Vis absorption spectrum should provide a quantitative evaluation of the relationship between LCST behavior and the formation of supramolecular complexes. In this chapter, the author demonstrated LCST behavior using CT interaction as a non-covalent bond.

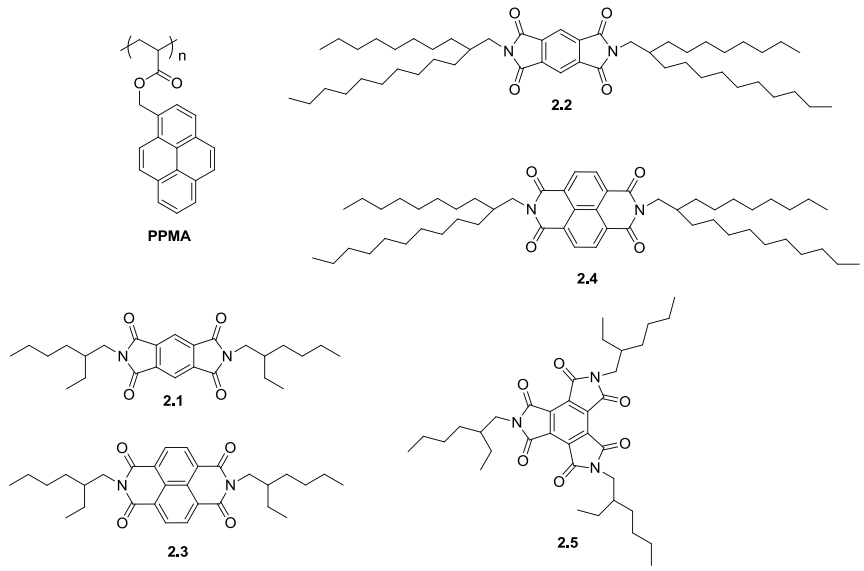


Figure 2_1. Structure of **PPMA** and acceptors **2.1**-**2.5**.

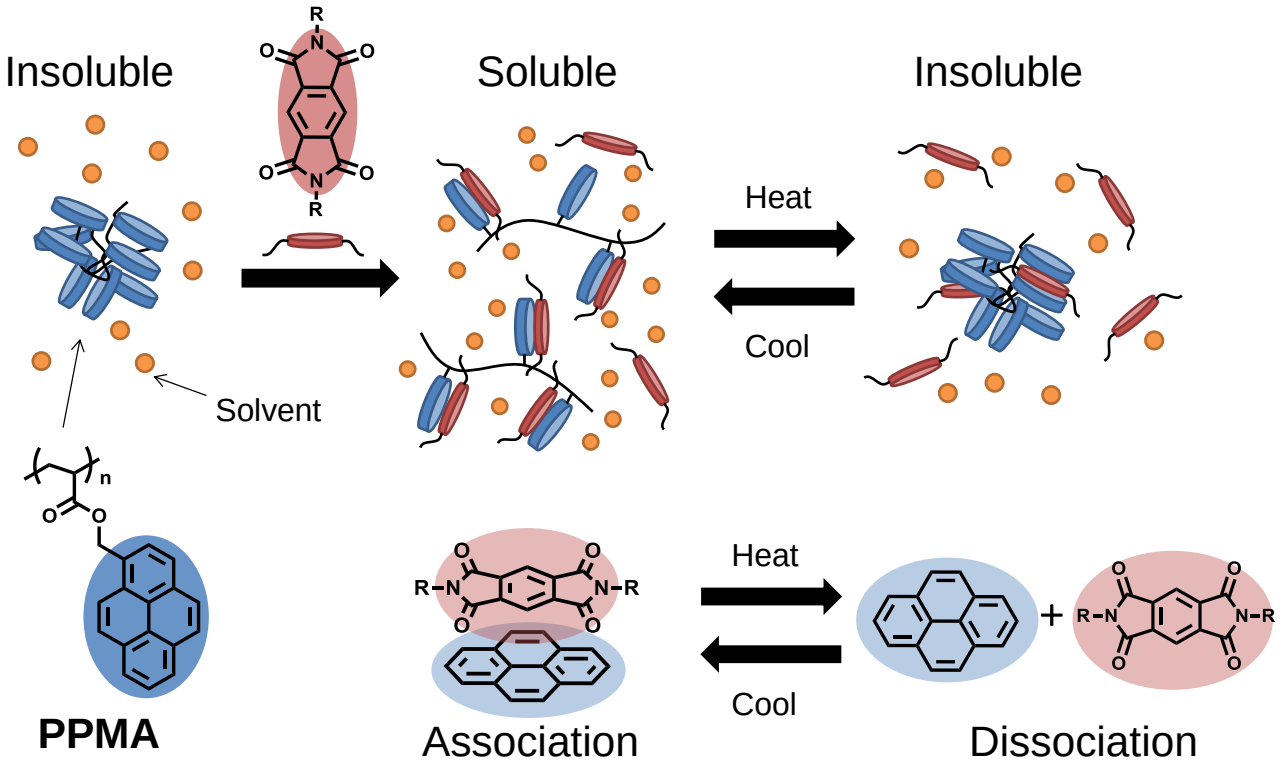


Figure 2_2. Concept of the LCST-type phase behavior of supramolecular complexes as caused by a CT interaction.

For designing LCST polymers, there are requirements for LCST behavior, using insoluble polymer: a high aggregation ability of the polymer without small molecules and an interaction that can be cleaved readily upon heating as discussed the chapter 1. This approach to the design of such a system rested on poly((1-pyrene)methyl acrylate) (**PPMA**), in which the pyrene units on the polymer side chain induce aggregation through a π-π interaction that results in reduced solubility of the polymer,[6] and the electron-accepting molecules **2.1**-**2.5** as small molecules to form CT complexes with **PPMA** (Figure 2_1). The long alkyl chains in **2.1**-**2.5** were expected to change the solubility of **PPMA** to organic solvents, and the relatively low binding constants between pyrene and the effectors were expected to give rise to the dissociation of CT complexes upon heating (Figure 2_2).

2.2. Results and Discussion

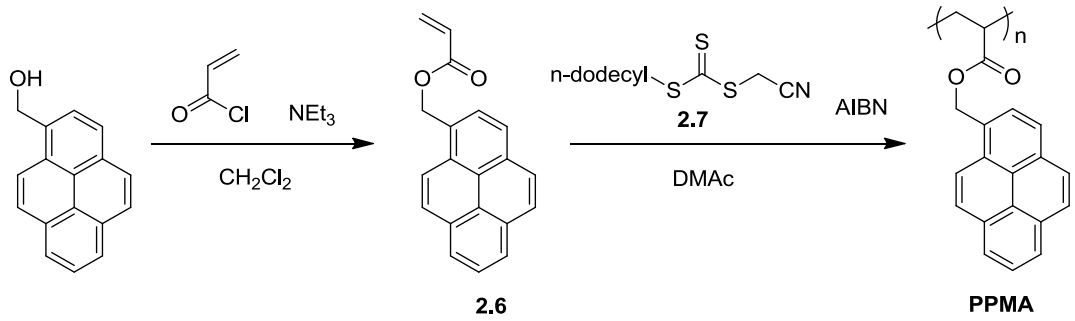
2.2.1. Synthesis of Acceptors and Polymerization and Characterization of PPMA

PPMA was prepared by the controlled radical polymerization of monomer **2.6**,[7] which was synthesized by a condensation reaction of acryloyl chloride with 1-pyrenemethanol (Scheme 2_1). The number-average and weight-average molecular weights of **PPMA** were determined to be

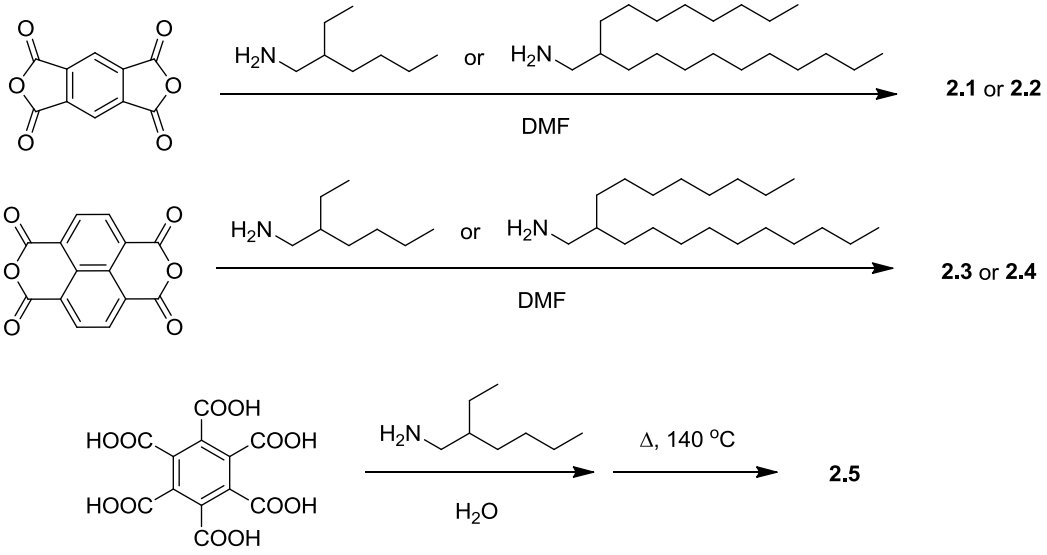
M_n=2.2 x 10^4 and M_w=4.4 x 10^4, respectively, by size-exclusion chromatography with polystyrene standards in chloroform. The acceptors **2.1**–**2.5** with long alkyl chains were synthesized by the corresponding dehydration–condensation reaction (Scheme 2_2), and the amine with a long alkyl chain was prepared from 1-bromo-2-octyldodecane by Gabriel reaction[8] (Scheme 2_3).

First, the solubility of **PPMA** (10 gL^{-1}) in various organic solvents at room temperature was investigated by direct observation using naked-eyes (Table 2_1). In some organic solvents, such as *N*,*N*-dimethylacetamide (DMAc), 1,1,2,2-tetrachloroethane, 1,2-dimethoxybenzene, and chloroform, **PPMA** showed high solubility. On the other hands, in the solvents, such as acetonitrile, acetone, ethyl acetate, 1,2-dichloroethane, toluene, and hexane, **PPMA** was practically insoluble as poor solvents, mainly because of the strong π–π interaction between the pyrene aromatic rings in the polymer chain. Thus, a small amount of the acceptor seemed to be necessary to solubilize **PPMA** by breaking of the π–π interaction in these media as the poor solvents.

Scheme 2_1. Polymerization of **PPMA**.



Scheme 2_2. Synthesis of acceptors **2.1**-**2.5**.



Scheme 2_3. Synthesis of amine with a long alkyl chain.

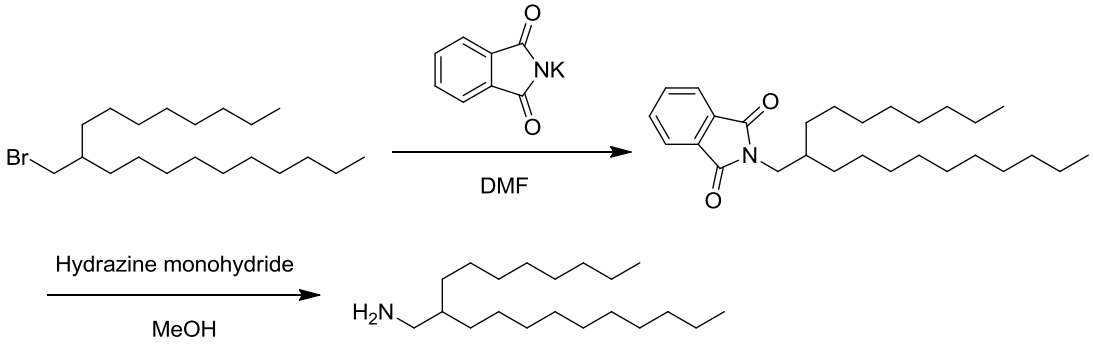


Table 2_1. Solubility test of **PPMA** in various organic solvents at room temperature (10 gL^{-1})

Solvent	Solubility
N,*N*-Dimethylacetamide	Soluble
Acetonitrile	Insoluble
Methanol	Insoluble
Acetone	Insoluble
1,1,2,2-Tetrachloroethane	Soluble
1,2-Dichloroethane	Insoluble
THF	Soluble
Ethyl acetate	Insoluble
Chloroform	Soluble
1,2-Dimethoxybenzene	Soluble
Toluene	Insoluble
Benzene	Insoluble

2.2.2. Solubility Property of PPMA in the Presence of Acceptors

As the poor solvent for **PPMA**, 1,2-dichloroethane was selected for the investigation of LCST behavior. Acceptor **2.1** was added to a suspension of **PPMA** in 1,2-dichloroethane at room temperature. Then, **PPMA** clearly dissolved at 0.14 M of **2.1** in 1,2-dichloroethane, and the white suspension became a clear yellow solution (Figure 2_3). The change in turbidity indicated that **PPMA** became soluble in 1,2-dichloroethane upon the addition of **2.1**. And the yellow color was attributed to the CT absorption band observed at 430 nm in the UV/Vis spectrum of **PPMA** in 1,2-dichloroethane in the presence of **2.1** (Figure 2_4). These results indicated that the formation of CT complexes between the acceptor **2.1** and the pyrene unit in **PPMA** caused the dissociation of stacked pyrene groups and the consequent dissolution of **PPMA** in 1,2-dichloroethane.

Figure 2_5a shows the change in the transmittance of **PPMA** (10 gL^{-1}, [pyrene unit in **PPMA**] =

0.035 M) in the presence of **2.1** (0.14 M) in 1,2-dichloroethane. A drastic change in transmittance upon heating (heating rate: 1 ^{o}C min^{-1}) was observed at 43 ^{o}C as a cloud point. The cloud point was determined as the temperature at which 90% transmittance was observed. Subsequent cooling induced recovering clearly, and **PPMA** dissolved completely again. Repeated heating-cooling cycles resulted in repeated changes in transmittance. The reversible LCST behavior was observed. Temperature dependence of the UV/Vis spectrum was measured below the temperature that provided clear solution. The absorption of the CT band decreased upon heating to 35 ^{o}C (Figure 2_4). These results indicated that the dissociation of CT complexes between **2.1** and **PPMA** at the evaluated temperatures led to decrease the solubility of **PPMA** and promoted aggregation, which resulted in precipitation.

In ethyl acetate and toluene as the poor solvents for **PPMA**, LCST-type phase behaviors also were induced by the addition of **2.1** (Figure 2_5b, c). The acceptor concentrations necessary to cause LCST behavior in ethyl acetate and toluene were larger than in 1,2-dichloroethane. Presumably it is because ethyl acetate and toluene have much poorer compatibility with **PPMA** compared to 1,2-dichloroethane.

Other acceptor molecules **2.2**-**2.5** were also investigated to induce LCST behavior of **PPMA** in 1,2-dichloroethane (Figure 2_6). Addition of these acceptors increased solubility of **PPMA**, and then reversible LCST behaviors were observed by temperature change successfully. On the basis of these findings, CT interactions should be able to function as efficient intermolecular interactions to trigger LCST behavior.

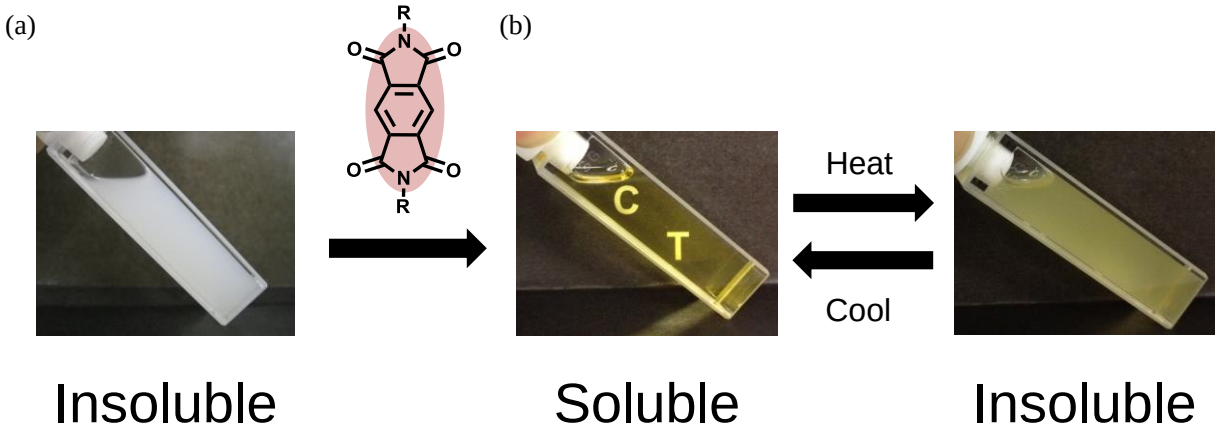


Figure 2_3. Images of **PPMA** in 1,2-dichloroethane solution (a) without acceptor **2.1** or (b) with acceptor **2.1**

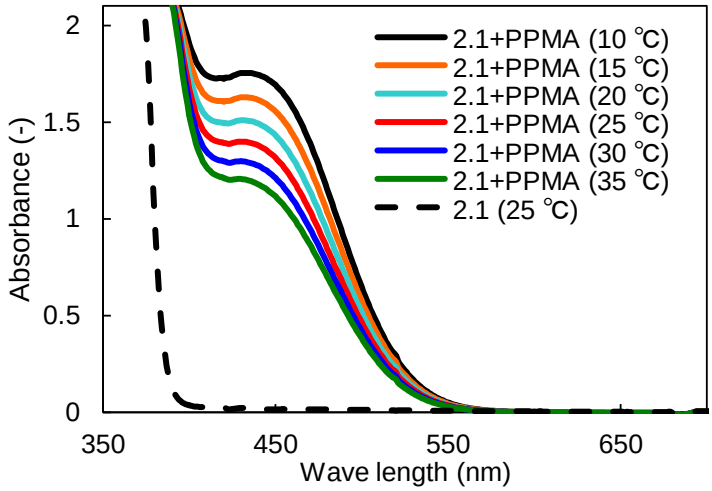


Figure 2_4. UV/Vis spectra of **2.1** in 1,2-dichloroethane with **PPMA** at various temperatures (solid lines) and without **PPMA** (dashed line). [**2.1**] = 0.14 M, [**PPMA**] = 10 gL^{-1} (0.035 M with respect the pyrene units in polymer)

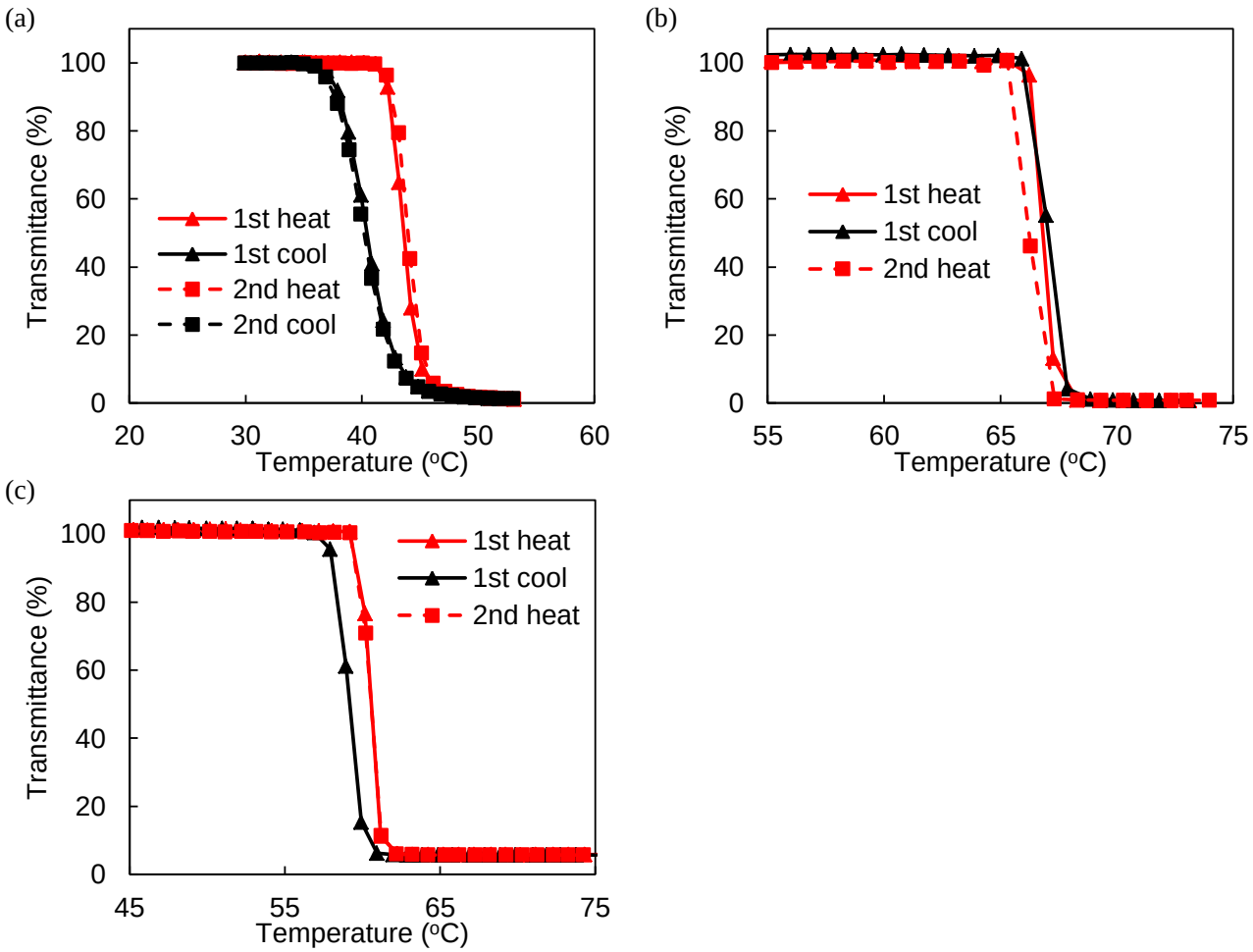


Figure 2_5. Transmittance (measured at 800 nm) as a function of temperature for **PPMA** (10 gL^{-1}) with **2.1** in (a) 1,2-dicroroethane ([**2.1**] = 0.14 M), (b) ethyl acetate ([**2.1**] = 0.80 M) and (c) toluene ([**2.1**] = 0.60 M), scan rate = 1 $^{o}C\ min^{-1}$.

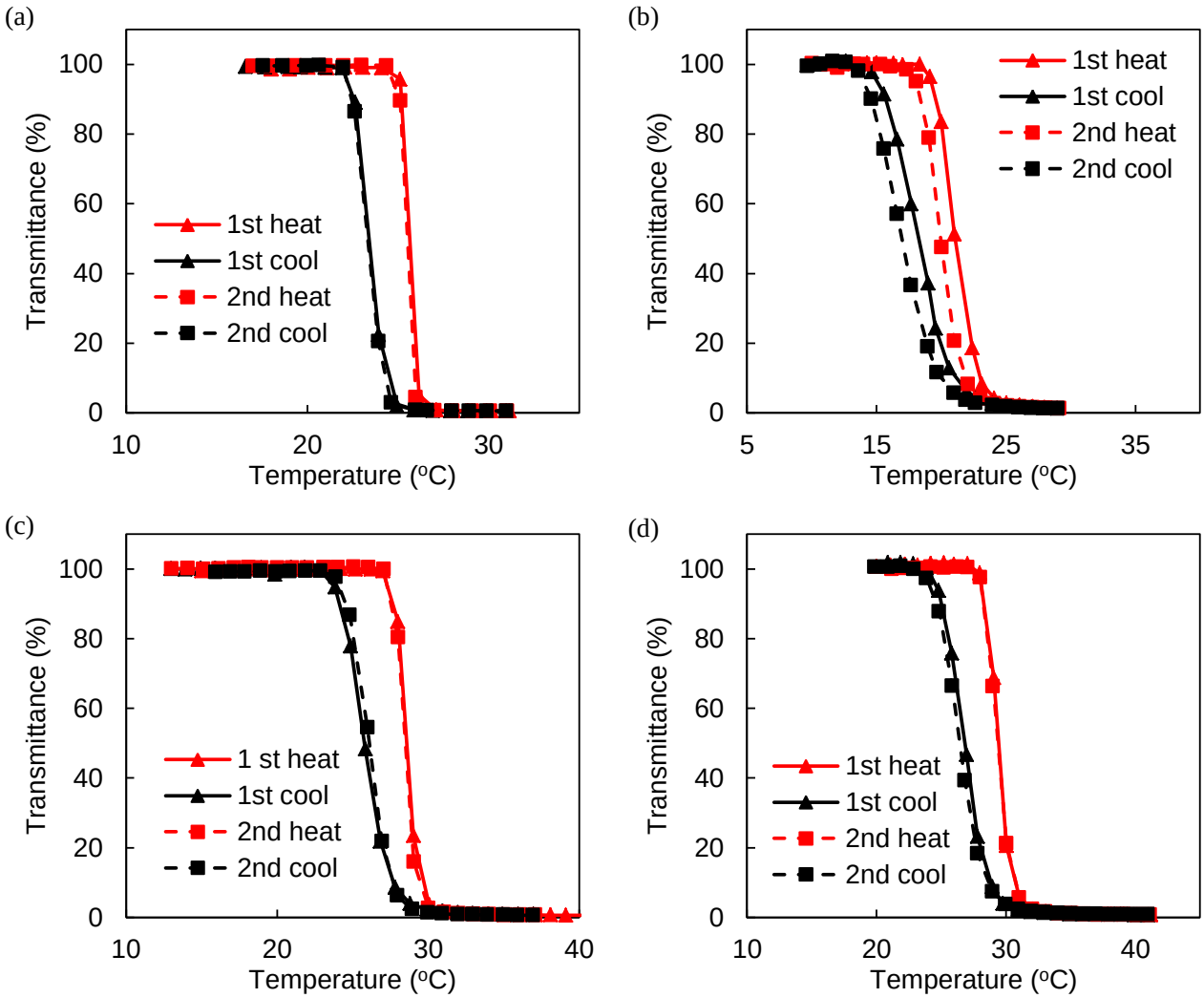


Figure 2_6. Transmittance as a function of temperature for **PPMA** with (a) **2.2**, (b) **2.3**, (c) **2.4** or (d) **2.5** in 1,2-dichloroethane. [**PPMA**] = 10 gL^{-1} (0.035 M pyrene units in the polymer), [**2.2**] = 0.16 M, [**2.3**] = 0.035 M, [**2.4**] = 0.032 M, [**2.5**] = 0.025 M, scan rate = 1 $^{o}C\ min^{-1}$.

2.2.3. Acceptor Concentration Dependence of LCST-type Phase Behavior

The dependence of the cloud point on the concentration of acceptors was investigated. The transmittance measurements of **PPMA** in 1,2-dichloroethane containing the acceptors in a variety of concentrations carried out at the constant concentration of **PPMA** (10 gL^{-1}). When the acceptor concentration increased, the cloud point gradually increased as plotted in Figure 2_7. It had a liner relationship between them. Solubility of **PPMA** increased with increasing acceptor concentration. Therefore, higher temperatures were required to break the CT complexes at high acceptor concentration. Furthermore, decrease in the cloud point was observed as the concentration of **PPMA** increased (Figure 2_8). These observations revealed that the equilibrium between the CT complex between the pyrene groups of **PPMA** and the acceptor and its dissociated state clearly

dominated the thermo-sensitivity and LCST behavior of the polymer.

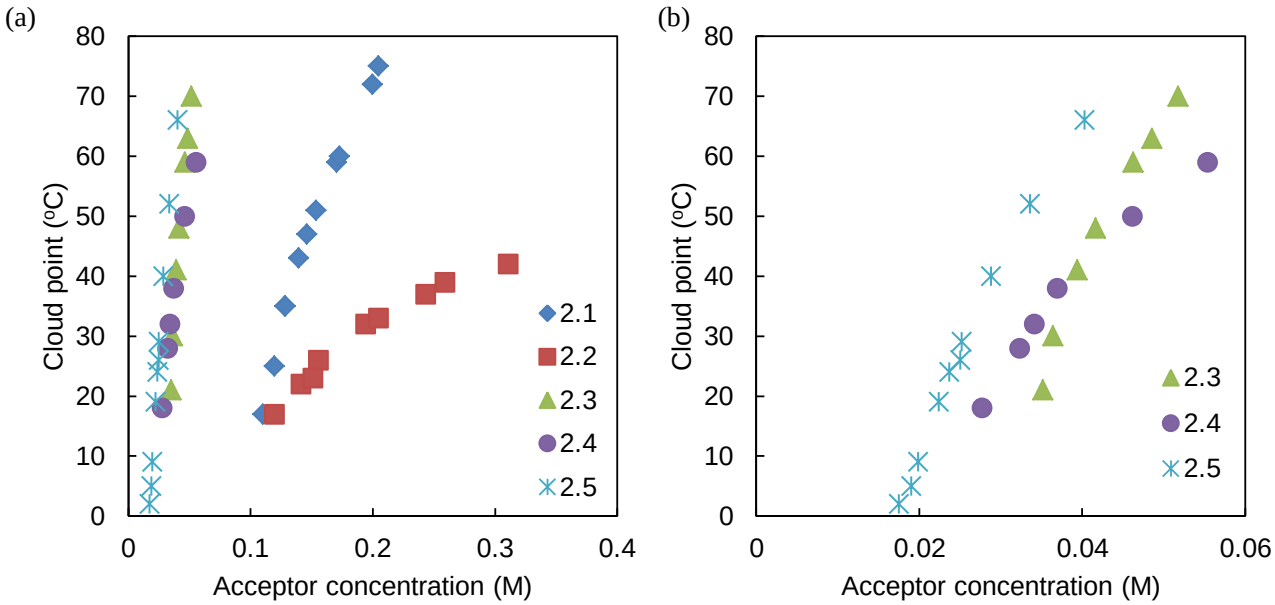


Figure 2_7. a) Dependence of the cloud point of **PPMA** in 1,2-dichloroethane on the concentration of the effector for effectors **2.1**-**2.5**. [**PPMA**] = 10 gL^{-1} (0.035 M with respect to the pyrene units in the polymer). b) Closeup of a).

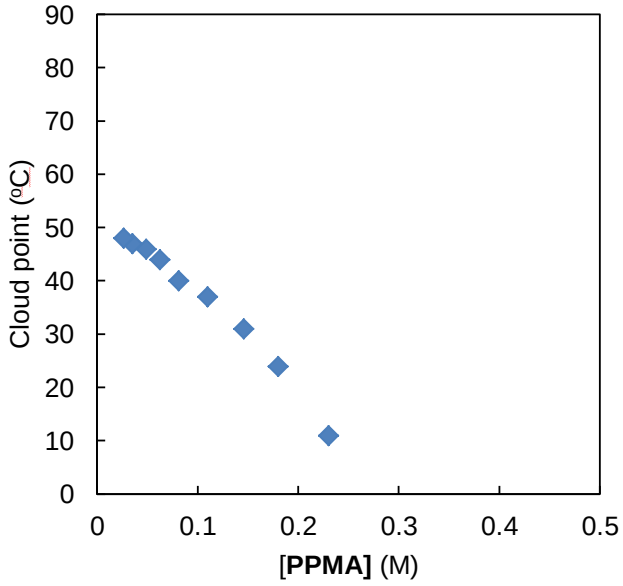


Figure 2_8. Cloud points plotted against the concentration of pyrene units in the **PPMA** in 1,2-dichloroethane in the presence of **2.5** ([**2.5**] = 0.030 M). [**PPMA**] = [the pyrene units in the polymer]

2.2.4. Association Constants and Association Degree between PPMA and Acceptor Molecules

To elucidate the relationship between the CT interaction and the thermo-sensitivity of **PPMA** in the presence of the acceptors, the association constants (K_a) between **PPMA** and acceptors **2.1**-**2.5** were investigated and the thermodynamic parameters for the association (ΔH_{CT} and ΔS_{CT}) were calculated. The association constants were determined according to Benesi-Hildebrand equation (equation 2_1) by the titration using UV/Vis spectrophotometry.[9] The thermodynamic parameters were calculated from the variation of the association constants with temperature by using van't Hoff equation (equation. 2_2).

Benesi-Hildebrand equation

$$\frac{[\mathrm{D}]_0 \cdot l}{d} = \frac{1}{K_a \cdot \varepsilon} \cdot \frac{1}{[\mathrm{A}]_0} + \frac{1}{\varepsilon} \qquad \text{(equation 2\_1)}$$

$[D]_0$: initial concentration of the donor, $[A]_0$: initial concentration of the acceptor, l: path length in cm of the optical cuvette, K_a: association constant, ε: molar absorbance coefficient of the complex formed, d: observed absorbance.

van't Hoff equation

$$\ln K_a = -\frac{\Delta \mathrm{H}}{\mathrm{R}} \cdot \frac{1}{\mathrm{T}} + \frac{\Delta \mathrm{S}}{\mathrm{R}} \qquad \text{(equation 2\_2)}$$

ΔH: formation enthalpy, ΔS: formation entropy, R: gas constant

The linearity of the Benesi-Hildebrand plots was observed in all cases as shown in Figure 2_14-2_18 in Experimental Section. It implies the formation of the CT complexes with a 1:1 donor-acceptor ratio. Table 2_2 shows evaluated association constants and thermodynamic parameters. All calculated association constants were relatively low (<10 M^{-1}) and they decreased with the elevation of temperature. And all the calculated ΔH_{CT} and ΔS_{CT} were negative. These results indicated that LCST-type phase behaviors of **PPMA** were mainly caused by reduction of the amount of CT complexes in the polymer chain. And the acceptors functions as a solubilizer to increase the solubility of **PPMA**.

Table 2_2. Evaluated association constants, molar absorbance coefficient, enthalpy and entropy of formed charge transfer complex in 1,2-dichloroethane.

Donor	Acceptor	Temperature [^{o}C]	K_a[a] [M^{-1}]	ε[a] [$cm^{-1}mol^{-1}L$]	-ΔS[b] [$JK^{-1}mol^{-1}$]	-ΔH[b] [$kJmol^{-1}$]
PPMA	**2.1**	15	0.96	450	56.7	16.2
		25	0.74	474		
		35	0.61	493		
		45	0.49	528		
		55	0.43	531		
PPMA	**2.2**	10	0.94	394	95.6	26.8
		15	0.73	439		
		20	0.60	479		
		25	0.50	519		
		30	0.45	532		
PPMA	**2.3**	25	4.23	465	62.1	22.0
		30	3.48	479		
		35	2.92	489		
		40	2.58	480		
		45	2.45	442		
PPMA	**2.4**	15	5.45	315	71.7	24.8
		25	3.99	285		
		35	2.82	287		
		45	2.02	295		
		55	1.59	293		
PPMA	**2.5**	15	6.42	407	67.7	24.0
		25	4.68	431		
		35	3.41	463		
		45	2.59	488		
		55	1.87	540		

[a] Association constants (K_a) were given by Benesi-Hildebrand method.

[b] Thermodynamic parameters were given by van't Hoff plot.

To obtain a deeper insight into the thermo-sensitiveness of **PPMA** with acceptors, the association degrees (α) that defined as $[D\cdot A]/[D]_0$ were evaluated, where $[D\cdot A]$ is concentration of the charge-transfer complex formed and $[D]_0$ is initial concentration of the pyrene units in the polymer (equation 2_3, 2_4). This parameter provided for the formation of CT complexes under the experimental conditions on the basis of the calculated thermodynamic parameters.

Figure 2_9 and Table 2_3 show the evaluated association degrees α. For example, under the conditions of a concentration of 0.119 M in **2.1** and 0.035 M (for pyrene unit) in **PPMA**, for which a cloud point of 25 °C was found, 8.1% of the pyrene units in the polymer chain were found to form a CT complex with **2.1**. In other words, **PPMA** in 1,2-dichloroethane became soluble through the formation of a CT complex involving **2.1** and 8.1% of the pyrene groups in **PPMA**. Similarly, the other acceptors **2.2-2.5** formed CT complexes around the cloud points with 6-12% of the pyrene moieties in the polymer chain. The utility of acceptors **2.1** and **2.2** which had low association constants, required larger acceptor concentration. Thus, these results clearly indicated existence of the critical association degree for LCST-type phase behavior (Table 2_3). The solubility of **PPMA** depended on the association degree of the pyrene groups in the polymer chain. The reversible thermo-sensitivity can be attributed to the relatively high temperature-dependence of association constant of the pyrene groups and acceptor molecules in the CT interaction. This study provides the first quantitative description of the relationship between thermo-sensitivity and the formation of a supramolecular complex; it had been assumed previously that the hydration number of poly(*N*-isopropylacrylamide) (PNIPAM) governed its thermo-sensitiveness.[10]

$$[\mathrm{D}\cdot\mathrm{A}] = \frac{\left\{[\mathrm{A}]_0 + [\mathrm{D}]_0 + \frac{1}{K_a} - \sqrt{([\mathrm{A}]_0 + [\mathrm{D}]_0 + \frac{1}{K_a})^2 - 4[\mathrm{A}]_0[\mathrm{D}]_0}\right\}}{2} \quad \text{(equation 2\_3)}$$

$$K_a = \mathrm{e}^{-\frac{\Delta \mathrm{H}}{\mathrm{RT}} + \frac{\Delta \mathrm{S}}{\mathrm{R}}} \quad \text{(equation 2\_4)}$$

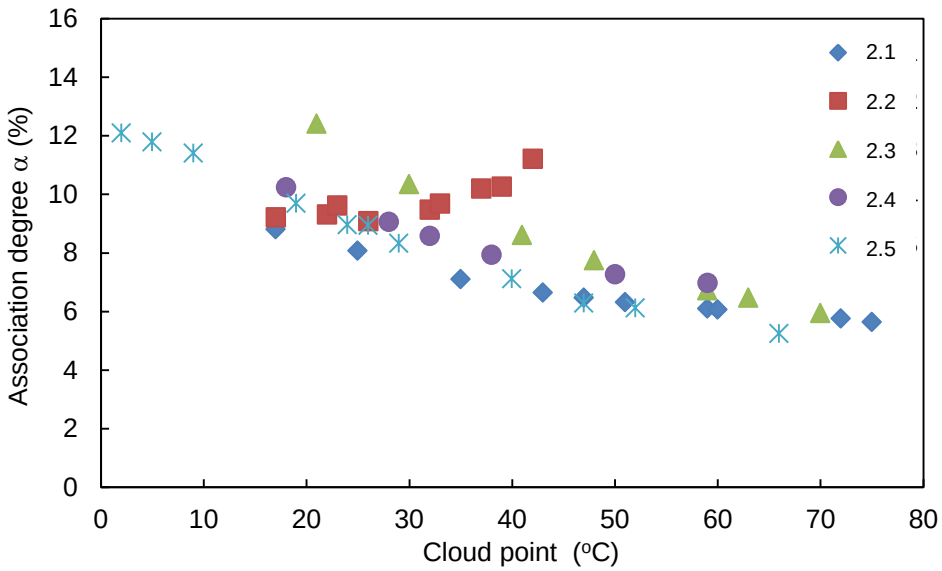


Figure 2_9. Association degrees of CT complexes between **PPMA** and acceptor **2.1**-**2.5** plotted against the cloud point under LCST condition in 1,2-dichloroethane.

Table 2_3. Association degrees of CT complexes between **PPMA** and acceptor molecules under the LCST conditions.

Acceptor	$[A]_0$ [M]	Cloud point [^oC]	K_a [M^{-1}] [a]	[D· A] [M]	α [%]
2.1	0.110	17	0.90	0.0031	8.8
	0.119	25	0.75	0.0028	8.1
	0.128	35	0.61	0.0025	7.1
	0.139	43	0.52	0.0023	6.6
	0.146	47	0.48	0.0023	6.5
	0.154	51	0.45	0.0022	6.3
	0.171	59	0.39	0.0021	6.1
	0.173	60	0.38	0.0021	6.1
	0.200	72	0.31	0.0020	5.8
	0.205	75	0.29	0.0020	5.6
2.2	0.119	17	0.87	0.0032	9.2
	0.141	22	0.74	0.0033	9.3
	0.151	23	0.72	0.0034	9.6
	0.155	26	0.66	0.0032	9.1
	0.194	32	0.55	0.0033	9.5
	0.205	33	0.53	0.0034	9.7
	0.243	37	0.47	0.0036	10.2
	0.259	39	0.45	0.0036	10.3
	0.311	42	0.41	0.0039	11.2
2.3	0.035	21	4.60	0.0043	12.4
	0.036	30	3.52	0.0036	10.3
	0.039	41	2.59	0.0030	8.6
	0.042	48	2.16	0.0027	7.7
	0.046	59	1.64	0.0024	6.7
	0.049	63	1.49	0.0023	6.5
	0.052	70	1.27	0.0021	5.9
2.4	0.028	18	4.73	0.0036	10.2
	0.032	28	3.42	0.0032	9.1
	0.034	32	3.02	0.0030	8.6
	0.037	38	2.52	0.0028	7.9
	0.046	50	1.80	0.0025	7.3
	0.055	59	1.42	0.0024	7.0
2.5	0.017	2	10.41	0.0042	12.1
	0.019	5	9.30	0.0041	11.8
	0.020	9	8.02	0.0040	11.3
	0.022	19	5.66	0.0034	9.7
	0.024	24	4.79	0.0031	9.0
	0.025	26	4.49	0.0031	8.9
	0.025	29	4.08	0.0029	8.3
	0.029	40	2.92	0.0025	7.1
	0.030	47	2.39	0.0022	6.3
	0.034	52	2.08	0.0021	6.1
	0.040	66	1.44	0.0018	5.2

[a] Association constants K_a given by using equation 2_4.

2.2.5. Quaternary System

To further control the LCST behavior of **PPMA** system, quaternary systems were investigated by addition of 1,2-dimethoxybenzene as a competitive donor and a good-solvent molecule (Table 2_1). First, in order to evaluate the effect of the additive for CT complexation, UV/Vis spectra were measured for quaternary system (**2.6**/**2.5**/1,2-dimethoxybenzene/1,2-dichloroethane), ternary system 1 (**2.6**/**2.5**/1,2-dichloroethane) and ternary system 2 (**2.5**/1,2-dimethoxybenzene/1,2-dichloroethane) at 25 ^{o}C. As a result, difference calculated by spectrum of ternary system 2 from one of quaternary system was small compared with ternary system 1 (Figure 2_10). This indicated that the charge-transfer absorption band originated in monomer **2.6** and acceptor **2.5** in 1,2-dichloroethane decreased upon the addition of 1,2-dimethoxybenzene, and then this additive indeed functioned as the competitive donor.

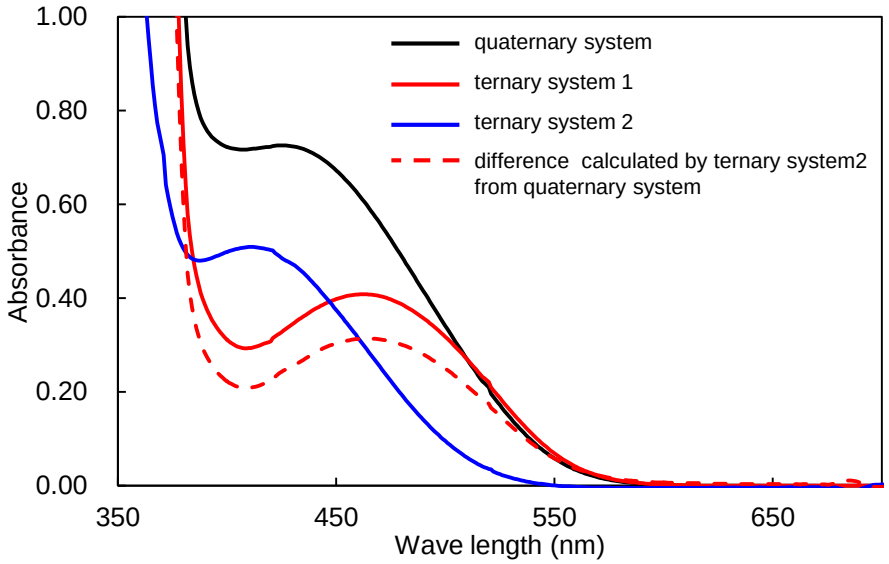


Figure 2_10. UV/Vis spectra of quaternary system (**2.6**/**2.5**/1,2-dimethoxybenzene/1,2-dichloroethane), ternary system 1 (**2.6**/**2.5**/1,2-dichloroethane) and ternary system 2 (**2.5**/1,2-dimethoxybenzene/1,2-dichloroethane) at 25 ^{o}C ([**2.6**] = 0.035 M, [**2.5**] = 0.025 M, [1,2-dimethoxybenzene] = 0.5 M). Difference calculated by spectrum of ternary system 2 from one of quaternary system (dashed line). The cell length is 1 mm.

Next, LCST behaviors in the presence of 1,2-dimethoxybenzene as the competitive donor were investigated. The addition of a small amount of 1,2-dimethoxybenzene induced a drastic decrease in the cloud point, although only 1,2-dimethoxybenzene was able to act as a good solvent for **PPMA** (Figure 2_11a). This phenomenon can be interpreted as a cononsolvency effect; the similar was also reported for the ternary system consisting of PNIPAM, H_2O, and a polar organic solvents such as methanol, DMSO and THF.[11] This result indicated that the molar fraction of **2.5** accessible to

PPMA, defined as effective acceptor concentration $[\mathbf{2.5}]_{eff}$, was diminished owing to the competitive CT interaction between 1,2-dimethoxybenzene and **2.5** (Figure 2_12).

Effective acceptor concentration $[\mathbf{2.5}]_{eff}$ were calculated by using equation 2_3, 2_4, 2_5 and the association constant of the complex between 1,2-dimethoxybenzen and acceptor **2.5** evaluated by Beneshi-Hildebrand plot (Table 2_4, Figure 2_19 (see Experimental Section)). For example, the effective concentration of **2.5** decreased from 0.025 to 0.018 M upon the addition of 1,2-dimethoxybenzene (0.70 M), and the cloud point decreased from 26 to 1 ^{o}C (Table 2_5). The calculated effective concentration agreed well with the observation that a ternary mixture of **2.5** (0.017 M) and **PPMA** showed a cloud point of 2 ^{o}C (without 1,2-dimethoxybenzene) (Table 2_3, Figure 2_13). The variation in solubility was caused by the competitive association of **2.5** with pyrene groups in the **PPMA** or with 1,2-dimethoxybenzene. In other words, the addition of 1,2-dimethoxybenzene diminished the association between **PPMA** and **2.5**. Whereas increase in the amount of 1,2-dimethoxybenzene resulted in decrease in the cloud point, the elevation of the cloud point was observed upon the addition of 1,1,2,2-tetrachloroethane, which is known to act as a good solvent for **PPMA** but not to affect to CT complexation with **2.5** (Figure 2_11b). From these results, the author concluded that the control of the association degree α between the pyrene groups in the polymer chain and the effectors enabled the solubility of the polymer to be changed as desired.

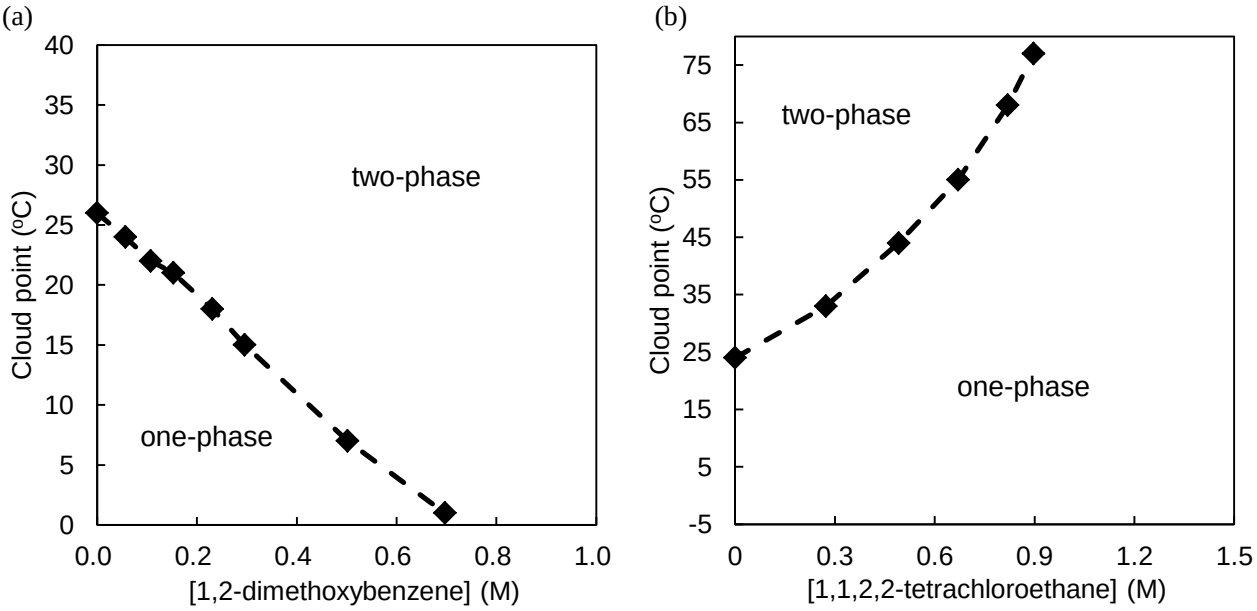


Figure 2_11. Cloud point of **PPMA** in 1,2-dichloroethane in the presence of **2.5** versus the concentration of (a) 1,2-dimethoxybenzene or (b) 1,1,2,2-tetrachloroethane. [**PPMA**] = 10 gL^{-1} (0.035 M with respect to the pyrene units in the polymer), [**2.5**] = 0.025 M^{-1}, scan rate = 1 ^{o}Cmin^{-1}. The dashed lines show the assumed boundaries between types of thermo-sensitivity.

Table 2_4. Evaluated association constants, molar absorbance coefficient, enthalpy and entropy of formed charge transfer complex between 1,2-dimethoxybenzene and **2.5** in 1,2-dichloroethane.

Donor	Acceptor	Temperature [^{o}C]	K_a [M^{-1}]	ε [$cm^{-1}mol^{-1}L$]	-ΔS [$JK^{-1}mol^{-1}$]	-ΔH [$kJmol^{-1}$]
1,2-dimethoxybenzene	**2.5**	25	0.52	1040	24.5	5.7
		35	0.47	1003		
		45	0.44	952		
		55	0.42	900		

$$[\mathbf{2.5}]_{eff} = [\mathbf{2.5}]_0 - [D_{comp} \cdot A] \quad \text{(equation 2\_5)}$$

$[D_{comp} \cdot A]$: concentration of charge-transfer complex formed between 1,2-dimethoxybenzene and **2.5**

Table 2_5. Cloud points and effective acceptor concentration $[\mathbf{2.5}]_{eff}$ in the quaternary system contained **2.5**, **PPMA**, 1,2-dimethoxybenzene and 1,2-dichloroethane.

[1,2-dimethoxybenzene] [M]	$[\mathbf{2.5}]_0$ [M]	Cloud point [^{o}C]	K_a [M^{-1}] [a]	$[D_{comp} \cdot A]$ [M]	$[\mathbf{2.5}]_{eff}$ [M]
0	0.025	26	0.51	0	0.0250
0.057	0.025	24	0.52	0.0007	0.0243
0.107	0.025	22	0.52	0.0013	0.0237
0.153	0.025	21	0.53	0.0018	0.0232
0.231	0.025	18	0.54	0.0027	0.0223
0.296	0.025	15	0.55	0.0035	0.0215
0.502	0.025	7	0.59	0.0057	0.0193
0.697	0.025	1	0.63	0.0075	0.0175

[a] Association constants K_a given by using equation 2_4.

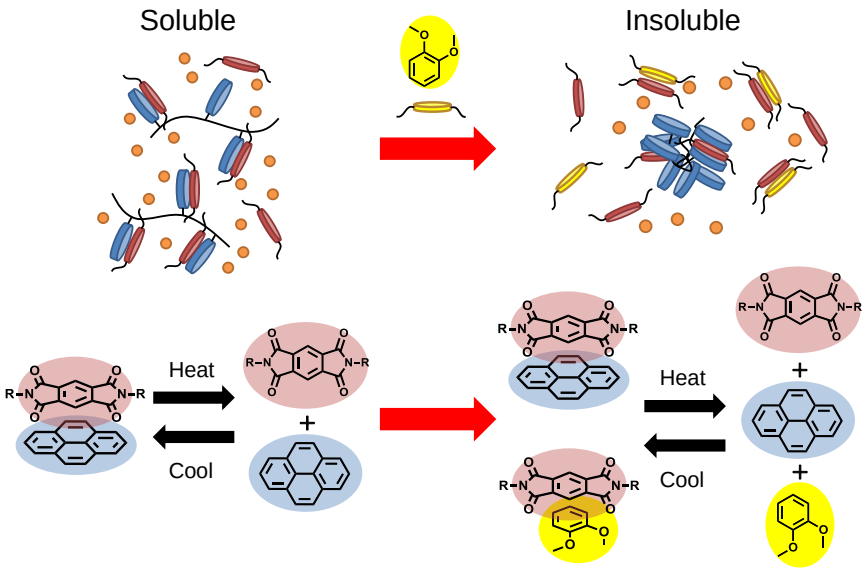


Figure 2_12. Presumed mechanism of competitive effect.

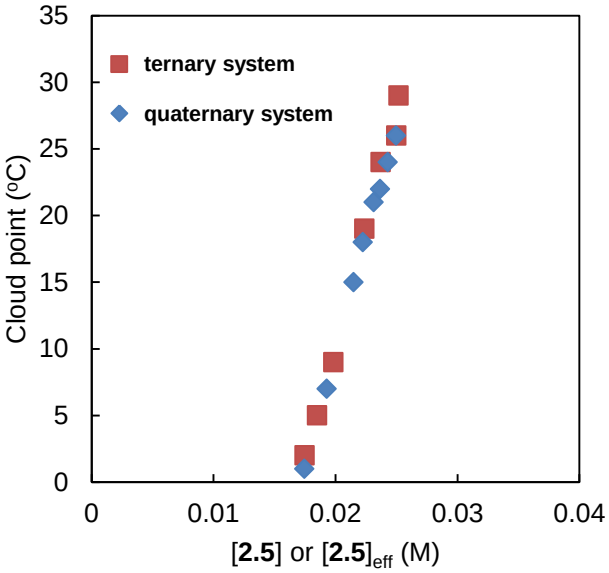


Figure 2_13. Cloud point of LCST behavior of ternary system (**2.5**/**PPMA**/1,2-dichloroethane) and quaternary system (**2.5**/**PPMA**/1,2-dimethoxybenzene/1,2-dichloroethane) against [**2.5**] or $[\mathbf{2.5}]_{eff}$, respectively ([**PPMA**] = 10 gL^{-1} (0.035 M pyrene units in the polymer)).

2.3. Conclusion

The author has demonstrated the controllable LCST-type phase behavior of **PPMA** in organic solvents with the effectors **2.1**–**2.5** and clearly showed a relationship between thermo-sensitivity and CT interaction. Since the association between pyrene units and the effectors plays a crucial role in determining the solubility of **PPMA**, the LCST-type phase behavior of **PPMA** can be controlled readily by changing the effector concentration or structure and by the further addition of a competitive donor. To the best of my knowledge, the design of polymers with LCST-type phase behavior on the basis of π–π interaction and CT interaction has not been described previously. The author concludes that proper selection of the intermolecular interaction between the pendant group of the polymer chain and the effector by employing knowledge based on supramolecular chemistry can govern the solubility and thermo-sensitivity of the polymer solution. Many other intermolecular interactions should provide a wide range of LCST behavior in various media and at various temperatures.

2.4. Experiment Section

Instrumentation

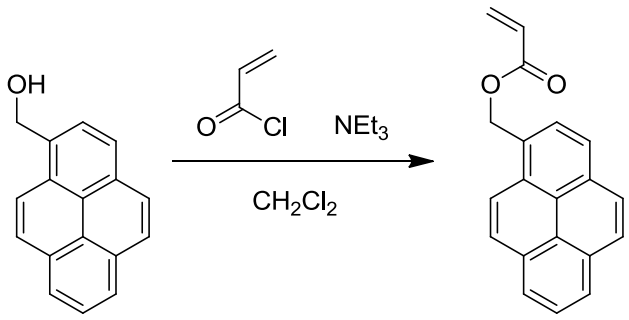
^{1}H and ^{13}C NMR measurements were recorded on a JEOL JNM-AL300 instrument at 300 MHz and Bruker AV500 instrument at 500 MHz at room temperature. Size exclusion chromatography (SEC) at room temperature was carried out on a SHIMADZU LC-9A system (SHODEX K-805L column) with a SPD-10AVP UV/Vis Detector using chloroform as an eluent, after calibration with the standard polystyrene samples. UV/Vis spectra were recorded on a JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. Fourier transform infrared (FTIR) spectra were observed with a JASCO FTIR-4100 SK spectrometer. Elemental analysis and electron spray ionization mass spectroscopy were performed at the Creative Research Institution of Hokkaido University.

Materials

All reagents were obtained from commercial sources and used without further purification. Cyanomethyl dodecyl trithiocarbonate (**2.7**)[12] and 1-bromo-2-octyldodecane[13] was synthesized and characterized according to the literatures.

Synthesis

Synthesis of (1-Pyrene)methyl acrylate (2.6)[7]

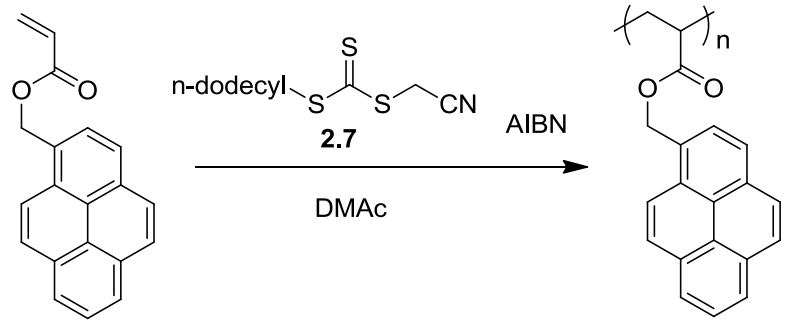


2.6

To a solution of 1-pyrenemethanol (1.16 g, 5 mmol) and triethylamine (0.55 g, 5.5 mmol) in dry dichloromethane (40 mL), acryloyl chloride (0.50 g, 5.5 mmol) was slowly added at 0 °C under N_2. After the mixture was stirred for additional 14 h at room temperature, it was poured into the water. The reaction mixture was washed with $NaHCO_3$ aq., water and dried over anhydrous Na_2SO_4, followed by evaporation to dryness. The residue was purified by silica column chromatography ($CHCl_3$/hexane=1:1 (v/v)) to obtain **2.6** as a white solid (1.00 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 5.84 (dd, *J* = 1.5, 10.3 Hz, 1H, alkenyl *H*), 5.92 (s, 2H, Ar-C*H*$_2$-) 6.18

(dd, *J* = 10.3, 17.2 Hz, 1H, alkenyl *H*), 6.47 (dd, *J*=1.5, 17.2 Hz, 1H, alkene *H*), 7.99-8.27 (m, 9H, Pyrene *H*). FTIR (ATR, cm^{-1}): 3037.3, 2964.1, 2924.5, 2853.2, 1716.3 (C=O), 1406.8, 1269.9, 1250.6, 1181.2, 1036.6, 974.8, 838.9, 811.9, 756.0, 702.9. Anal. Calcd for $C_{20}H_{14}O_2$: C 83.90, H 4.93, N 0.00, Found: C 83.94, H 5.01, N 0.00. HRMS(EI) Calcd for $C_{26}H_{14}O_2$: m/z 286.0994, Found: m/z 286.0994.

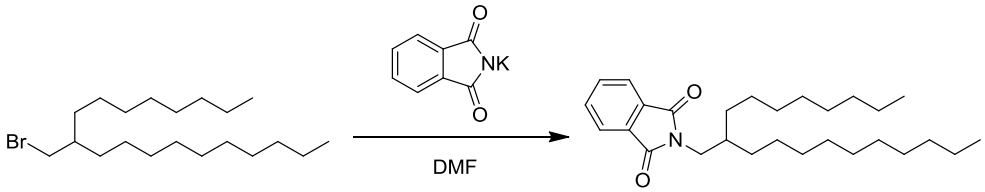
Synthesis of Poly((1-pyrene)methyl acrylate) (PPMA)



2.6 **PPMA**

A solution **2.6** (2.14 g, 7.5 mmol), **2.7** (4.7 mg, 15 μmol) and AIBN (1.2 mg, 7.5 μmol) in dryDMAc (0.75 mL) was prepared. The solution was transferred to an ampule, degassed, with three freeze-evacuate-thaw cycles, and sealed. The ampule was heated at 80 °C for 48 h. After the ampule was cooled, reaction mixture was reprecipitated with diethyl ether, filtered and dried to obtain **PPMA** as a pale yellow powder (0.62 g). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 1.80-2.05 (br), 2.35-2.65 (br), 5.10-5.40 (br, Ar-C*H*$_2$-), 7.00-7.80 (br, Ar-*H*). FTIR (ATR, cm^{-1}): 3041.2, 2954.4, 1730.8, 1448.3, 1243.9, 1153.2, 1106.9, 1062.6, 960.4, 938.2, 840.8, 755.0, 707.7.

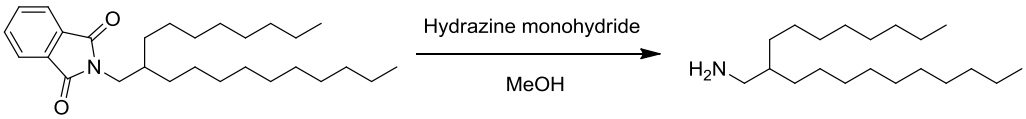
Synthesis of *N*-(2-octyldodecyl)phthalimide



1-Bromo-2-octyldodecane (12.5 g, 35 mmol) and potassium phthalimide (6.85 g, 37 mmol) were taken up in 45 mL of DMF and stirred for 10 h at 90 ^{o}C. After the mixture was cooled, it was poured to water (150 mL) and extracted with dichloromethane (80 mL x3). The combined organic layer was washed with 0.2 N KOH aq. (150 mL), water (150 mL) and saturated NH_4Cl aq. (150 mL). After dried over anhydrous Na_2SO_4, it was evaporated and purified by silica column chromatography (CH_2Cl_2/hexane=1:4 (v/v)) to obtain a colorless oil (13.3 g, 90 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.70-0.94 (m, 6H, -*CH*$_3$), 1.20-1.40(m, 32H, -C*H*$_2$-), 1.87 (br-s, 1H, -C*H*<),

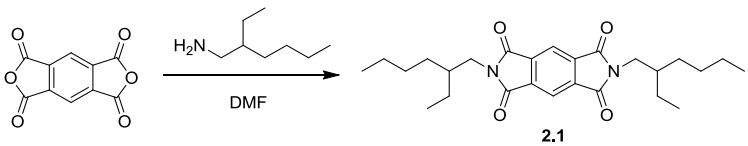
3.57 (d, *J*=7.3 Hz, 2H, N-C*H*$_2$-), 7.71 (dd, *J*=3.1, 5.4 Hz, 2H, Ar-*H*), 7.84 (dd, *J*=3.1, 5.4 Hz, 2H, Ar-*H*). FTIR (ATR, cm^{-1}): 2953.5, 2922.6, 2853.2, 1773.2, 1713.4, 1466.6, 1435.7, 1395.3, 1360.5, 1331.6, 1187.9, 1064.5, 955.6, 919.9, 790.7, 721.2, 712.6, 625.8. HRMS(EI) Calcd for $C_{28}H_{45}NO_2$: m/z 427.3450, Found: m/z 427.3450;

Synthesis of 2-octyldodecylamine[8]



To a solution of *N*-(2-octyldodecyl)phthalimide (7.0 g, 16.4 mmol) in MeOH (90 mL), hydrazine monohydride (2.46 g, 49.1 mmol) was added. After the mixture was refluxed for 8 h, it was cool and then filtrated. The solution was evaporated and then added to dichloromethane. The organic layer was washed with 10 wt% KOH aq. (100 mL x2). The aqueous layer was extract with dichloromethane (50 mL x3). The organic layer was combined and washed with the saturated NaCl aq. (100 mL x2), dried over anhydrous Na_2SO_4. The organic layer was concentrated to give a colorless oil (5.15 g). This compound was used to next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.83-0.94 (m, 6H, -C*H*$_3$), 1.15-1.40(m, 33H, -C*H*$_2$-, -C*H*<), 2.60 (d, *J*=3.8 Hz, 2H, N-C*H*$_2$-). FTIR (ATR, cm^{-1}): 2955.4, 2920.7, 2852.2, 1617.0, 1577.5, 1464.7, 1377.9, 1302.7, 1062.6, 778.1, 721.2. HRMS(ESI) Calcd for $C_{20}H_{44}N$ [$(M+H)^+$]: m/z 298.3468, Found: m/z 298.3468.

Synthesis of *N,N'*-bis-(2-ethylhexyl)pyromellitic diimide (2.1)[14]

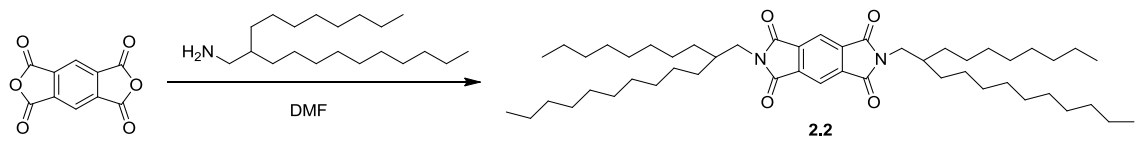


2.1

To a suspension of pyromellitic dianhydride (0.87 g, 4 mmol) in dry DMF (20 mL), 2-ethylhexylamine (1.29 g, 10 mmol) was added under N_2. After the mixture was refluxed for 10 h, it was cool and then filtrated. The residue was purified by silica column chromatography ($CHCl_3$/hexane=3:1 (v/v)) to obtain **2.1** as a white solid (0.83 g, 47 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.88 (t, *J*=6.7 Hz, 6H, -C*H*$_3$ (hexyl)), 0.92 (t, *J*=7.4 Hz, 6H, -C*H*$_3$ (ethyl)), 1.20-1.45(m, 16H, -C*H*$_2$-), 1.85 (quint, *J*=6.2 Hz, 2H, -C*H*<) 3.64 (d, *J*=7.2 Hz, 4H, N-C*H*$_2$-), 8.27 (s, 2H, Ar-*H*). FTIR (ATR, cm^{-1}): 2957.3, 2928.4, 2858.0, 1765. 5, 1699.0, 1462.7,

1442.5, 1395.3, 1357.6, 1154.2, 1121.4, 1081.9, 1054.9, 945.9, 891.0, 731.9, 620.0. HRMS(EI) Calcd for $C_{26}H_{36}N_2O_4$: m/z 440.2675, Found: m/z 440.2680.

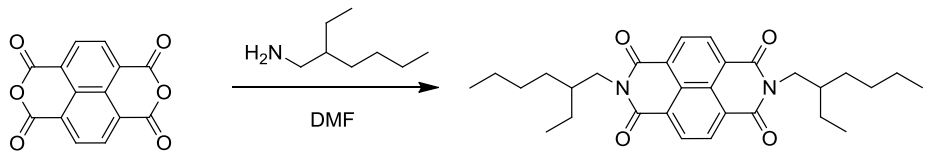
Synthesis of *N,N'*-bis-(2-octyldodecyl)pyromellitic diimide (2.2)



2.2

To a suspension of pyromellitic dianhydride (0.87 g, 4 mmol) in dry DMF (20 mL), 2-octyldodecylamine (2.50 g, 8.4 mmol) was added under N_2. After the mixture was refluxed for 14 h, it was cool and then filtrated. The residue was purified by silica column chromatography ($CHCl_3$/hexane=1:1 (v/v)) to obtain **2.2** as a white solid (1.61 g, 54 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.84-0.92 (m, 12H, -C*H*$_3$), 1.18-1.38 (m, 64H, -C*H*$_2$-), 1.89 (br-s, 2H, -C*H*<), 3.63 (d, *J*=7.2 Hz, 4H, N-C*H*$_2$-), 8.27 (s, 2H, Ar-*H*). ^{13}C NMR (125 MHz, $CDCl_3$, r.t.) : δ (ppm) 166.7, 137.3, 118.3, 43.1, 37.1, 32.1, 32.0, 31.6, 30.1, 29.8, 29.7, 29.7, 29.5, 29.4, 26.4, 22.8, 22.8, 14.3. FTIR (ATR, cm^{-1}): 2953.5, 2919.7, 2850.3, 1779.0, 1708.6, 1466.6, 1397.2, 1356.7, 1077.1, 919.9, 808.0, 724.1, 627.7. Anal. Calcd for $C_{50}H_{84}N_2O_4$: C 77.27, H 10.89, N 3.60, Found: C 77.23, H 11.14, N 3.51; HRMS(EI) Calcd for $C_{50}H_{84}N_2O_4$: m/z 776.6431, Found: m/z 776.6427.

Synthesis of *N,N'*-bis-(2-ethylhexyl)-1,4,5,8-naphthalentetracarboxydiamide (2.3)

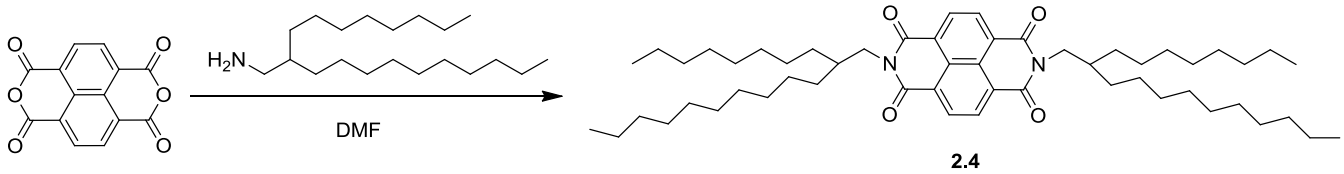


2.3

To a suspension of 1,4,5,8-naphthalenetetracarboxylic acid dianhydride (1.07 g, 4 mmol) in dry DMF (20 mL), 2-ethylhexylamine (1.29 g, 10 mmol) was added under N_2. After the mixture was refluxed for 15 h, it was cool and then filtrated. The residue was purified by silica column chromatography ($CHCl_3$/hexane=4:1 (v/v)) to obtain **2.3** as a pale yellow solid (0.65 g, 33 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.88 (t, *J*=7.0 Hz, 6H, -C*H*$_3$ (hexyl)), 0.94 (t, *J*=7.4 Hz, 6H, -C*H*$_3$ (ethyl)), 1.20-1.45(m, 16H, -C*H*$_2$-), 1.94 (quint, *J*=6.5 Hz, 2H, -C*H*<) 4.10-4.20 (m, 4H, N-C*H*$_2$-), 8.76 (s, 4H, Ar-*H*). FTIR (ATR, cm^{-1}) 2960.2, 2930.3, 2858.0, 1699.9, 1653.7, 1580.4, 1454.1, 1373.1, 1335.5, 1241.0, 1182.2, 1090.6, 1059.7, 893.8, 808.0, 771.4, 718.4, 615.2.

HRMS(EI) Calcd for $C_{30}H_{38}N_2O_4$: m/z 490.2832, Found: m/z 490.2827.

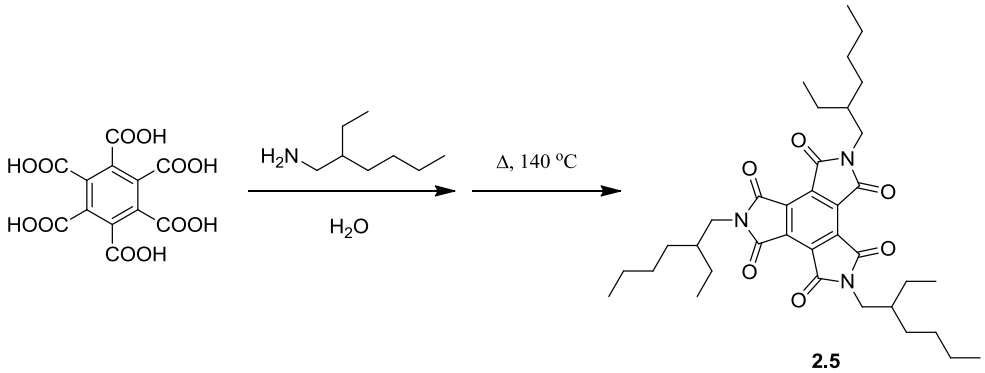
Synthesis of *N,N'*-bis-(2-octyldodecyl)-1,4,5,8-naphthalentetracarboxydiamide (2.4).



2.4

To a suspension of 1,4,5,8-naphthalenetetracarboxylic acid dianhydride (0.26 g, 0.95 mmol) in dry DMF (5 mL), 2-octyldodecylamine (0.60 g, 2 mmol) was added under N_2. After the mixture was refluxed for 6 h, it was cool and then poured into the water. The reaction mixture was extracted with dichloromethane (60 mL x2). The organic layer was washed with $NaHCO_3$ aq. and dried over anhydrous Na_2SO_4, followed by evaporation to dryness. The residue was purified by silica column chromatography ($CHCl_3$/hexane=1:1 (v/v)) to obtain **2.4** as a pale yellow (0.39 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.80-0.95 (m, 12H, -C*H*$_3$), 1.15-1.45 (m, 64H, -C*H*$_2$-), 1.89 (br, 2H, -C*H*<), 4.13 (d, *J*=7.1 Hz, 4H, N-C*H*$_2$), 8.75 (s, 4H, Ar-*H*). ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): δ (ppm) 163.4, 131.2, 126.9, 126.7, 45.1, 36.8, 32.1, 32.0, 31.8, 30.1, 29.8, 29.7, 29.7, 29.5, 29.4, 26.6, 22.8, 22.8, 14.2. FTIR (ATR, cm^{-1}) 2954.4, 2921.6, 2850.3, 1700.9, 1654.6, 1578.5, 1455.0, 1376.0, 1337.4, 1244.8, 1176.4, 1080.9, 971.9, 893.8, 771.4, 721.2. Anal. Calcd for $C_{54}H_{86}N_2O_4$: C 78.40, H 10.48, N 3.39, Found: C 78.45, H 10.77, N 3.26. HRMS(EI) Calcd for $C_{54}H_{86}N_2O_4$: m/z 826.6588, Found: m/z 826.6583.

Synthesis of *N,N',N''*-tris-(2-ethylhexyl)mellitic triimide (2.5).



2.5

To a stirred solution of mellitic aicd (5.00 g, 15.0 mmol) in water (200 mL), 2-ethylhexylamine (5.81 g, 45 mmol) was added. After stirring for 10 minutes the mixture was evaporated to dryness under vacuum. The residue was then transferred to a vacuum drying oven maintained at 140 °C for 96 h. After cooling to room temperature the residue was dissolved with chloroform (150 mL) and then

filtrated. The filtrate was evaporated and purified by silica column chromatography ($CHCl_3$) to obtain **2.5** as a white solid (1.10 g, 12%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.): δ (ppm) 0.89 (t, *J*=6.8 Hz, 9H, -C*H*$_3$ (hexyl)), 0.92 (t, *J*=7.5 Hz, 9H, -C*H*$_3$ (ethyl)), 1.20-1.44 (m, 24H, -C*H*$_2$-), 1.90 (quint, *J*=6.3 Hz, 3H, -C*H*<), 3.70 (d, *J*=7.2 Hz, 6H, N-C*H*$_2$-). ^{13}C NMR (125 MHz, $CDCl_3$, r.t.): δ (ppm) 162.9, 133.5, 43.3, 38.4, 30.1, 28.7, 24.1, 23.0, 14.2, 10.5. FTIR (ATR, cm^{-1}): 2956.3, 2926.5, 2859.0, 1776.1 (C=O), 1722.1(C=O), 1632.5, 1457.9, 1435.7, 1389.5, 1349.9, 1160.9, 1119.5, 1068.4, 760.8, 726.1, 625.8. Anal. Calcd for $C_{36}H_{51}N_3O_6$: C 69.54, H 8.27, N 6.76, Found: C 69.53, H 8.43, N 6.51. HRMS(EI) Calcd for $C_{36}H_{51}N_3O_6$: m/z 621.3778, Found: m/z 621.3770.

Transmittance Measurement

Transmittance measurements were carried out by using JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. The cell length is 1 cm. The cloud points of the polymer solutions were determined from the transmittance at 800 nm on cooling at 1.0 $^oC\ min^{-1}$ as the temperature with 90% transmittance.

Benesi-Hildebrand Plot and van't Hoff Plot

UV/Vis spectra were recorded on a JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. The cell length is 1 cm. UV/Vis spectra of system **PPMA** in 1,2-dichloroethane in the presence of acceptors were measured under the condition $[A]_0 >> [D]_0$, where $[A]_0$ and $[D]_0$ refer to initial concentration of acceptor and donor compounds, respectively. $[D]_0$ were used as concentration of the pyrene units in the polymer [**PPMA**]. In some cases, the absorption of acceptor overlapped with the absorption of complex. Thus, the acceptor component of the absorption was removed using a solution of the same acceptor concentration. The thermodynamic parameters were evaluated from the variation of the association constant with temperature.

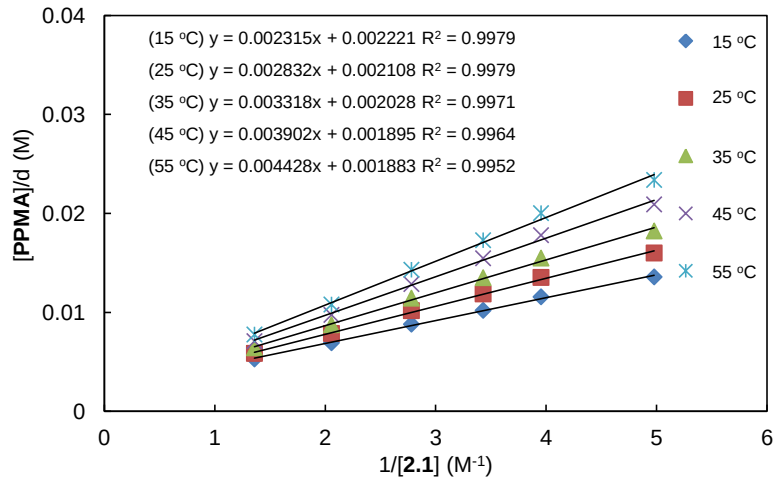


Figure 2_14. Benesi-Hildebrand plot for the system of **2.1** and **PPMA** in 1,2-dichloroethane (0.20 M < [**2.1**] < 0.74 M)

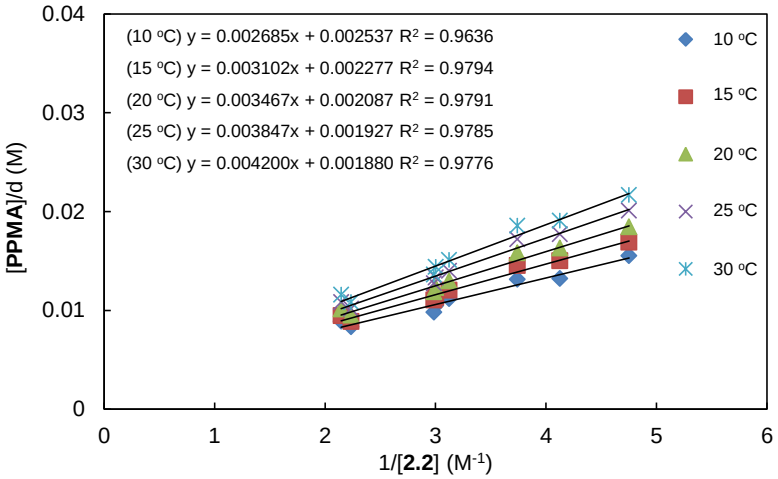


Figure 2_15. Benesi-Hildebrand plot for the system of **2.2** and **PPMA** in 1,2-dichloroethane (0.21 M < [**2.2**] < 0.47 M).

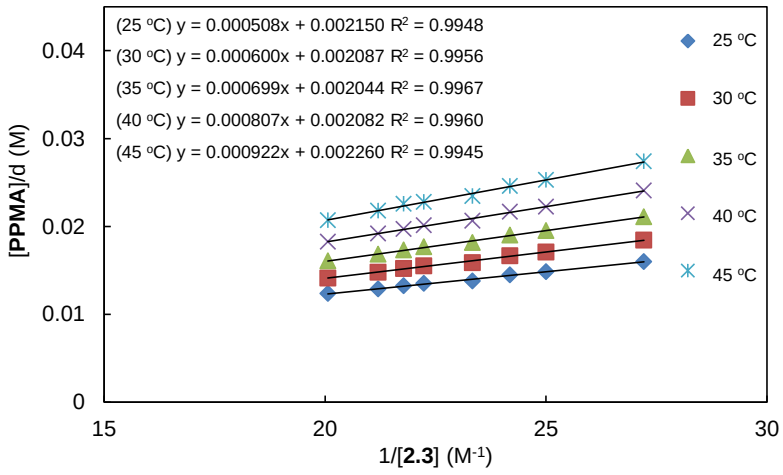


Figure 2_16. Benesi-Hildebrand plot for the system of **2.3** and **PPMA** in 1,2-dichloroethane (0.037 M < [**2.3**] < 0.050 M).

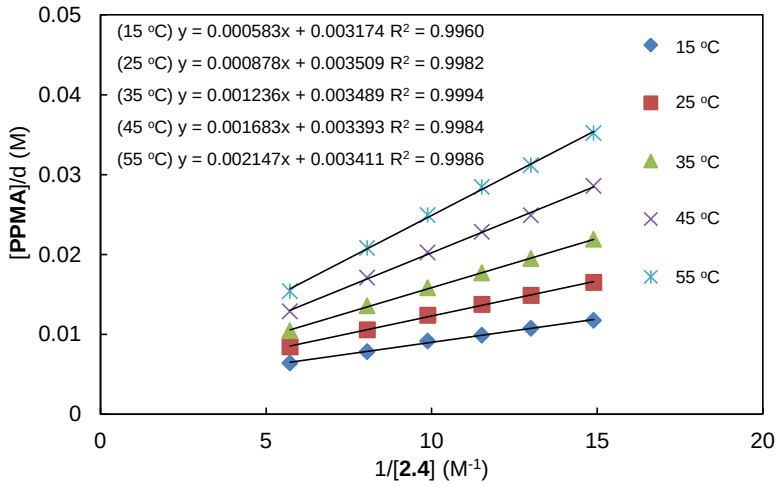


Figure 2_17. Benesi-Hildebrand plot for the system of **2.4** and **PPMA** in 1,2-dichloroethane (0.067 M < [**2.4**] < 0.124 M).

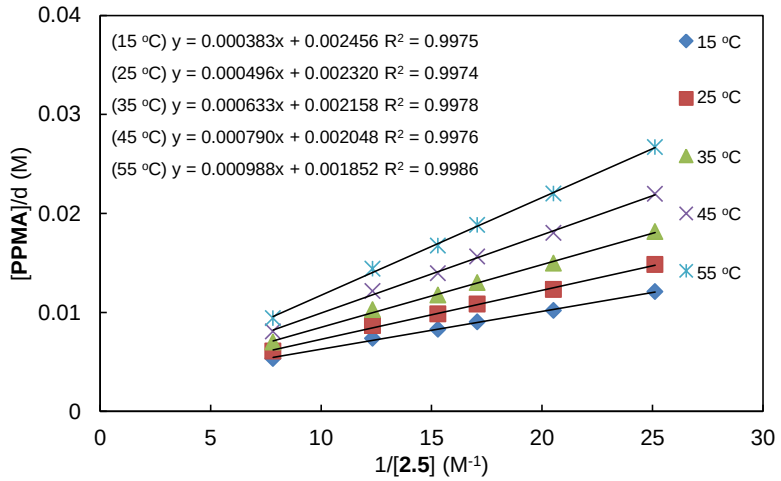


Figure 2_18. Benesi-Hildebrand plot for the system of **2.5** and **PPMA** in 1,2-dichloroethane (0.040 M < [**2.5**] < 0.128 M).

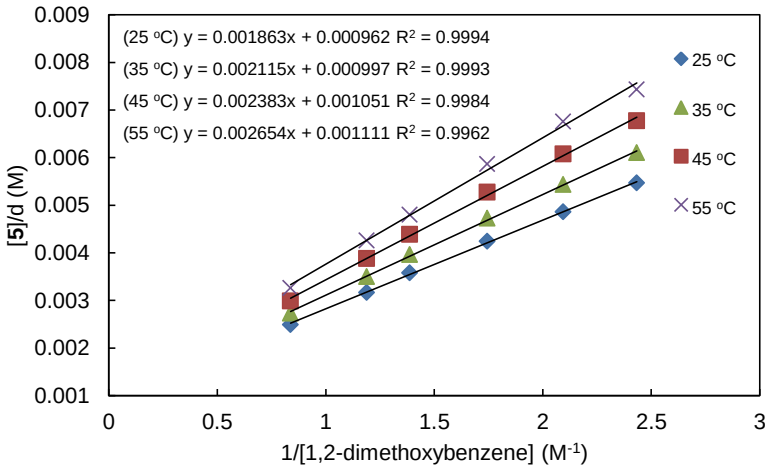


Figure 2_19. Benesi-Hildebrand plot for the systems of **2.5** and 1,2-dimethoxybenzene in 1,2-dichloroethane (0.41 M < [1,2-dimethoxybenzene] < 1.20 M).

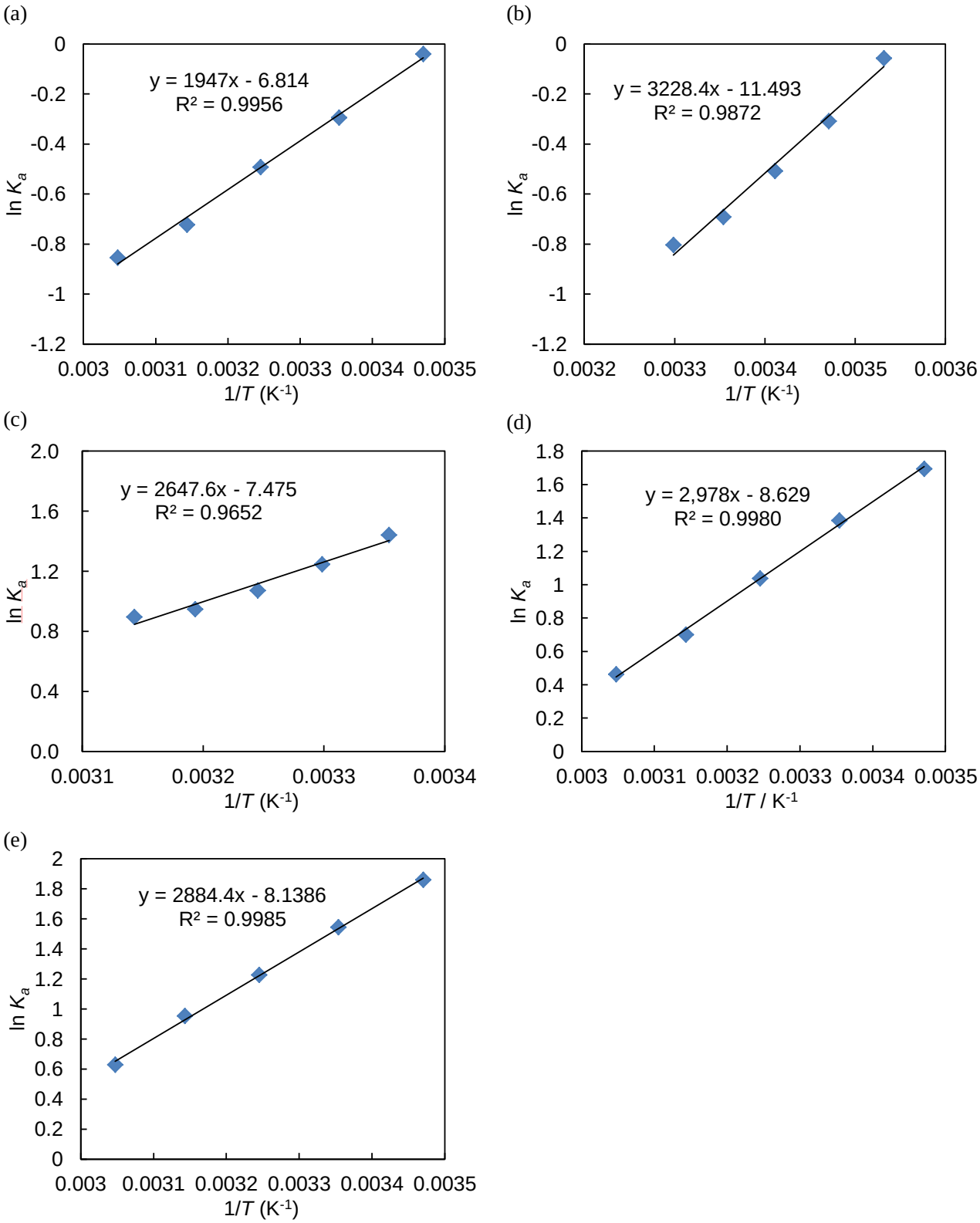


Figure 2_20. van't Hoff plot for the system of **PPMA** and acceptor (a) **2.1**, (b) **2.2**, (c) **2.3**, (d) **2.4** or (e) **2.5** in 1,2-dichloethane.

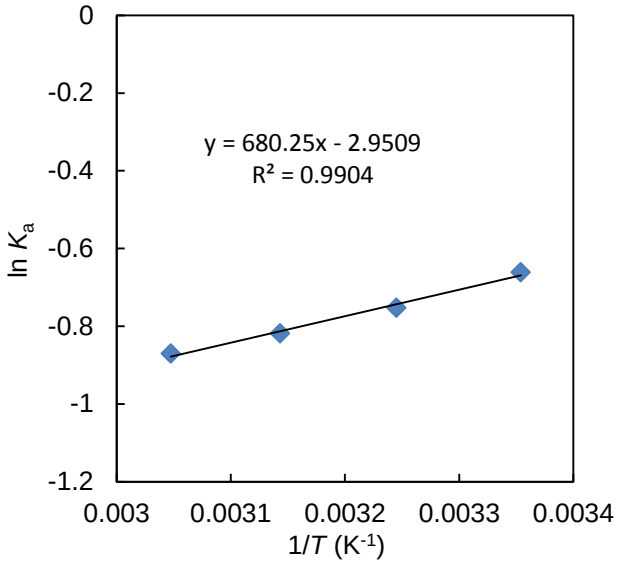


Figure 2_21. van't Hoff plot for the system of **2.5** and 1,2-dimethoxybenzene in 1,2-dichloroethane.

2.5. Reference

1) a) Wudl, F.; Yamochi, H.; Suzuki, T. Isotalo, H.; Fite, C.; Kasmai, H.; Liou, K.; Srdanov, G. *J. Am. Chem. Soc.* **1990**, *112*, 2461-2462. b) Saito, G.; Sasaki, H.; Aoki, T.; Yoshida, Y.; Otsuka, A.; Yamochi, H.; Drozdova, O. O.; Yakushi, K.; Kitagawa, H.; Mitani, T. *J. Mater. Chem.* **2002**, *12*, 1640-1649. c) Jerome, D. *Chem. Rev.* **2004**, *104*, 5565-5591.

2) a) Maitara, U.; Kumar, P. V.; Chandra, N.; D'Souza, L. J.; Prasanna, M. D.; Raju, A. R.; *Chem. Commun. 1999*, 595-596. b) Friggeri, A.; Gronwald, O.; van Bommel, K. J. C.; Shinkai, S.; Reinhoudt, D. N. J. Am. Chem. Soc. 2002, 124, 10754-10758. c) Babu, P.; Sangeetha, N. M.; Vijaykumar, P.; Maitra, U.; Rissanen, K.; Raju, A. R. *Chem. Eur. J.* **2003**, *9*, 1922-1932. d) Rizkov, D.; Gun, J.; Lev, O.; Sicsic, R.; Melman, A. *Langmuir* **2005**, *21*, 12130-12138. e) Mukhopadhyay, P.; Iwashita, Y.; Shirakawa, M.; Kawano, S.; Fujita, N.; Shinkai, S. *Angew. Chem.* **2006**, *118*, 1622-1625; *Angew. Chem. Int. Ed.* **2006**, *45*, 1592-1595. f) Rao, K. V.; Jayaramulu, K.; Maji, T. K.; George, S. J. *Angew. Chem.* **2010**, *122*, 4314-4318; *Angew. Chem. Int. Ed.* **2010**, *49*, 4218-4222.

3) a) Klivansky, L. M.; Koshkakaryan, G.; Cao, D.; Liu, Y. *Angew. Chem.* **2009**, *121*, 4249-4253; *Angew. Chem.* **2009**, *48*, 4185-4189. b) Ikeda, T.; Higuchi, M; Kurth, D. G.; *J. Am. Chem. Soc.* **2009**, *131*, 9185-9159. c) Olsen, J.-C.; Fahrenbach, A. C.; Trabolsi, A.; Friedman, D. C.; Dey, S. K.; Gothard, C. M.; Shveyd, A. K.; Gasa, T. B.; Spruell, J. M.; Olson, M. A.; Wang, C.; Jacquot de Rouville, H.-P.; Botros, Y. Y.; Stoddart, J. F. *Org. Biomol. Chem.* **2011**, *9*, 7126-7133.

4) a) Park, J. S.; Yoon, K. Y.; Kim, D. S.; Lynch, V. M.; Bielawski, C. W.; Johnston, K. P.; Sessler, J. L. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 20913-20917. b) Fernandez, G.; Perez, E. M.; Sanchez, L.; Martin, N. *Angew. Chem.* **2008**, *120*, 1110-1113; *Angew. Chem. Int. Ed.* **2008**, *47*, 1094-1097. c) Liu, Y.; Yu, Y.; Gao, J.; Wang, Z.; Zhang, X. Angew. Chem. 2010, 122, 6726-6729; *Angew. Chem. Int. Ed.* **2010**, *49*, 6576-6579.

5) a) Aseyev, V.; Tenhu, H.; Winnik, F. M. *Adv. Polym. Sci.* **2011**, *242*, 29-89. b) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163-249.

6) You, J.; Yoon, J. A.; Kim, J.; Huang, C. F.; Matyjaszewski, K.; Kim, E. *Chem. Mater.* **2010**, *22*, 4426-4434.

7) Petrov, P. D.; Georgiev, G. L. *Chem. Commun.* **2011**, *47*, 5768-5770.

8) Letizia, J. A.; Salata, M. R.; Tribout, C. M.; Facchetti, A.; Ratner, M. A.; Marks, T. J. *J. Am. Chem. Soc.* **2008**, *130*, 9679-9694.

9) Simionescu, C. I.; Grigoras, M. *Prog. Polym. Sci.* **1991**, *16*, 907-976.

10) Ono, Y.; Shikata, T.; *J. Am. Chem. Soc.* **2006**, *128*, 10030-10031.

11) a) Schild, H. G.; Muthukumar, M.; Tirrell, D. A. *Macromolecules* **1991**, *24*, 948-952. b) Yamauchi, H.; Maeda, Y. *J. Phys. Chem. B* **2007**, *111*, 12964-12968.
12) Chong, Y. K.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2007**, *40*, 4446-4455.
13) Ellinger, S.; Ziener, U.; Thewalt, U.; Landfester, K.; Möller, M. *Chem. Mater.* **2007**, *19*, 1070-1075.
14) Rasberry, R. D.; Smith, M. D.; Shimizu, K. D. *Org. Lett*. **2008**, *10*, 2889-2892.

Chapter 3: Thermo-Sensitive Behavior of Polymer having Urea Units in the Presence of Hydrogen-Bonding Molecules

3.1. Introduction

Hydrogen bonds are an attractive interaction between an electron-deficient hydrogen and a region of high electron density. A hydrogen atom attached to a relatively electronegative atom such as oxygen, nitrogen or fluorine act as a hydrogen bond donor, and the electronegative atom is a hydrogen bond acceptor. The hydrogen bond is among the most widely used as one of non-covalent interactions. This is because hydrogen bonds are thermally reversible and the strength can be tuned easily by (1) varying the number of hydrogen bonds from single, dual, triple, quadruple to sextuple or even higher order hydrogen bonding motifs, (2) changing solvent or temperature, or (3) altering the acidity and/or basicity of the proton donors and acceptors.

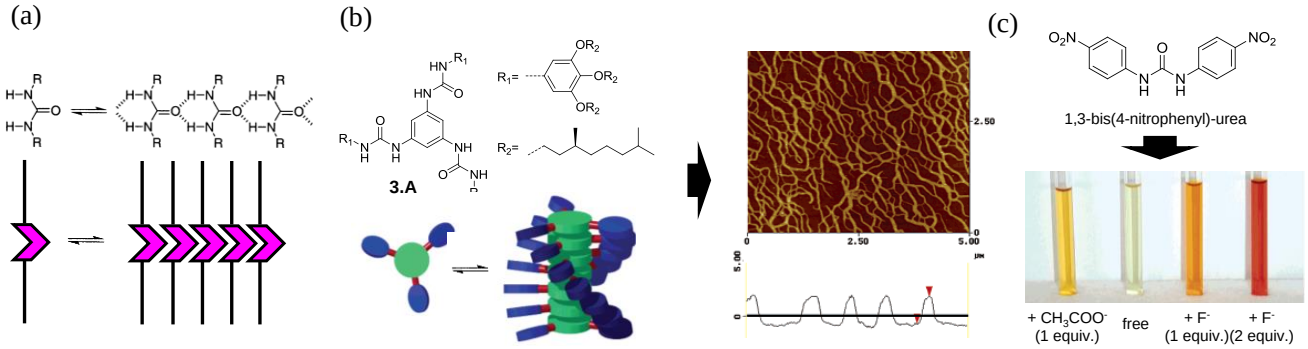


Figure 3_1. (a) self-association of ureas by the intermediary of hydrogen bond. (b) Structure and AFM pictures of 3A.[1a] (c) Color changes observed with the addition of anions to an MeCN solution of 1,3-bis(4-nitrophenyl)-urea.[2a]

A dialkyl urea group, which has two NHs as hydrogen bond donors and one C=O as a hydrogen bond acceptor, is broadly used in building blocks for various supramolecular structure such as low-molecular-weight gelators and supramolecular polymers.[1] Especially, for designing gelators and supramolecular polymer, it is important that remarkable ability to form self-association among urea groups to yields one-dimensional supramolecular structure (Figure 3_1a). For example, Meijer *et al*. reported that supramolecular gel of **3.A** consisting of three urea units by hydrogen bond between the urea units (Figure 3_1b).[1a] Moreover various anion receptors containing urea groups have been reported, because they had higher association constants between the urea and anions, and appropriate molecular design resulting in colorimetric or spectral (^{1}H NMR, IR) change by

receptor-anion interaction (Figure 3_1c).[2] In many cases, the media are limited in apolar solvents, and in water or any other hydrogen bond-forming medium (e.g., alcohols) they don't form the hydrogen bond complex, since they compete with the urea for formation of hydrogen bond. In other words, such alcohols can easily interact with the ureas through hydrogen bond. Moreover, the association among ureas or between and other molecules can be collapsed readily by heating.

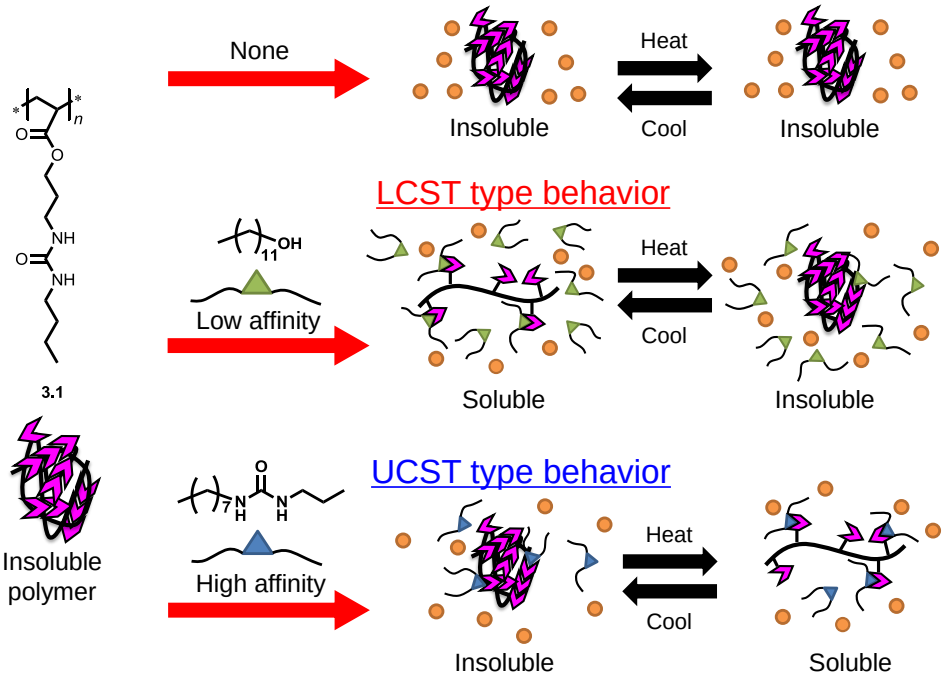


Figure 3_2. Concept of the thermosensitive polymer with LCST-type and UCST-type phase behavior controlled by additives.

In chapter 1, the author explained that *de novo* design of LCST behavior in non-polar solvent using insoluble polymer and polymer-small molecules interaction by non-covalent bonds. It denoted that the ternary system consisting of cohesive polymer, effector which can interact with the polymer, and organic solvents. Indeed, the author demonstrated LCST-type phase behavior of the polymer having pyrene groups in the presence of the acceptors as shown in chapter 2.[3]

In this chapter, in order to realize a desirable thermo-sensitivity at ambient temperature, the author chose the urea groups that meet the above requirements due to the high self-association capacity and remarkable ability to interact with various hydrogen bonding compounds as effectors. Therefore, as a platform polymer for the LCST behavior system, urea-modified acrylate polymer **3.1** was designed (Figure 3_2). And some alcohols, amides, ureas, carboxylic acid, and bromide anion were used as effectors. They have different hydrogen bonding ability, respectively. Here, the author accomplished that chemo-selective switching of the thermal behavior by changing the

strength of the hydrogen bonding functional group in the effector (Figure 3_2).

3.2. Results and Discussion

3.2.1. Synthesis and Characterization of Urea Polymer

The urea-modified monomer **3.3** was synthesized in a good yield by the condensation reaction of acryloyl chloride and urea-modified alcohol **3.2** (Scheme 3_1).[4] The structure of monomer **3.3** was confirmed by ^{1}H NMR and IR spectroscopy, electron ionization mass spectrometry, and elemental analysis. Polymer **3.1** was obtained via controlled radical polymerization (CRP) of monomer **3.3** using dithioester **3.4** as the chain-transfer agent (CTA).[5] The molecular weight and polydispersity index of polymer **3.1** were determined to be M_n = 2.47 × 10^4 and M_w/M_n = 1.92, respectively, using size exclusion chromatography (SEC) with poly(ethylene oxide) standards and 10 mM LiBr in DMF as an eluent solvent. The polydispersity index was relatively large in spite of chain-transfer polymerization, because of self-association between the monomer **3.1** affected chain-transfer reaction.[6]

The solubility of polymer **3.1** in various organic solvents was investigated (Table 3_1). In aprotic solvents such as acetonitrile, tetrahydrofuran, 1,2-dichloroethane (DCE), and hexane, **3.1** was practically insoluble (>100 gL^{-1}) because of the strong hydrogen bonds between the urea groups on the polymer chain. On the contrary, in protic solvents such as methanol, ethanol, and hexanol, the polymer showed high solubility (>100 gL^{-1}) because their formed the hydrogen bonds with the urea groups of the polymer **3.1** and cleave the association of the urea groups, regardless of permittivity of the solvents. This result further prompted the author to investigate control of the LCST and UCST-type phase behavior of **3.1** in the presence of "effectors" in above aprotic solvents having low solubility for **3.1**

Scheme 3_1. Synthetic route for urea polymer **3.1**.

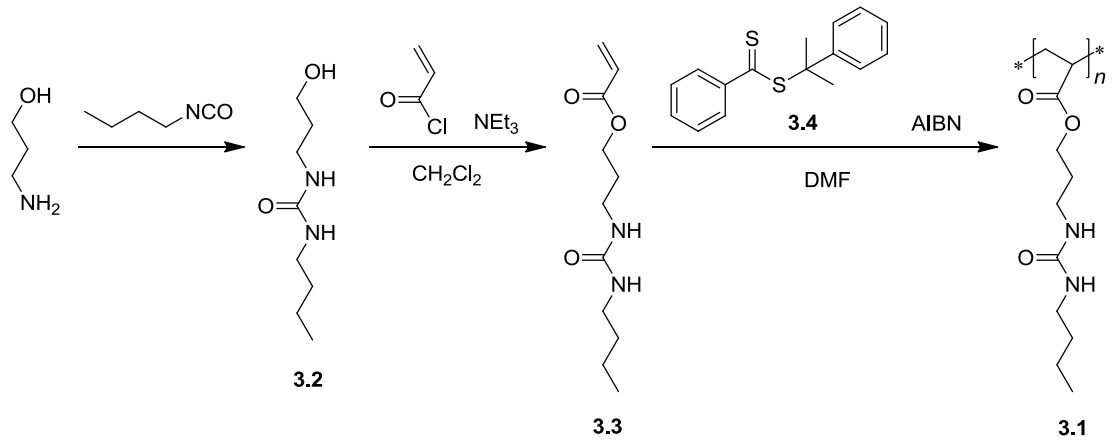


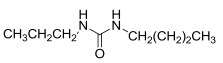
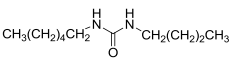
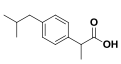
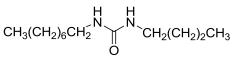
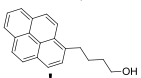
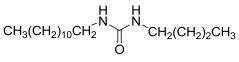
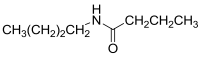
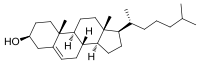
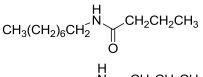
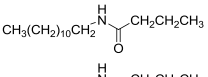
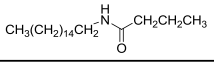
Table 3_1. Solubility test of urea polymer **3.1** in various organic solvent at room temperature (100 gL^{-1})

Solvent	Solubility	Solvent	Solubility
Acetonitrile (ε = 37.5)	Insoluble	1,2-Dichloroethane (DCE) (ε = 10.4)	Insoluble
Methanol (ε = 33.0)	Soluble	THF (ε = 7.5)	Insoluble
Ethanol (ε = 24.6)	Soluble	Ethyl Acetate (ε = 6.4)	Insoluble
Acetone (ε = 20.6)	Insoluble	Toluene (ε = 2.4)	Insoluble
1-Propanol (ε = 20.5)	Soluble	Benzene (ε = 2.3)	Insoluble
1-Hexanol (ε = 13.3)	Soluble	*n*-Hexane (ε = 2.0)	Insoluble

3.2.2. Solubility Property of 3.1 in 1,2-Dichloroethane in the Presence of Hydrogen Bonding Molecules

Changes in the solubility of **3.1** were investigated by naked-eyes in DCE as the poor solvent in the presence of various small molecules as listed in Table 3_2. As the amount of the small molecule was gradually increased, 25 gL^{-1} of **3.1** (0.11 M urea units in the polymer) in DCE turned to be insoluble to soluble except acetonitrile and hexane, which unchanged the polymer solubility. Those results indicate that those small molecules functioned as effectors which disturb the hydrogen bonds among the urea groups of the polymer chain and resulted in increase of the solubility of **3.1**.

Table 3_2. Thermal behavior of polymer **3.1** (25 gL^{-1} (0.11 M)) in the presence of small molecules in DCE.

Entry	Additives	Solubility	Entry	Additives	Solubility	Entry	Additives	Solubility
1	None	Insoluble	11		UCST (32 °C, 5.8 eq.)	19		UCST (28 °C, 0.1 eq.)
2	CH_3CN	Insoluble	12		UCST (44 °C, 3.5 eq.)	20		UCST (39 °C, 0.6 eq.)
3	$CH_3(CH_2)_4CH_3$	Insoluble	13		UCST (37 °C, 3.1 eq.)	21		LCST (55 °C, 4.7 eq.)
4	$CH_3(CH_2)_4COOH$	UCST (41 °C, 1.6 eq.)	14		UCST (41 °C, 2.4 eq.)	22		LCST (50 °C, 9.5 eq.)
5	$CH_3(CH_2)_6COOH$	UCST (40 °C, 1.2 eq.)	15		UCST (33 °C, 8.5 eq.)	23		LCST (57 °C, 4.7 eq.)
6	$CH_3(CH_2)_{10}COOH$	UCST (44 °C, 0.8 eq.)	16		UCST (63 °C, 6.3 eq.)	24		UCST (51 °C, 3.2 eq.)
7	$CH_3(CH_2)_{14}COOH$	UCST (40 °C, 0.6 eq.)	17		LCST (51 °C, 5.9 eq.)	25		UCST (76 °C, 2.8 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, 5.0 eq.)	18		LCST (47 °C, 5.9 eq.)			

* Concentration of small molecules and phase transition temperatures are given in parentheses.

The temperature dependence of the solubility of **3.1** in DCE in the presence of effectors was investigated. For examples, Figure 3_3a shows the drastic transmittance change of **3.1** in the presence of 5 equiv of 1-dodecanol in DCE upon heating, and the LCST-type phase transition was observed at 43 °C as a cloud point. In addition, the solution returned to be clear with decreasing temperature again. This result showed that reversible LCST behavior was accomplished by using the ternary system as expected. On the other hands, transmittance of polymer **3.1** with 3 equiv of *N*,*N*'-butyloctylurea in DCE drastically increased with increasing temperature, and UCST-type phase transition was observed at 37 ^{o}C as the cloud point (Figure 3_3b). The thermo-sensitive phase behavior of this solution was reversible, after the repeated cycles of cooling and heating.

The transmittance measurements of **3.1** in DCE containing 1-dodecanol or *N*,*N*'-butyloctylurea in a variety of concentrations were carried out at the constant concentration of **3.1** (25 gL^{-1}) (Figure 3_4). In the case of 1-dodecanol, the cloud point of LCST gradually increased as plotted in Figure 3_4a, when the effector concentration increased. In contrast, the cloud point of UCST decreased with increasing concentration of *N*,*N*'-butyloctylurea (Figure 3_4b). Both two phenomena indicated that the solubility of **3.1** increased with increasing effector concentration and that the effectors play an important role of increase of solubility of the polymer. *N*,*N*'-Butyloctylurea had a stronger effect on the solubility than 1-dodecanol, because much smaller amount of the effector was required for inducing the thermo-sensitive behavior.

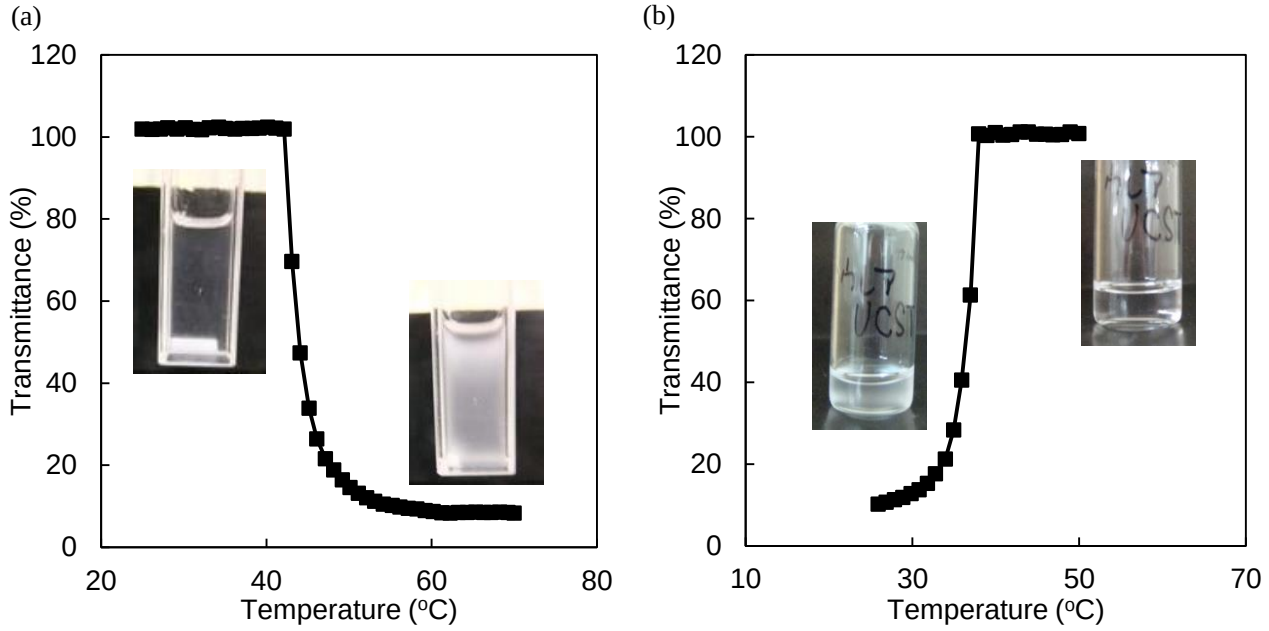


Figure 3_3. Transmittance of **3.1** (25 gL^{-1}, 0.11 M urea units in the polymer) as a function of temperature in the presence of (a) 1-dodecanol (0.55 M) or (b) *N*,*N*'-butyloctylurea (0.31 M) in DCE. The data were recorded at 700 nm at heating and cooling rates of 1 ^{o}C/min.

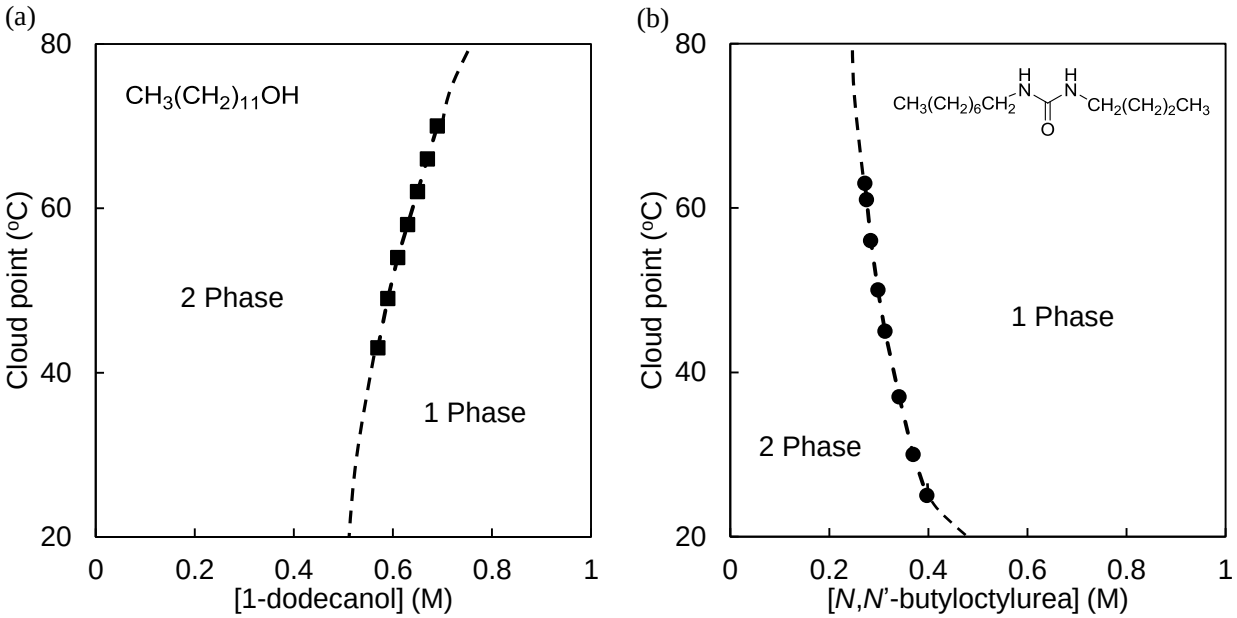


Figure 3_4. Dependence of the cloud point of **3.1** in DCE on the concentration of the (a) 1-dodecanol or (b) *N*,*N*'-butyloctylurea. [**3.1**] = 25 gL^{-1}.

Thermo-sensitiveness and their cloud points of the DCE solution of **3.1** in the presence of the effectors listed in Table 3_2. Addition of amides with long alkyl chain and mono-alcohols such as 1-dodecanol, pyrenebutanol, and cholesterol resulted in the LCST-type phase behavior. In contrast, UCST-type phase behavior was observed upon addition of aliphatic carboxylic acids, dialkylureas, amides with alkyl chain, tetrahexylammonium bromide, and polyhydroxy compounds. For a series of aliphatic amides with different alkyl chain lengths, shorter and longer alkylamides exhibited the UCST-type and LCST-type type phase behavior, respectively. Furthermore, polyhydroxy compounds such as neopentyl glycol and triethanolamine exhibited UCST-type phase separation, indicating that increasing the number of hydroxyl groups changed from the LCST-type phase behaviors to the UCST-type phase ones. These results presumably indicated that the strength of the hydrogen bonding to the urea groups played a key role in controlling the thermosensitivity. The effectors that could interact more strongly tended to induce the UCST-type phase behavior, and those with more weakly interacting induced the LCST-type behavior.

3.2.3. Estimate the Association Constant between the Urea Groups and the Effectors

To estimate the binding ability between the effectors and urea moieties, ^{1}H NMR titration of monomer **3.3** were performed in DCE-d_4 in the presence of the effectors such as tetrahexylammonium bromide, 1-dodecanoic acid, *N*-butylpropylamide, and *N*-octylpropylamide for

the UCST-type phase behavior and *N*-dodecylpropylamide, *N*-hexadecylpropylamide, and 1-dodecanol for the LCST-type phase behavior. Although there were dissimilarities between polymer **3.1** and monomer **3.3**, influence on thermo-sensitive behavior of chemical structure can qualitatively be estimated. ^{1}H NMR spectra of the system were carried out at the constant concentration 5 mM of **3.3** at 30 ^{o}C.

Benesi-Hildebrand equation

$$\frac{1}{\Delta\delta_{obs}} = \frac{1}{\Delta\delta K_a} * \frac{1}{[\mathrm{E}]_0} + \frac{1}{\Delta\delta} \qquad \text{equation 3\_1}$$

$$\Delta\delta = \Delta\delta_{max} - \Delta\delta_{min}$$

$\Delta\delta_{obs}$: observed change of chemical shift of N-H, K_a: association constant, $[\mathrm{E}]_0$: initial concentration of effector
$\Delta\delta_{max}$: chemical shift of N-H hydrogen-bonded, $\Delta\delta_{min}$: chemical shift of N-H at diluted

In all cases, with increasing the amount of the effectors, the urea N−H signal shifted to lower magnetic field, but the shift values for each effector widely differed (Figure 3_9-3_15, Table 3_5-3_11 in Experimental section). The lower shifts were attributed to hydrogen bonding between the urea group of **3.3** and the hydrogen-bonding group of effectors. The association constants (K_a) for the **3.3**/effector pairs were determined using Benesi−Hildebrand plots[7] of $1/\Delta\delta_{obs}$ versus $1/[\mathrm{E}]_0$, where $\Delta\delta_{obs}$ is the variation of chemical shift and $[\mathrm{E}]_0$ is initial concentration of the effector (equation 3_1, Figure 3_5, Table 3_3). Larger K_a values (>50 M^{-1}) were observed in the presence of tetrahexylammonium bromide and 1-dodecanoic acid, which induced the UCST-type phase behavior. On the other hand, 1-dodecanol showed a smaller K_a (<1 M^{-1}) and induced the LCST-type phase behavior. In the case of dialkylsubstituted amides, which showed intermediate K_a values (1−3 M^{-1}), the thermal phase behavior depended on their alkyl chain lengths. The hydrogen bonding groups and the balance between hydrophobicity and hydrophilicity governed the thermo-sensitivity of the effectors with an intermediate K_a value.

On the basis of these findings, the author envisions the following mechanism: When the polymer−effector interactions are weaker than the polymer−polymer interactions (e.g., for alcohols and amides with long alkyl chains), heating preferentially breaks the polymer−effector interactions, and the polymer turns to be insoluble even in the presence of the effectors. 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-type phase behaviors. These results showed that thermo-sensitivity of polymer solution of **3.1** in DCE can be precisely controlled by hydrogen bonding ability of the effectors.

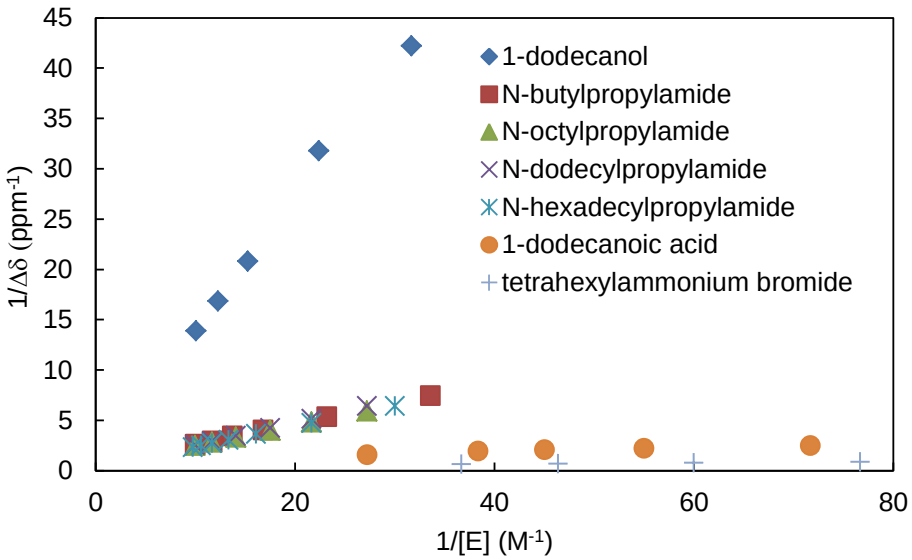


Figure 3_5. Benesi-Hildebrand plots based on the chemical shift (N-H) in various effectors concentration in DCE-d_4 (500 Mz, 30 ^{o}C).

Table 3_3. association constants K_a and thermo-sensitivity of effectors.

Effector	K_a (M^{-1})	Thermo-sensitivity
tetrahexylammonium bromide	66	UCST
1-dodecanoic acid	80	UCST
N-butylpropylamide	2.9	UCST
N-octylpropylamide	2.5	UCST
N-dodecylpropylamide	1.3	LCST
N-hexadecylpropylamide	1.7	LCST
1-dodecanol	0.5	LCST

3.2.4. Quaternary System

To develop a desirable thermo-sensitive system, the author investigated the quaternary systems using two kinds of effectors, one inducing the LCST-type phase behavior and the other doing the UCST-type phase behavior. The solubility of **3.1** (25 gL^{-1}) was investigated in the presence of both 1-dodecanol for the LCST-type phase behavior and *N*,*N*′-butyloctylurea for the UCST-type phase behavior in DCE. When the amount of *N*,*N*′-butyloctylurea increased, the UCST-type phase behavior was easily observed, and the LCST-type phase behavior was caused by increasing of the amount of 1-dodecanol. Amazingly, when appropriate amounts of 1-dodecanol (0.34 M) and *N*,*N*′-butyloctylurea (0.09 M) were used, both LCST-type and UCST-type phase separation were

achieved in one sample as shown in Figure 3_6. Furthermore, the system exhibited reproducibility upon cooling and heating, indicating that the balance of hydrogen bonding between **3.1** and the two additives should originate to this phenomena.

To provide an in-depth understanding for the quaternary system, the systematic study was carried out for a wide ranges of concentrations of *N*,*N*′-butyloctylurea and 1-dodecanol for preparation of phase diagram. The phase diagram of the solubility of **3.1** shown in Figure 3_7, it distinctly divided into 5 types, LCST-type, UCST-type, and LCST+UCST-type phase behavior, insoluble, and soluble (5-80 ^{o}C). 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 3_8, Table 3_4). It is well known that inducing both LCST and UCST phase behavior at ambient temperature is difficult.[8] Nevertheless, these data suggest that our fundamental molecular design is applicable to the coincidence of the two transitions.

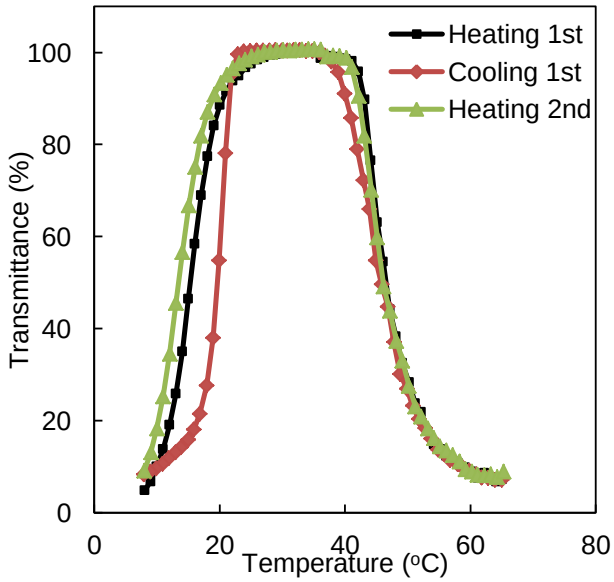


Figure 3_6. Transmittance of **3.1** (25 gL^{-1}) as a function of temperature in the presence of 1-dodecanol (0.34 M) and *N*,*N*'-butyloctylurea (0.09 M) in DCE. The data were recorded at 700 nm at heating and cooling rate of 1 ^{o}C min^{-1}

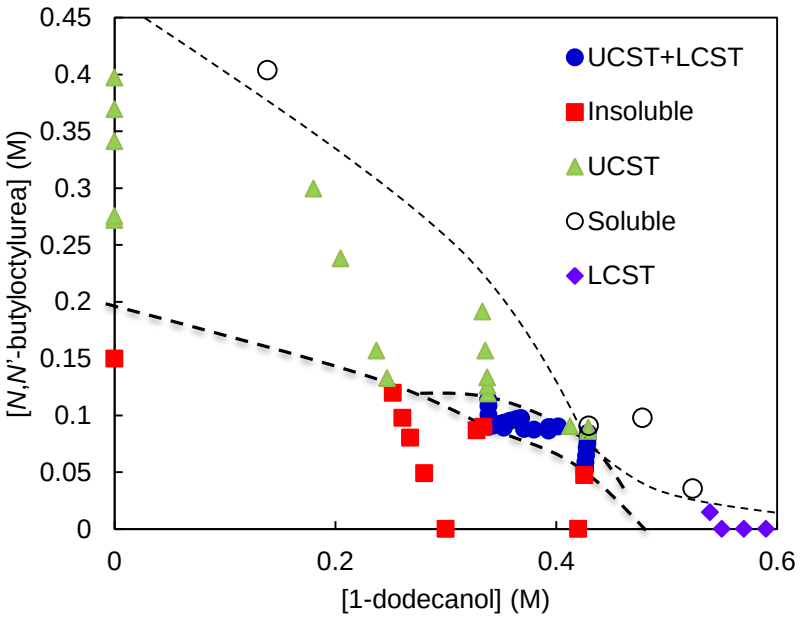


Figure 3_7. Distribution of solubility of **3.1** in DCE in the presence of 1-dodecanol and *N*,*N*'-butyloctylurea between 5 and 80 °C. The dashed lines represent the assumed boundaries between types of thermo-sensitivity.

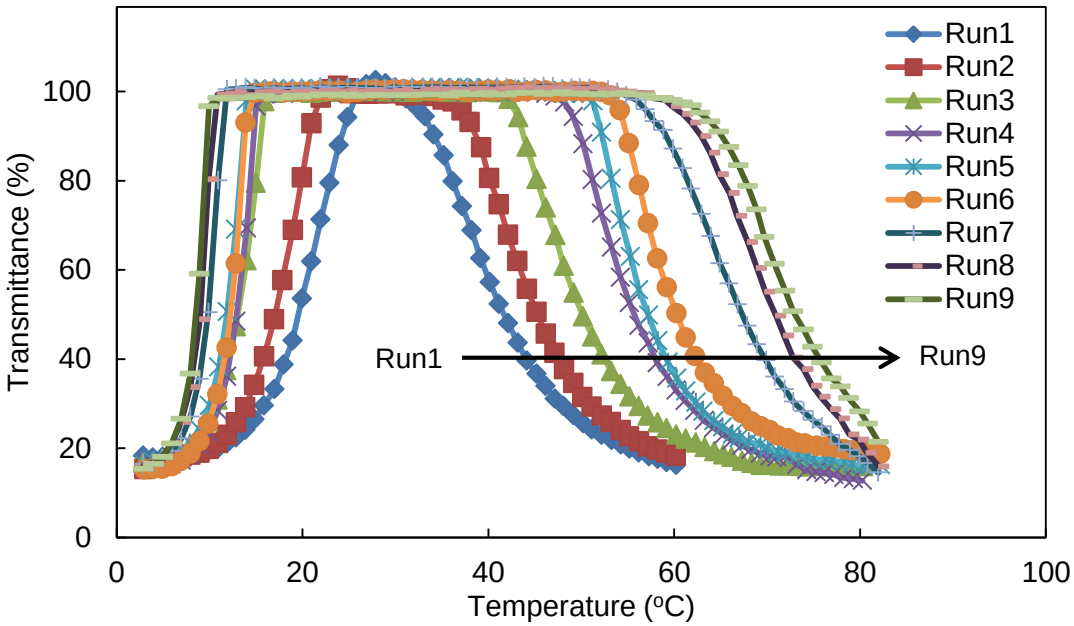


Figure 3_8. Temperature dependence of transmittance of polymer **3.1** upon addition of two kinds of small molecules in DCE at various concentration of small molecules ([**3.1**]: 25 gL^{-1}, scan rate: 1 °C min^{-1})

Table 3-4. The phase transition temperatures of polymer **3.1** in DCE upon addition two kinds of small molecules.

Run	1-Dodecanol (M)	*N*,*N*'-Butyloctyl urea (M)	Sum of small molecules (M)	UCST (^{o}C)	LCST (^{o}C)
Run 1	0.3391	0.0900	0.4291	24	35
Run 2	0.3433	0.0911	0.4344	20	39
Run 3	0.3476	0.0923	0.4399	15	44
Run 4	0.3520	0.0934	0.4454	14	50
Run 5	0.3565	0.0946	0.4511	13	53
Run 6	0.3588	0.0952	0.4540	13	55
Run 7	0.3635	0.0965	0.4600	11	60
Run 8	0.3659	0.0971	0.4630	10	63
Run 9	0.3683	0.0977	0.4660	9	66

3.3. Conclusion

In conclusion, the author has demonstrated thermo-sensitiveness by employing the polymer **3.1** in DCE with the addition of effectors on the basis of the author's design. The thermo-sensitivity of **3.1** was induced by using hydrogen bonding as the non-covalent bond for polymer-polymer and polymer-effector interactions. This is the first example to developing reversible and precisely controllable thermo-sensitiveness of supramolecular complexes between the polymer and effectors in non-aqueous media using hydrogen bonds. The hydrogen-bonding ability of the effector substantially governs the thermo-sensitivity, resulting in facile switching between LCST-type and UCST-type phase behaviors and also in their additivity (i.e., their coincidence). To date, few examples of LCST polymers in organic solvents have been reported[9] because of the lack of molecular design, and they were found accidentally or by through laborious trial and error. More generally, effectors having high affinities for polymers induce UCST-type phase behavior, because of breaking the interactions between the polymers, whereas those having low affinities cannot interact with the polymers at high temperature, resulting in LCST-type phase behavior. In chapter 2, **PPMA** showed only LCST-type phase behavior, because of relative weakly CT interaction. Utilizing the hydrogen bonds whose strength can be tuned easily, exotic and exciting thermo-sensitive behaviors were accomplished.

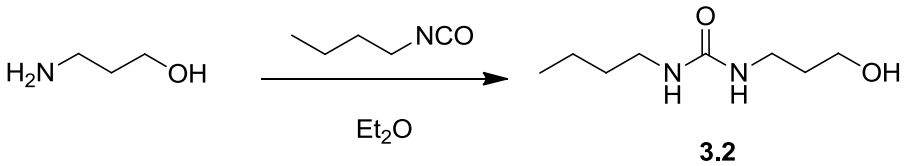
3.4. Experimental Section

Instrumentation

All synthetic experiments were carried out under nitrogen atmosphere. ^{1}H and ^{13}C NMR measurements were recorded on a Bruker AV300 and JEOL JNM-AL300 instruments at 300 MHz, and Bruker AV500 instrument at 500 MHz at room temperature. Size exclusion chromatography (SEC) was carried out on a SHIMADZU LC-9A system (SHODEX KD-805 and K-804 column) with a SHIMADZU RID-10A refractive index detector using DMF (10 mM LiBr) as an eluent, after calibration with the standard poly(ethylene oxide) (PEO) samples. UV-vis spectra were recorded on a JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. Fourier transform infrared (FTIR) spectra were observed with a JASCO FTIR-4100 spectrometer. Elemental analysis and electron spray ionization mass spectroscopy were performed at the Creative Research Institution of Hokkaido University.

Materials All synthetic experiments were carried out under nitrogen atmosphere. Unless stated otherwise, all reagents were obtained from commercial sources and used without further purification. Cumyl dithiobenzoate (**3.4**) was synthesized and characterized according to the literature.[10]

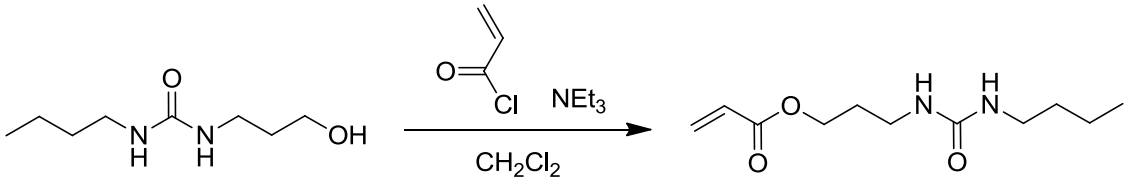
***N*-butyl-*N'*-(3-hydroxypropyl)-urea (3.2)**[4]



3.2

n-Butyl isocyanate (9.91 g, 100 mmol) was added at vigorous stirring to a solution of 3-amino-1-propanol (7.51 g, 100 mmol) in dry diethyl ether (45 mL). The reaction mixture was stirred for 1 h at room temperature, and filtered off. The resulting solid was washed diethyl ether and obtained **3.2** as white powder (16.98 g, 97.5 %). ^{1}H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.) δ (ppm) 0.92 (t, *J*=7.2 Hz, 3H, -C*H*$_3$), 1.41-1.52 (m, 2H, -C*H*$_2$-), 1.65 (quin, *J*=5.8 Hz, 2H, -C*H*$_2$-), 3.15 (q, *J*=6.6 Hz, 2H, -C*H*$_2$-), 3.35 (q, *J*=6.0 Hz, 2H, -C*H*$_2$-), 3.65 (q, *J*=5.7 Hz, 2H, -C*H*$_2$-), 3.77 (t, *J*=6.2 Hz, 1H, O*H*), 4.71 (s, 1H, N*H*), 4.90 (s, 1H, N*H*).

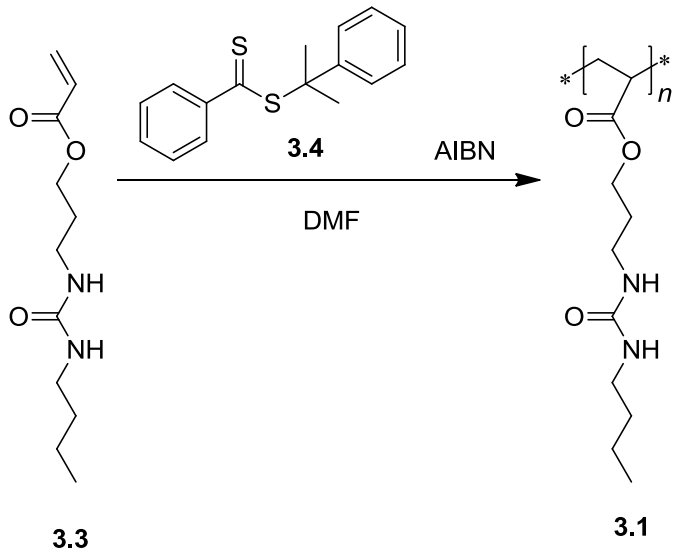
2-(3-Butylureido)propyl acrylate (**3.3**)



3.2 **3.3**

To a solution of **3.2** (8.71 g, 50 mmol) and triethylamine (5.57 g, 55 mmol) in dry CH_2Cl_2 (150 mL), acryloyl chloride (4.98 g, 55 mmol) was slowly added at 0 ^oC. After the mixture was stirred for additional 3 h at room temperature, it was poured into the water. The reaction mixture was washed with $NaHCO_3$ aq., water, dried over anhydrous Na_2SO_4, followed by evaporation to dryness. The residue was purified by column chromatography (CH_2Cl_2/acetone= 9:1 (*v*/*v*)) to obtain **3.3** as a white solid (6.44 g, 56 %). ^1H NMR (300 MHz, $CDCl_3$, TMS standard, r.t.) δ (ppm) 0.92 (t, *J*=7.2 Hz, 3H, -C*H*$_3$), 1.27-1.40 (m, 2H, -C*H*$_2$-), 1.41-1.54 (m, 2H, -C*H*$_2$-), 1.88 (quin, *J*=6.3 Hz, 2H, -C*H*$_2$-), 3.15 (q, *J*=6.6 Hz, 2H, -C*H*$_2$), 3.27 (q, *J*=6.4 Hz, 2H, -C*H*$_2$), 4.26 (t, *J*=6.2 Hz, 2H, -C*H*$_2$-), 4.35 (s, 1H, N*H*), 4.70 (s, 1H, N*H*), 5.85 (dd, *J*=1.5, 10.2 Hz, 1H, alkene-*H*), 6.12 (dd, *J*=10.5, 17.4 Hz, 1H, alkene-*H*), 6.42 (dd, *J*=1.5, 17.1 Hz, 1H, alkene-*H*). FTIR (ATR, cm^{-1}): 3323.7, 2965.5, 2931.8, 2873.9, 1716.8, 1616.5, 1580.4, 1480.1, 1415.1, 1295.0, 1200.0, 1049.1, 983.0, 811.4. Anal. Calcd for $C_{11}H_{20}N_2O_3$: C 57.87, H 8.83, N 12.27, Found: C 57.82, H 8.83, N 12.27. HRMS (EI) Calcd for $C_{11}H_{20}N_2O_3$: m/z 228.1474, Found: m/z 228.1465.

Polymerization of 3.3 using 3.4 as the chain transfer agent



3.3 **3.1**

A solution of **3.3** (4.56 g, 20.0 mmol), **3.4** (10.9 mg, 0.04 mmol)[2] and AIBN (3.3 mg, 0.02 mmol) in DMF (3.0 mL) was prepared. The solution was transferred to ampule, degassed, with three

freeze-evacuate-thaw cycles, and sealed. The ampule was heated at 60 ^{o}C for 48 h. After the ampule was cooled, reaction mixture was reprecipitated with diethyl ether, filtered and dried to obtain **3.1** as a pale red solid (3.13 g). ^{1}H NMR (300 MHz, DMSO-d_6, TMS standard, r.t.): δ (ppm) 0.85 (t, J=6.9 Hz, 3H, -CH_3), 1.18-1.48 (m, 2H, -CH_2-), 1.53-1.74 (br, 2H, -CH_2-), 1.74-1.92 (br, 2H, -CH_2-), 2.02-2.39 (br, 2H, -CH_2-), 2.85-3.12 (br, 2H, -CH_2-), 3.77-4.10 (br, 2H, -CH_2-), 5.80-6.00 (br, 2H, NH). FTIR (ATR, cm^{-1}): 3324.7, 2957.3, 2930.8, 2871.5, 1728.9, 1624.7, 1568.8, 1446.8, 1240.5, 1160.0, 1052.9.

Transmittance measurement

Transmittance measurements were carried out by using JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. The cell length is 1 cm. The cloud points of the polymer solutions were determined from the transmittance at 700 nm on cooling at 1.0 ^{o}Cmin^{-1} as the temperature with 90% transmittance.

NMR titration

^{1}H NMR measurements were recorded on a Bruker AV500 instrument at 500 MHz in DCE-d_4 at 30 ^{o}C. The effectors concentrations are listed in Table 3_5-3_11. Concentration of monomer **3.3** is at constant of 5 mM.

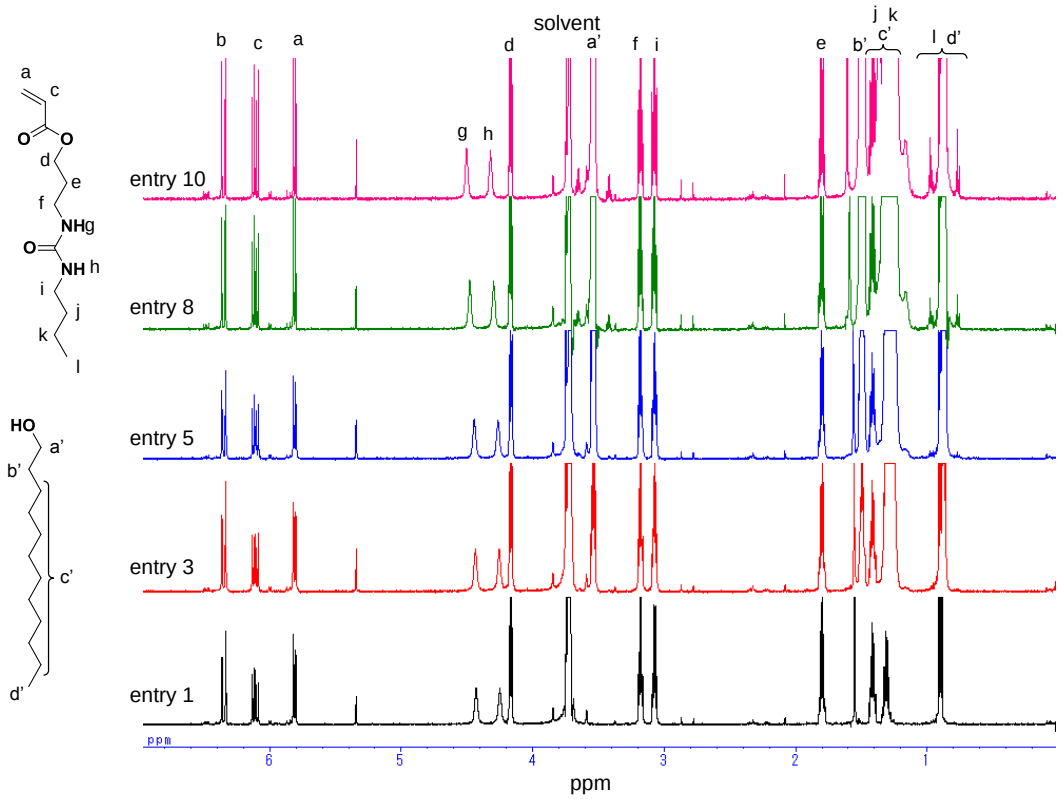


Figure 3_9. ^{1}H NMR spectra of **3.3** (5 mM) with 1-dodecanol at various concentration in DCE-d_4 (30 ^{o}C).

Table 3_5. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with 1-dodecanol in DCE -d_4 (30 ^{o}C).

	1-dodecanol (mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0.0	4.431	0.000
entry 2	2.5	4.432	0.001
entry 3	7.2	4.436	0.005
entry 4	11.8	4.438	0.007
entry 5	20.2	4.446	0.014
entry 6	31.6	4.445	0.014
entry 7	44.7	4.463	0.032
entry 8	65.5	4.479	0.048
entry 9	81.5	4.491	0.060
entry 10	99.4	4.503	0.072

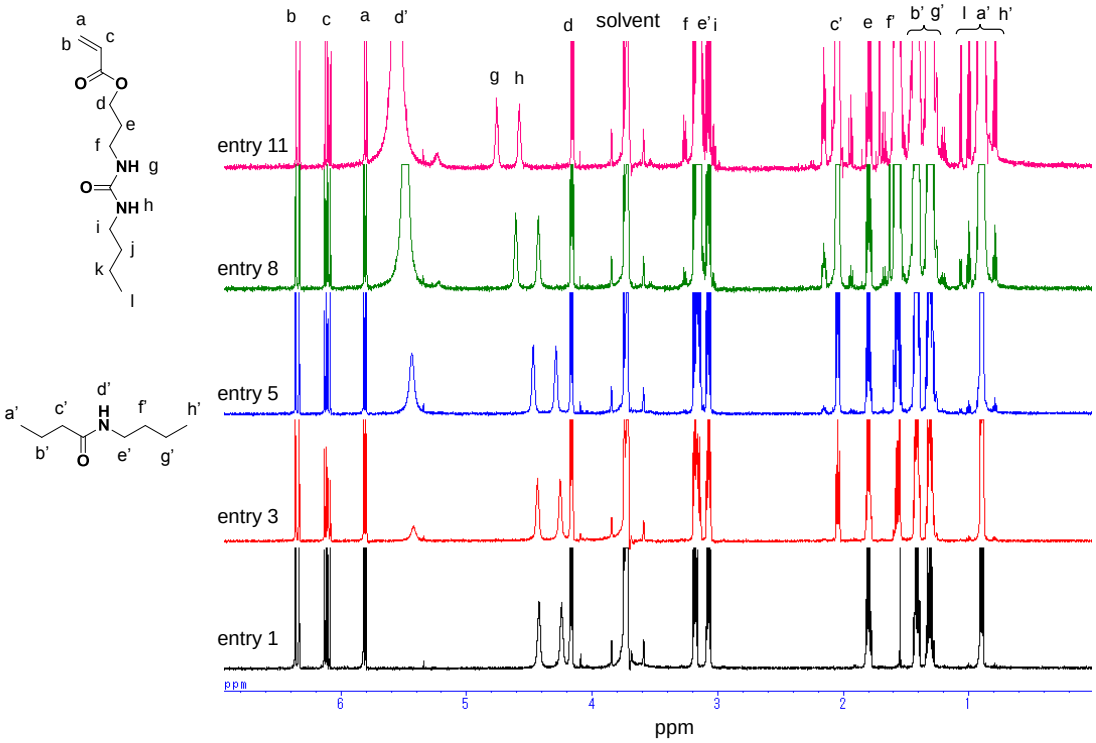


Figure 3_10. ^{1}H NMR spectra of **3.3** (5 mM) with *N*-butylbutylamide at various concentration in DCE -d_4 (30 ^{o}C).

Table 3_6. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with *N*-butylbutylamide in DCE -d_4 (30 ^{o}C).

	N-butylbutylamide (mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0.0	4.423	0.000
entry 2	0.5	4.428	0.005
entry 3	2.5	4.436	0.013
entry 4	4.9	4.447	0.024
entry 5	9.5	4.470	0.047
entry 6	18.2	4.508	0.085
entry 7	29.8	4.557	0.134
entry 8	43.1	4.610	0.187
entry 9	59.6	4.672	0.249
entry 10	73.0	4.713	0.290
entry 11	85.7	4.762	0.339
entry 12	100.0	4.806	0.383

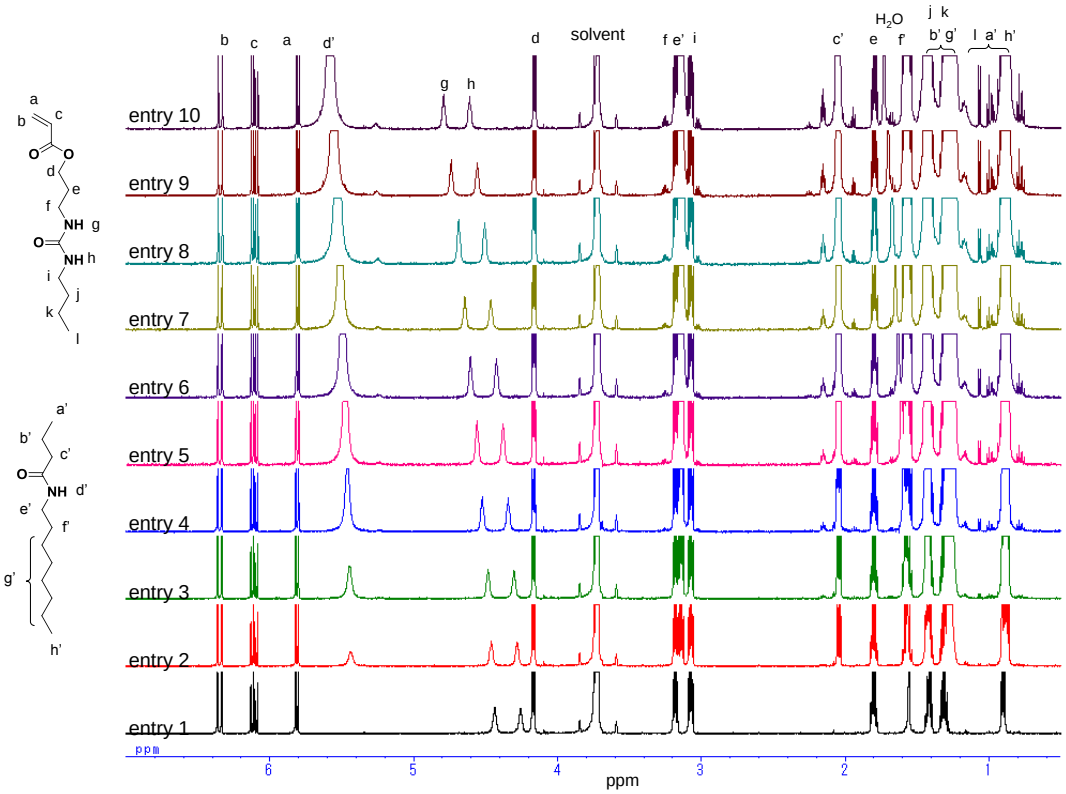


Figure 3_11. ^{1}H NMR spectra of **3.3** (5 mM) with *N*-octylbutylamide at various concentration in DCE –d_4 (30 ^{o}C).

Table 3_7. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with *N*-octylbutylamide in DCE -d_4 (30 ^{o}C).

	N-octylbutylamide (mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0	4.436	0
entry 2	4.9	4.460	0.024
entry 3	9.5	4.483	0.047
entry 4	18.2	4.523	0.087
entry 5	26.1	4.559	0.123
entry 6	36.7	4.605	0.169
entry 7	46.2	4.644	0.208
entry 8	57.1	4.687	0.251
entry 9	71.0	4.738	0.302
entry 10	85.7	4.791	0.355
entry 11	100.0	4.839	0.403

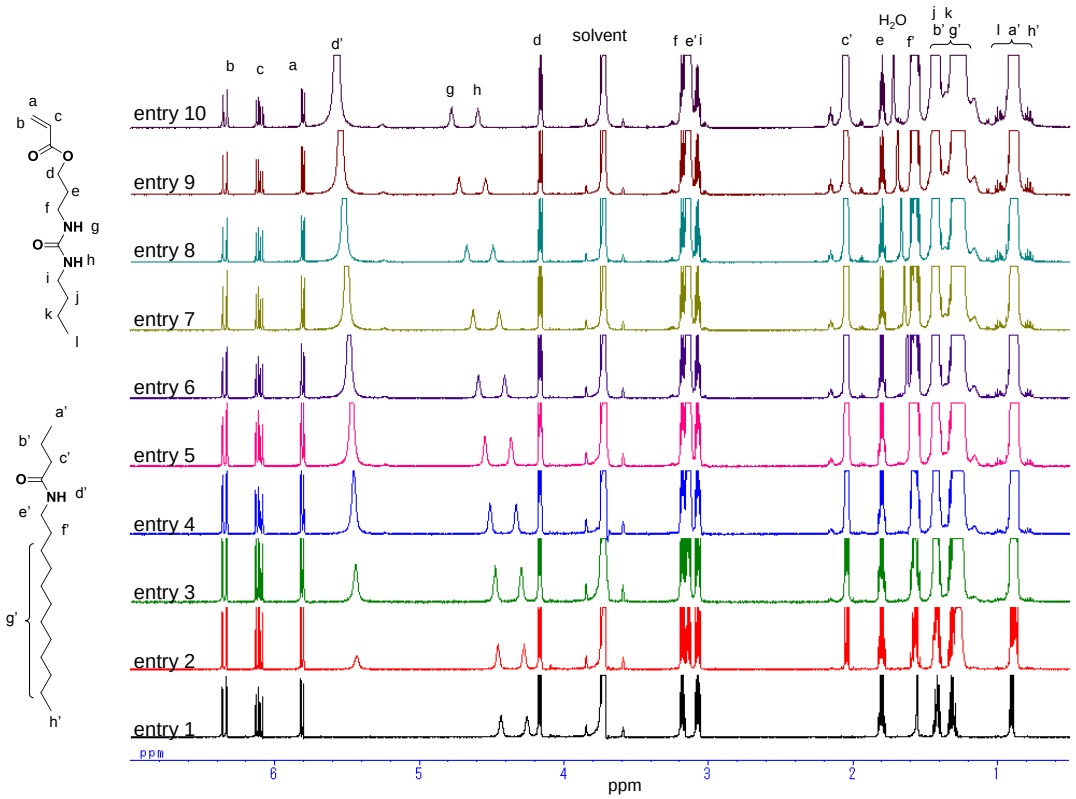


Figure 3_12. ^{1}H NMR spectra of **3.3** (5 mM) with *N*-dodecylbutylamide at various concentration in DCE -d_4 (30 ^{o}C).

Table 3_8. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with *N*-dodecylbutylamide in DCE -d_4 (30 ^{o}C).

	N-dodecylbutylamide (mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0	4.433	0
entry 2	4.9	4.455	0.022
entry 3	9.5	4.474	0.041
entry 4	18.2	4.510	0.077
entry 5	26.1	4.547	0.114
entry 6	36.7	4.589	0.156
entry 7	46.2	4.628	0.195
entry 8	57.1	4.671	0.238
entry 9	71.0	4.723	0.290
entry 10	85.7	4.776	0.343
entry 11	100.0	4.826	0.393

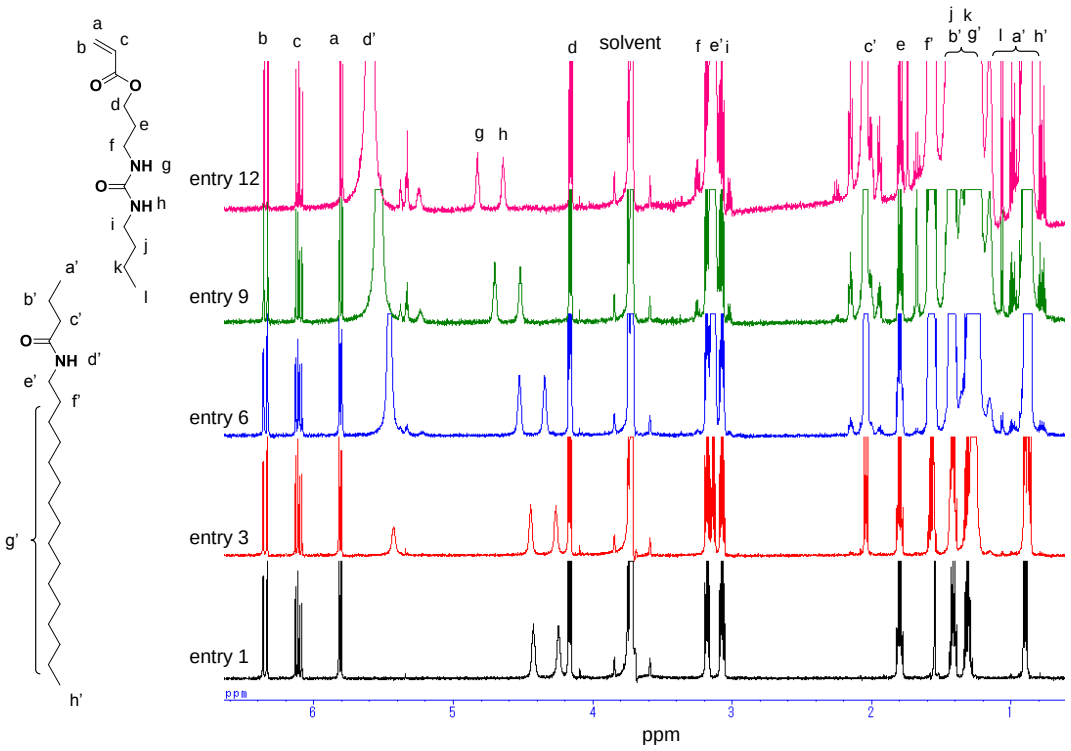


Figure 3_13. ^{1}H NMR spectra of **3.3** (5 mM) with *N*-hexadodecylbutylamide at various concentration in DCE -d_4 (30 ^{o}C).

Table 3_9. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with *N*-hexadodecylbutylamide in DCE -d_4 (30 ^{o}C).

	N-hexadodecylbutylamide(mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0.0	4.426	0.000
entry 2	2.5	4.436	0.010
entry 3	4.9	4.445	0.019
entry 4	9.5	4.467	0.041
entry 5	14.0	4.487	0.062
entry 6	22.2	4.527	0.102
entry 7	33.3	4.581	0.156
entry 8	46.2	4.637	0.212
entry 9	62.1	4.703	0.277
entry 10	75.0	4.755	0.330
entry 11	85.7	4.795	0.370
entry 12	94.7	4.827	0.402

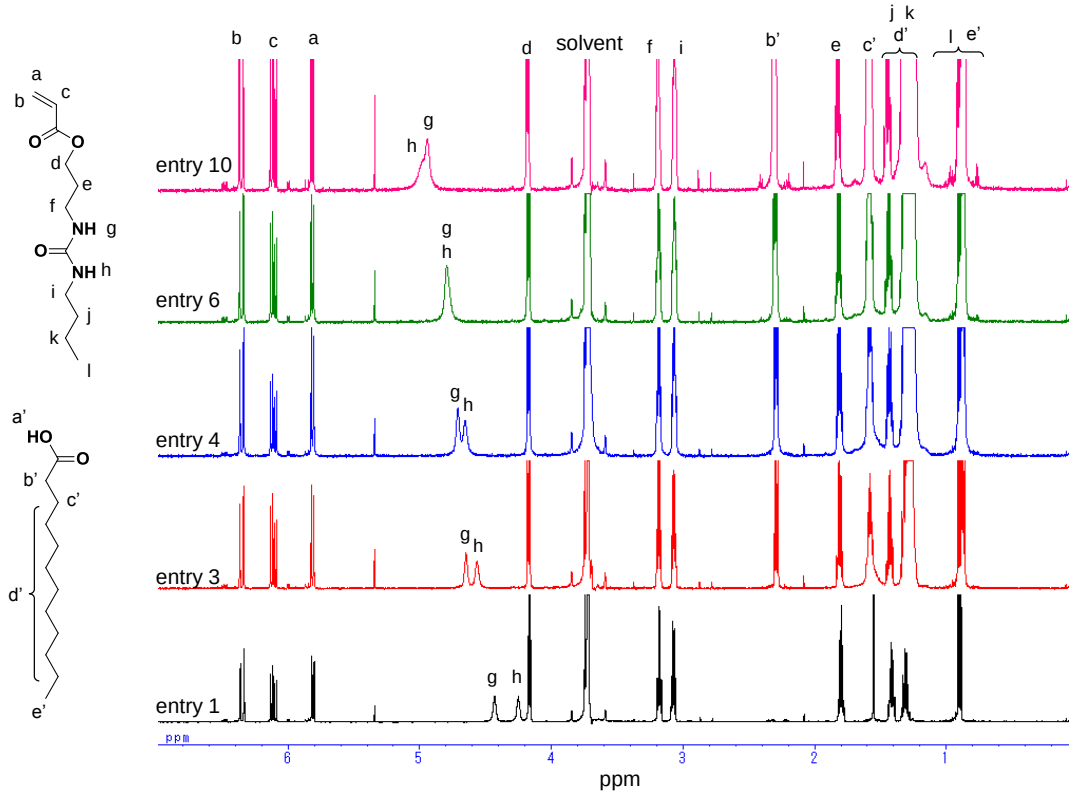


Figure 3_14. ^{1}H NMR spectra of **3.3** (5 mM) with 1-dodecanoic acid at various concentration in DCE -d_4 (30 ^{o}C).

Table 3_10. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with 1-dodecanoic acid in DCE -d_4(30 ^{o}C).

	1-dodecanoic acid (mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0.0	4.431	0.000
entry 2	2.5	4.559	0.128
entry 3	4.9	4.650	0.219
entry 4	7.2	4.712	0.281
entry 5	9.5	4.761	0.330
entry 6	11.8	4.797	0.365
entry 7	14.0	4.830	0.399
entry 8	18.2	4.880	0.449
entry 9	22.2	4.916	0.484
entry 10	26.1	4.942	0.511
entry 11	36.7	5.073	0.642

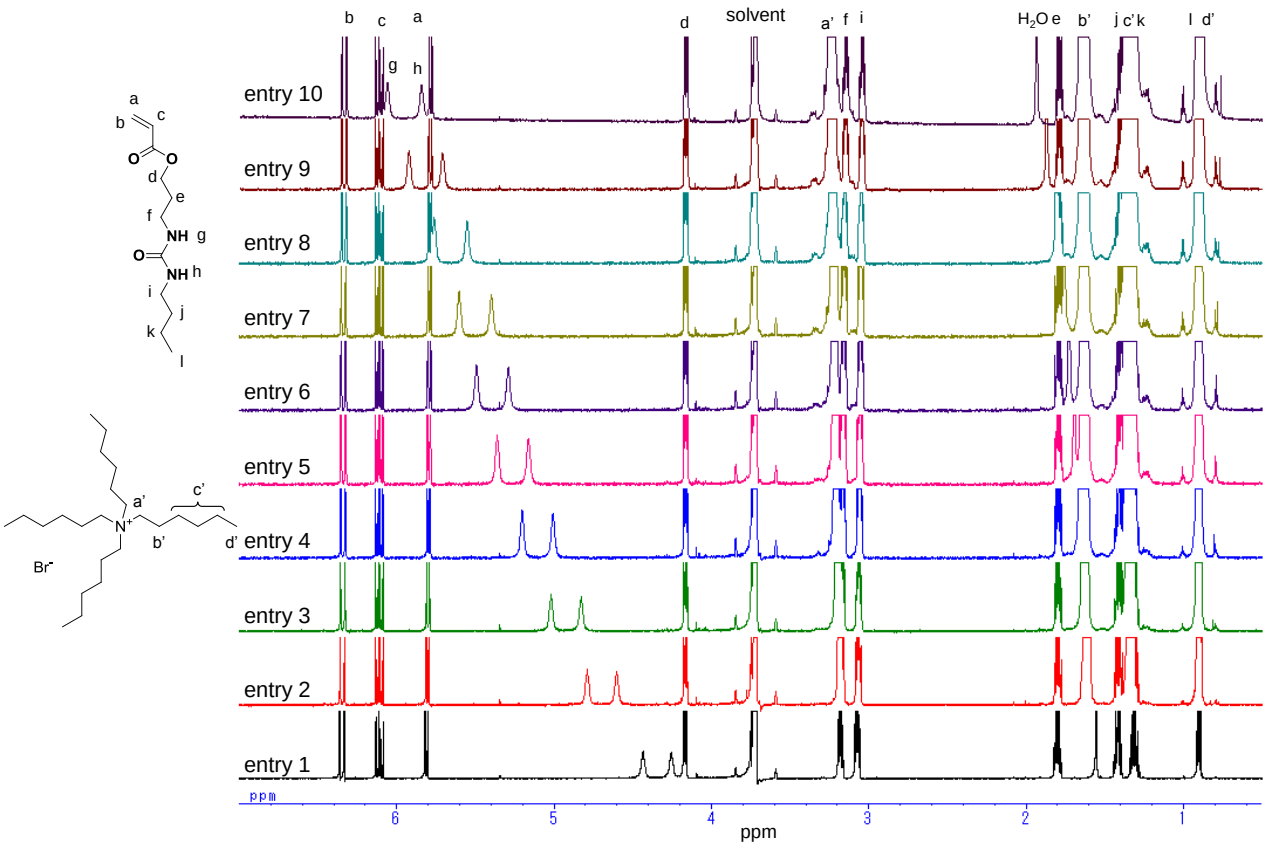


Figure 3_15. ^{1}H NMR spectra of **3.3** (5 mM) with tetrahexylammonium bromide at various concentration in DCE -d_4 (30 ^{o}C).

Table 3_11. Condition of ^{1}H NMR experiment of **3.3** (5 mM) with tetrahexylammonium bromide DCE -d_4 (30 ^{o}C).

	tetrahexylammonium bromide (mM)	chemical shift (ppm)	$\Delta\delta_{obs}$ (ppm)
entry 1	0	4.434	0
entry 2	2.4	4.789	0.355
entry 3	4.8	5.019	0.585
entry 4	7.0	5.202	0.768
entry 5	9.1	5.362	0.928
entry 6	11.1	5.494	1.060
entry 7	13.0	5.604	1.170
entry 8	16.7	5.762	1.328
entry 9	21.6	5.922	1.488
entry 10	27.3	6.059	1.625

3.6. Reference

1) a) Van Gorp, J. J.; Vekemans, J. J. M.; Meijer, E. W. *J. Am. Chem. Soc.* **2002**, *124*, 14759-14769. b) Boileau, S.; Bouteiller, L.; Laupretre, F.; Lortie, F. *New J. Chem.* **2000**, *24*, 845-848. c) Bouteiller, L.; Colombani, O.; Lortie, F.; Terech, P. *J. Am. Chem. Soc.* **2005**, *127*, 8893-8898. d) Brocorens, P.; Linares, M.; Guyard-Duhayon, C.; Guillot, R.; Andrioletti, B.; Suhr, D.; Isare, B.; Lazzaroni, R.; Bouteiller, L. *J. Phys. Chem. B* **2013**, *117*, 5379-5386. e) Lortie, F.; Boileau, S.; Bouteiller, L.; Chassenieux, C.; Deme, B.; Ducouret, G.; Jalabert, M.; Laupretre, F.; Terech, P. *Langmuir* **2002**, *18*, 7218-7222. f) Bellot, M.; Bouteiller, L. *Langmuir* **2008**, *24*, 14176-14182. g) Pensee, S.; Nouvel, N.; Guilleman, A.; Creton, C.; Boue, F.; Bouteiller, L. *Macromolecules* **2010**, *43*, 2529-2534.

2) a) Boiocchi, M.; Boca, L. D.; Gomez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507-16514. b) Pescatori, L.; Arduini, A.; Pochini, A.; Ugozzoli, F.; Secchi, A. *Eur. J. Org. Chem.* **2008**, *109*, 120. c) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369-370. d) Bryantsev, V. S.; Hay, B. P. *J. Am. Chem. Soc.* **2006**, *128*, 2035-2042. e) Nabeshima, T.; Saiki, T.; Iwabuchi, J.; Akine, S. *J. Am. Chem. Soc.* **2005**, *127*, 5507-5511. f) Gunnlaugsson, T.; Glynn, M.; Tocci, G. M.; Kruger, P. E.; Pferffer, F. M. *Coord. Chem. Rev.* **2006**, *250*, 3094.

3) Amemori, S.; Kokado, K.; Sada, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4174-4178.

4) Leonov, O. N.; Shcherbakov, V. M.; Devichensky, V. M.; Kryukova, L. Y.; Vorontsov, E. A.; Kuznetsov, S. L.; Kryukov, L. N. *Russ. J. Bioorg. Chem.* **2001**, *27*, 191.

5) Moad, G.; Chiefari, J.; Krstina, J.; Postma, A.; Mayadunne, R. T. A.; Rizzardo, E.; Thang, S. H. *Polym. Int.* **2000**, *49*, 993.

6) Jansen, J. F. G. A.; Dias, A. A.; Dorschu, M.; Coussens, B. *Macromolecules* **2003**, *36*, 3861-3873.

7) a) Benesi, H. A.; Hildebrand, J. H.; *J. Am. Chem. Soc.* **1949**, *71*, 2703-2707. b) Deranleau, D. A. *J. Am. Chem. Soc.* **1969**, *91*, 4050-4054.

8) a) Van Durme, K.; Rahier, H.; Van Mele, B. *Macromolecules* **2005**, *38*, 10155. b) Plamper, F. A.; Schmalz, A.; Ballauff, M.; Müller, A. H. E. *J. Am. Chem. Soc.* **2007**, *129*, 14538.

9) Seno, K.-I.; Kanaoka, S.; Aoshima, S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5724. (b) Mugisawa, M.; Ohnishi, K.; Sawada, H. *Langmuir* **2007**, *23*, 5848.

10) Guo, T. Y.; Liu, P.; Zhu, J. W.; Song, M. D.; Zhang, B. H. *Biomacromolecules* **2006**, *7*, 1196.

Chapter 4: Thermo-Sensitive Behavior of Lipophilic Polyelectrolyte Bearing Urea Units

4.1. Introduction

Modification of ionic groups, which are composed of hydrophilic ions such as CO_2^-, SO_3^-, Na^+, and K^+, into polymer chains has been generally utilized for dissolution of lipophilic polymers in water.[1] Solvation of water molecules and electrostatic repulsions among ion pairs enhance solubility of the resulting polymer. On the other hands, in the low-permittivity organic solvents, introduction of such hydrophilic ionic groups provide association of the polymer chain due to the strong electrostatic attraction among the ion pairs.[2] This is attributed to the low dissociation degree of the ion pairs or aggregations of the ions by dipole-dipole interaction in non-polar media, and a good contrast with easy dissociation in highly polar media such as water and DMF. Therefore, in order to enhance polymer solubility, bulky hydrophobic alkyl groups[3] or bulky lipophilic ionic groups should be entirely incorporated into the polymer chains instead of the hydrophilic ones.

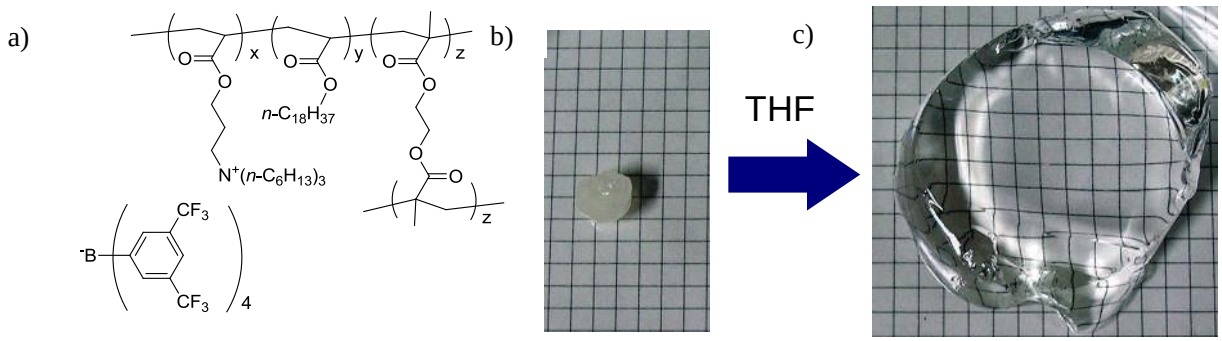


Figure 4_1. (a) Structure, (b) dried state, and (c) swelled state of super-absorbent polymer for low-permittivity solvent containing lipophilic ion pair.

Recently, our group reported that the ionic polymer gel with tetrahexylammonium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (THATFPB) as the lipophilic ion pairs acts as super-absorbent polymers for the non-polar solvents such as THF, dichloromethane and 1,2-dichloroethane (Figure 4_1).[4] This lipophilic ion pair covalently bonded to the gel can easily ionize under these conditions, and the electrostatic repulsion among ones and good compatibility of the polymer chain expands polymer chains.[5] Dissociation of the lipophilic ion pairs in the non-polar solvents is attributed to large ion radius and lipophilic substituent groups surrounding the ionic core.[6] Therefore, introduction of the lipophilic ion pairs into a polymer chain allows

dissolution of the polymer chain in the non-polar solvents due to repulsion among the ionized ionic groups. In this chapter, the author demonstrated the attempt for dissolution of the polymer by introduction of their lipophilic ion pairs into highly aggregated polymer chain and the creation of UCST-type thermo-sensitive polymers in the non-polar solvents (Figure 4_2).

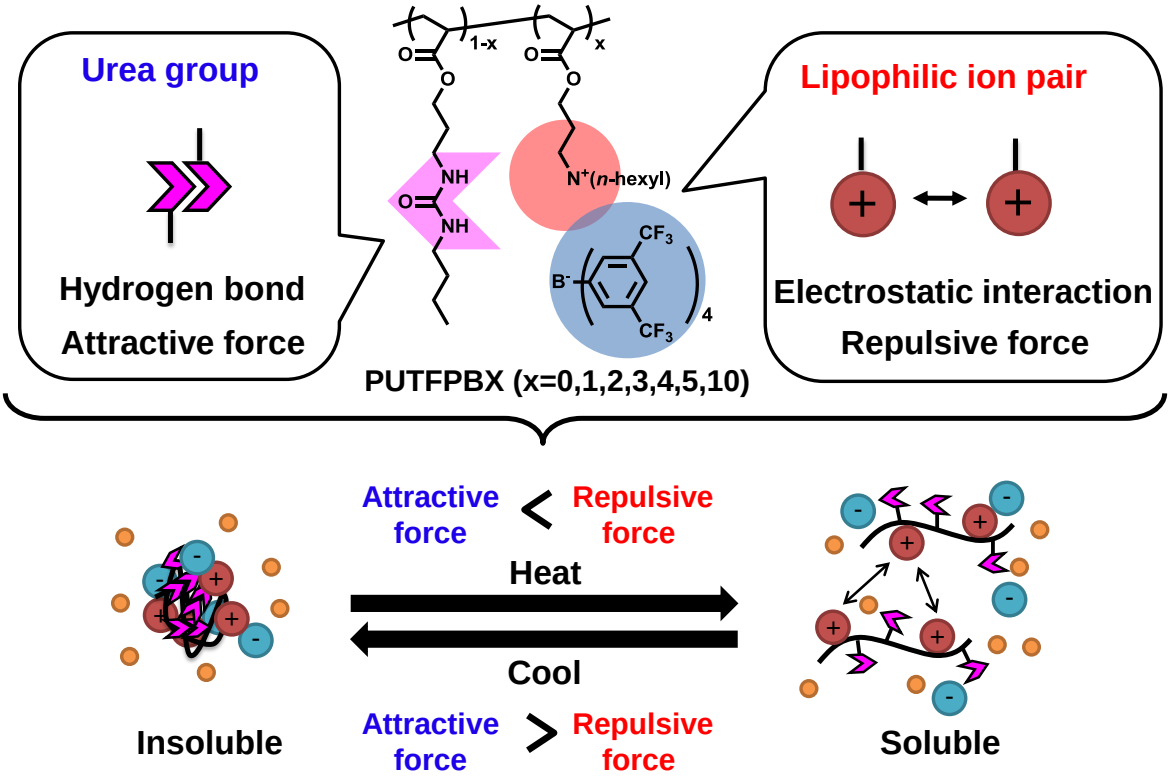


Figure 4_2. Concept of the UCST-type thermo-sensitive behavior of polymer containing urea group and lipophilic ion pair.

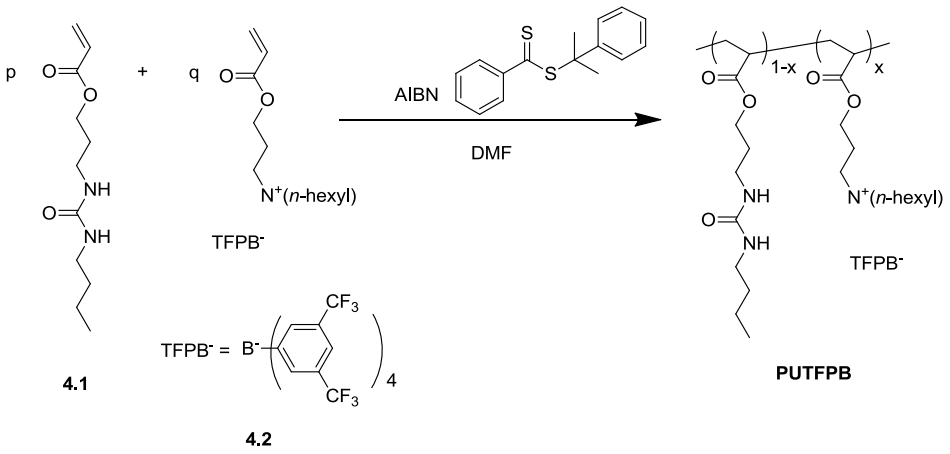
UCST-type thermo-sensitive polymers show drastic solubility change of the polymer solution from immiscibility to miscibility with increasing temperature in various medium.[7] As discussed the chapter 1, generally, the polymers have strong polymer-polymer and solvent-solvent interactions compared to polymer-solvent interactions.[8] And it is important for UCST-type phase behavior that the cleavage of the polymer-polymer interaction upon heating resulting in the diminishing of attractive force among the polymer chain.

In Chapter 3, the author demonstrated UCST-type phase behavior of the polymer having urea groups in organic solvents in the presence of small molecules "effectors" such as bromide anion, ureas, and carboxylic acids.[9] They were able to interact strongly with the urea groups of the polymer chain. The polymer-effector interactions disturbed the polymer-polymer interaction and induced increase of the polymer solubility. At an appropriate effector concentration, the attractive force among the polymer chains were partially weaken by the effectors, and then cleavage of

interaction among the polymer completely occurred upon heating, resulting in the UCST-type phase behavior in them. Therefore, the UCST-type phase behavior or dissolution (at r.t.) of the polymer should be induced not by addition of effectors but by modification of an appropriate ionic group, that prompts dissolution of the polymer.

Here, the author showed that preparation of the polymer (**PUTFPBs**) having the urea groups for attraction between the polymer chain and the lipophilic ion pairs for repulsion between the dissociated ion pairs in order to reveal the effect of lipophilic ion pairs for dissolution of the polymer and develop the UCST-type phase behavior (Figure 4_2, Scheme 1). In order to evaluate improvement of polymer solubility, the author synthesized a series of the urea polymer **PUTFPBs** with various mole fractions of TFPB ion pairs (Scheme 1).

Scheme 4_1. The structure and synthesis of polyelectrolyte with urea groups and lipophilic ion pairs.



4.2. Result and Discussion

4.2.1. Polymer Synthesis and Characterization

PUTFPBs were prepared by the copolymerization of monomer **4.1** having urea group and monomer **4.2** having TFPB ion pair with several different monomer ratios via chain-transfer polymerization[10] as outlined in Scheme 4_1. Both the monomers are prepared according to the previous reports.[4a, 9] The copolymerization ratios determined by ^{1}H NMR was found to be similar to the feed ratio as summarized in Table 4_1. Size-exclusion chromatography analysis of these polymers was carried out using 10 mM LiBr in DMF as an eluent solvent and polystyrene standards for calibration. The polydispersity indexes of all the polymers were relatively large in spite of chain-transfer polymerization. Perhaps, the acceleration of the propagation rate by strong hydrogen-bond between the monomer **4.1** affected chain-transfer reaction.[11]

Table 4_1. Characteristic data of **PUTFPBs**

	p	q	x[*1]	M_n[*2]	M_w[*2]	M_n/M_w[*2]
PUTFPB0	1.00	0.00	0.000	1.16×10^5	2.12×10^5	1.84
PUTFPB1	0.99	0.01	0.009	1.30×10^5	2.58×10^5	1.99
PUTFPB2	0.98	0.02	0.018	1.20×10^5	2.60×10^5	2.16
PUTFPB3	0.97	0.03	0.028	1.10×10^5	2.19×10^5	2.00
PUTFPB4	0.96	0.04	0.039	1.73×10^5	4.42×10^5	2.55
PUTFPB5	0.95	0.05	0.046	1.01×10^5	1.75×10^5	1.73
PUTFPB10	0.90	0.10	0.099	1.12×10^5	2.23×10^5	1.99

*1 The copolymerization ratios of the **PUTFPBs** was estimated by ^{1}H NMR in DMSO-d_6. *2 The number-average and weight-average molecular weights and molecular weight distribution were estimated by size-exclusion chromatography with polystyrene standards in DMF (10 mM LiBr).

4.2.2. Solubility of PUTFPBs in Organic Solvents

The solubility of these polymers was checked by direct observation using naked-eyes in various organic solvents as shown Table 4_2. In the protic solvents or highly polar solvents such as methanol, ethanol, DMF, and DMSO, all the **PUTFPBs** dissolved practically irrespective of the incorporation ratio of lipophilic ion pairs in the polymer chain, because these solvents were capable to form hydrogen bonds and inhibit the aggregation of the urea groups in the polymer chains. Indeed, it is known that self-association ability of ureas in those solvents is lower than in aportic solvents.[12] In the extremely low polar organic solvents ($\varepsilon < 6$) such as hexane, toluene, and chloroform, **PUTFPBs** were practically insoluble in spite of introduction of lipophilic ion pairs, because TFPB ion pairs hardly dissociated.[5] On the other hands, in aprotic and non-polar solvents such as acetone, 1,2-dichloroethane, and THF, solubility of **PUTFPBs** was changed from insoluble to soluble with increasing contents of the lipophilic ion pairs. In those solvents, the urea groups and TFPB ion pairs acted as an attractive functional group to aggregate the polymer chains and as a repulsive one to expand, respectively. When the latter repulsive interaction among the ionized ionic groups overcame the former attractive one among the urea groups by means of increase of TFPB component, the solubility of the polymer changed from immiscible to miscible. Amazingly, introducing small amount (2 mol%) of TFPB ionic group caused a large solubility change in these

solvents. There results indicated that the repulsive force prompted dissolution of the polymer chain even in non-polar solvents due to ionic dissociation.

Table 4-2. Solubility or thermo-sensitiveness of **PUTFPBs** in various organic solvent (25 gL^{-1}) between 25 ^{o}C and boiling point of solvents.

Solvent	**PUTFPB 0**	**PUTFPB 1**	**PUTFPB 2**	**PUTFPB 3**	**PUTFPB 4**	**PUTFPB 5**	**PUTFPB 10**
Acetonitrile (ε=37.5)	I	I	I	I	UCST (57) *2	UCST (52) *2	S
Methanol (ε=32.6)	S	S	S	S	S	S	S
Ethanol (ε=24.6)	S	S	S	S	S	S	S
Acetone (ε=20.6)	I	I	I	S	S	S	S
1,2-Dichloroethane (ε=10.4)	I	I	I	I	UCST (65)	UCST (48)	S
Dichloromethane (ε=8.9)	I	I	S	S	S	S	S
Toluene (ε=2.4)	I	I	I	I	I	I	I
Hexane (ε=1.9)	I	I	I	I	I	I	I

*I = insoluble, S = soluble, UCST = UCST-type phase behavior, Phase transition temperatures are given in parentheses. *2 Polymer concentration = 100 gL^{-1}.

In acetonitrile and 1,2-dichloroethane, the solution of **PUTFPB4** and **PUTFPB5** ware drastically increased with increasing temperature. And the UCST-type phase behaviors were observed reversibly by transmittance measurement (Figure 4_3, 4_4). The cloud points of **PUTFPB5** were lower than those of **PUTFPB4** in these solvents. This is because higher content of TPFB ion pairs induced dissolution of the polymer more easily due to electric repulsion among dissociated ion pairs. Since the self-association of the urea groups were strongly dependent on temperature,[12] but ionization of ion pairs was slightly affected by temperature, great decrease of the attractive force and

slight decrease of the repulsive force[13] occurred dissolution by heating and induced the UCST-type phase behavior. Therefore, the author assumed that the UCST-type phase behaviors were induced, when repulsive force among ionized TFPB ion pairs overwhelmed attractive force among the urea groups upon heating.

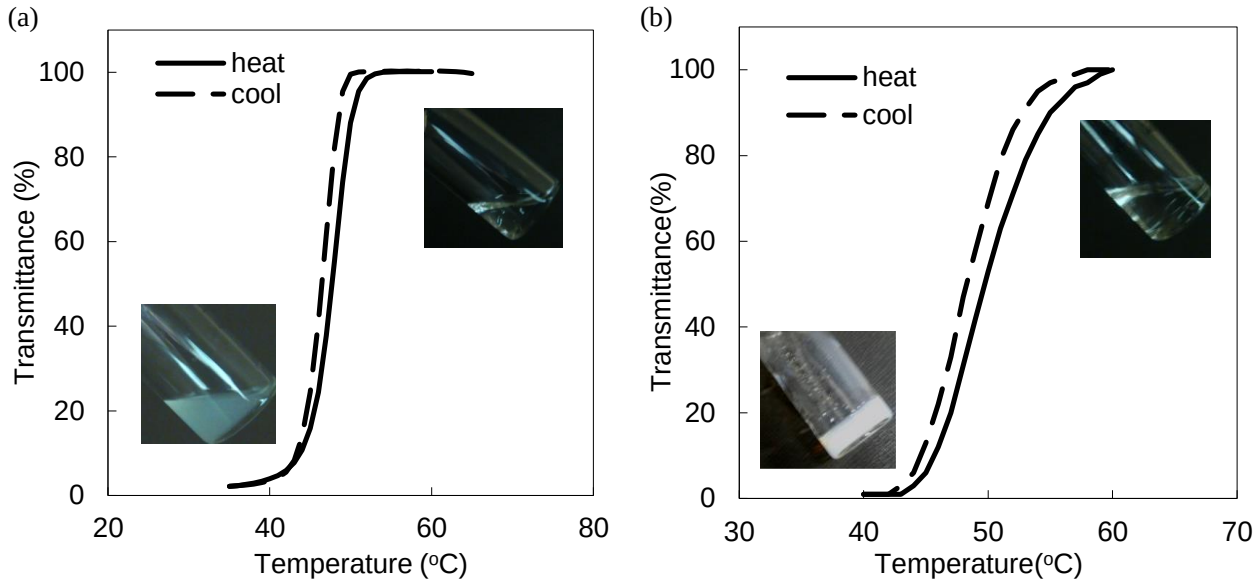


Figure 4_3. Transmittance (measured at 800 nm) as a function of temperature for **PUTFPB5** in (a) 1,2-dichloroethane ([**PUTFPB5**] = 25 gL^{-1}) and (b) acetonitrile ([**PUTFPB5**] = 100 gL^{-1}).

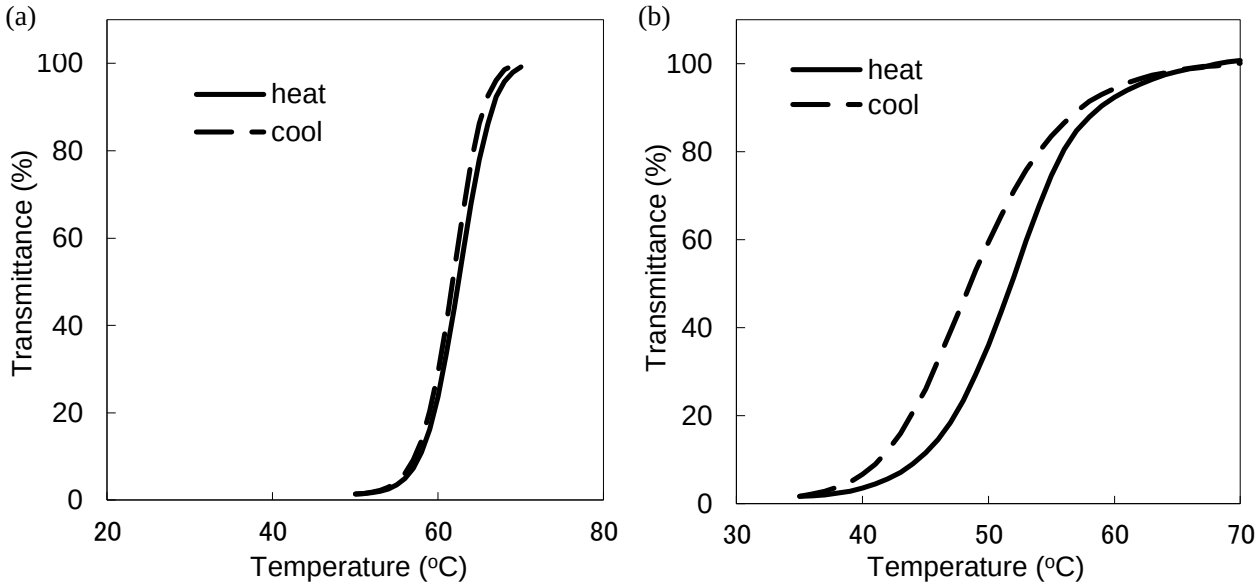


Figure 4_4. Transmittance (measured at 800 nm) as a function of temperature for **PUTFPB4** in (a) 1,2-dichloroethane ([**PUTFPB4**] = 25 gL^{-1}) and (b) acetonitrile ([**PUTFPB4**] = 100 gL^{-1}).

4.2.3. UCST Behaviors of PUTFPBs in the Presence of the Salt

In order to obtain insights into the relation of solubility and ionization of the ionic groups, the author added tetra(*n*-butyl)ammonium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) (**TBATFPB**) for common-ion effect into the polymer solution of **PUTFPB5** or **PUTFPB10** in 1,2-dichloroethane. Since the addition of **TBATFPB** reduced concentration of ionized species of TFPB salt in the polymer chain by common-ion effect, weakening the repulsive force could be expected.[5]

As shown Figure 4_5a, the transmittance curves of solution of **PUTFPB5** in 1,2-dichloroethane moved to lower temperature, and decrease of the cloud points were observed with increasing concentration of **TBATFPB**. Although the solution of **PUTFPB10** in 1,2-dichloroethane was completely soluble between 10-80 ^{o}C, the solubility behavior were changed to the UCST-type phase behavior by the addition of **TBATFPB**, and then the cloud points decreased with increasing the concentration of **TBATFPB** (Figure 4_5b). These results indicated that the ionization of the ionic groups attached in the polymer chain was suppressed by the presence of common-ion salt, and then weakening the repulsive force among them caused the decrease of the polymer solubility. Because of higher concentration of the ionized groups in **PUTFPB10** as compared with **PUTFPB5**, larger amount of **TBATFPB** was required to induce the solubility change of **PUTFPB10**.

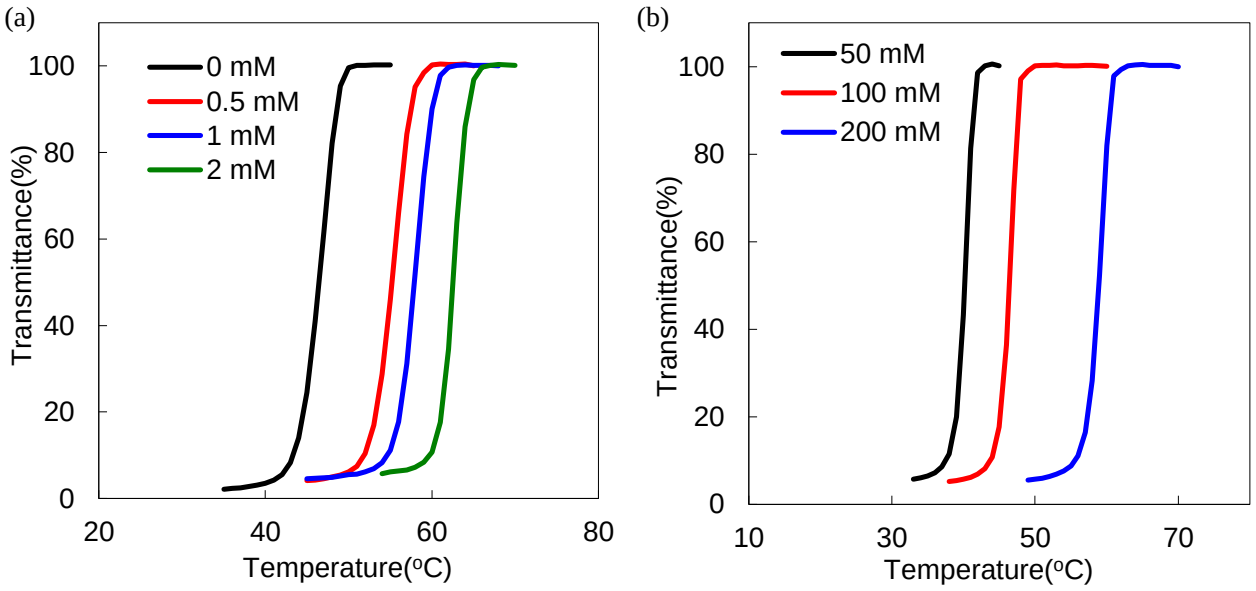


Figure 4_5. Dependence of the transmittance curves (700 nm) of (a) **PUTFPB5** and (b) **PUTFPB10** in 1,2-dichloroethane on TBATFPB concentration. ([**PUTFPB5**] = [**PUTFPB10**] = 25 gL^{-1}, cooling rate = 1 ^{o}C min^{-1})

4.2.4. UCST Behaviors of PUTFPBs in Mixed Solvent

To obtain a deeper understanding, the author evaluated the effect of permittivity for the UCST-type phase behavior of **PUTFPB5** using binary mixtures of two solvents (Figure 4_6). Generally, the association constant of an ion pair decreases with increasing permittivity of the media.[6] In this experiment, 1,2-dichloroethane and acetonitrile were used as the components of the binary mixtures , the former act as a low permittivity solvent and the latter high permittivity one. The mixed solvents with 100/0, 99/1, 98/2, 97/3, and 96/4 (volume of 1,2-dichloroethane / volume of acetonitrile) were used. With increasing amount of acetonitrile, the permittivity of the mixed solvents increased, and the cloud points decreased, and the polymer solubility increased. This is due to the fact that ionization of TFPB ion pairs was promoted by increasing permittivity of the media. It means that the increase of the repulsive force among the ionic groups resulted in dissolution of the polymer. Ionization of the lipophilic ionic groups played a key role of the UCST-type phase behavior.

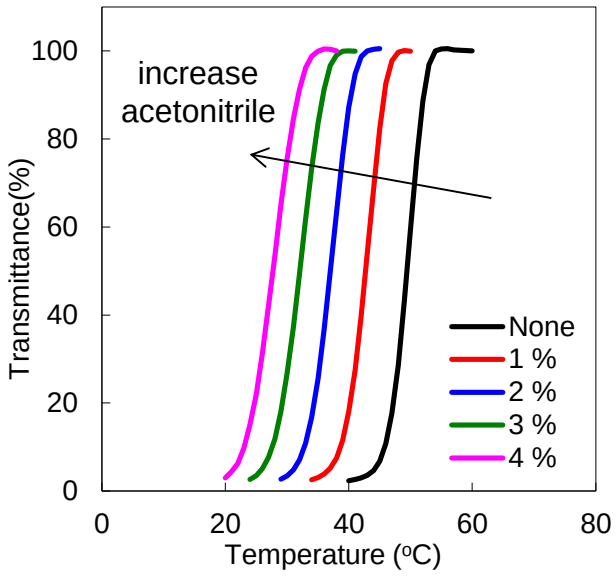


Figure 4_6. Dependence of the transmittance curves (700 nm) of **PUTFPB5** in 1,2-dichloroethane/acetonitrile (v/v) ([**PUTFPB5**] = 25 gL^{-1}, cooling rate = 1 $^{o}C\ min^{-1}$)

4.3. Conclusion

The preparation of the polymers **PUTFPBs** having the urea groups and lipophilic ionic groups were accomplished. The solubility of the polymers depended on the balance between the attractive force induced by hydrogen bonding among the urea groups and the repulsive force

attributed to dissociation of the ionic groups. In aprotic and non polar solvents, solubility of **PUTFPBs** was changed from insoluble to soluble with the increasing contents of the ionic groups. Moreover, in acetonitrile and 1,2-dichloroethane, the UCST-type phase behavior were observed. This result indicated the UCST-type phase behaviors were induced by cleavage of the hydrogen bonds among urea groups upon heating at which the repulsive force among the ionized ion groups overwhelmed the attractive force. The author showed this simple strategy for UCST-type phase behavior in some organic solvents. Utilizing the lipophilic ion pairs and other attractive groups, it should be expected to de novo design of UCST-type thermo-sensitive polymers in any media.

4.4. Experimental Section

Instrumentation and Methods

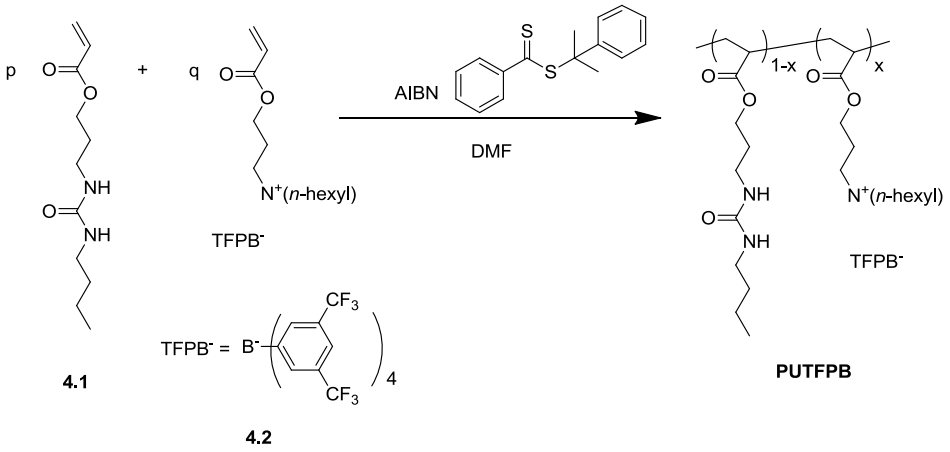
Size exclusion chromatography (SEC) was carried out on a SHIMADZU LC-9A system (SHODEX KD-805 and K-804 column) with a SHIMADZU RID-10A refractive index detector using DMF (10 mM LiBr) as an eluent, after calibration with the standard polystyrene samples. Transmittance measurements were recorded on a JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. Cloud points of the polymer solutions were determined from the transmittance at 700 nm on cooling at 1.0 ^{o}C min^{-1} as the temperature with 90% transmittance. ^{1}H and ^{13}C NMR measurements were recorded on a Bruker AV300 and JEOL JNM-AL300 instruments at 300 MHz at room temperature. Solubility test were carried out by direct observation using naked-eyes in various organic solvents at the concentration of 25 gL^{-1} at room temperature. The solvents were used without further purification.

Materials

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. 2,2'-Azobis(isobutyronitrile) (AIBN) was recrystallized using methanol. *N*, *N*-Dimethylformamide was distilled under reduced pressure. 2-(3-butylureido)propyl acrylate (**4.1**), *N*-[3-(acryloyloxy)propyl]-*N*, *N*, *N*-trihexylammonium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (**4.2**), and cumyl dithiobenzoate were synthesized according to the literature.[8]

Polymerizations

Copolymers of **4.1** with **4.2** were prepared via controlled radical polymerization using cumyl dithiobenzoate as the chain-transfer agent. The preparation of **PUTFPB5** is described below as examples. The feed ratios were summarized in Table 4_1.



A solution of **4.1** (2.18 g, 9.5 mmol), **4.2** (0.62 g, 0.05 mmol), cumyl dithiobenzoate (5.5 mg, 0.02 mmol) and AIBN (1.6 mg, 0.01 mmol) in DMF(1.5 mL) was prepared. The solution was transferred to ample, degassed with three freeze-evacuate-thaw cycles, and sealed. The ampule was heated at 60 ^{o}C for 48 h. After the ampule was cooled, the reaction mixture was reprecipitated with diethyl ether, filtered and dried to obtain **PUTFPB5** (1.92 g). ^{1}H NMR (300 MHz, DMSO-d_6, TMS standard, r.t.): δ (ppm) 0.80-0.90 (br, 66 H), 1.10-1.70 (m, 180H) 2.10-2.30 (br, 20H), 2.90-3.15 (br, 84H), 3.80-4.10 (br, 40H), 5.80-6.10 (br, 38H), 7.61 (s, 8H, ArH), 7.72 (s, 4H, ArH).

4.6. References

1) a) Patil, A. O.; Ikenoue, Y.; Wudl, F.; Heeger, A. J. *J. Am. Chem. Soc*. **1987**. *109*. 1858-1859. b) Stork, M.; Gaylord, B. S.; Heeger, A. J.; Bazan, G. C. *Adv. Mater.* **2002**, *14*, 361. c) Huang, F.; Wu, H.; Wang, D.; Yang, W.; Cao, Y. *Chem. Mater.* **2004**, *16*, 708-716.

2) a) Lantman, C. W.; Macknight, W. J.; Lundberg, R. D. *Annu. Rev. Mater. Sci.* **1989**, *19*, 295-317. b) Chakrabarty, K.; Seery, T. A. P.; Weiss, R. A. *Macromolecules* **1998**, *31*, 7385-7389. c) Chakrabarty, K.; Weiss, R. A.; Sehgal, A.; Serry, T. A. P. *Macromolecules* **1998**, *31*, 7390-7397. d) Lantman, C. W.; MacKnight, W. J.; Peiffer, D. G.; Sinha, S. K.; Lundberg, R. D. *Macromolecules* **1987**, *20*, 1096-1101. e) Bronich, T. K.; Popov, A. M.; Eisenberg, A.; Kabanov, V. A.; Kabanov, A. V. *Langmuir* **2000**, *16*, 481-489.

3) a) Chern, Y.-T.; Tsai, J.-Y. *Macromolecules* **2008**, *41*, 9556-9564. b) Lin, S.-H.; Li, F.; Cheng, S. Z. D.; Harris, F. W. *Macromolecules* **1998**, *31*, 2080-2086.

4) a) Ono, T.; Sugimoto, T.; Shinkai, S.; Sada, K. *Nat. Mater.* **2007**, *6*, 429-433. b) Ono, T.; Shinkai, S.; Sada, K. *Soft Matter* **2008**, *4*, 748-750. c) Ono, T.; Sugimoto, T.; Shinkai, S.; Sada, K. *Adv. Funct. Mater.* **2008**, *18*, 3936-3940. d) Iseda, K.; Ohta, M.; Ono, T.; Sada, K. *Soft Matter* **2011**, *7*, 5938-5940. e) Ono, T.; Ohta, M.; Iseda, K.; Sada, K. *Soft Matter* **2012**, *8*, 3700-3704.

5) Ono, T.; Ohta, M.; Sada, K. *ACS Macro Lett.* **2012**, *1*, 1270-1273.

6) a) Covington, A. K.; Dickinson, T. *Physical Chemistry in Organic Solvent Systems*, Plenum Press, Berlin, **1973**. b) Bjerrum, N. *K. Dan. Vidensk. Selsk. Mat-Fys. Medd.* 1926, 7, 9.

7) a) Buscall, R.; Corner, T. Eur. *Polym. J.* **1982**, *18*, 967-974. b) Schulz, D. N.; Peiffer, D. G.; Agarwal, P. K.; Larabee, J.; Kaladas, J. J.; Soni, L.; Handwerker, B.; Garner, R. T. *Polymer* **1986**, *27*, 1734-1742. c) Seno, K.; Date, A.; Kanaoka, S.; Aoshima, S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 4392-4406.

8) a) Seuring, J.; Agarwal, S. *Macromol. Rapid Commun.* **2012**, *33*, 1898-1920. b) Seuring, J.; Agarwal, S. *ACS Macro. Lett.* 2013, 2, 597-600. c) Koningsveld, R.; Stockmayer, W. H.; Nies, E. *Polymer Phase Diagrams*, Oxford University Press, Oxford, **2001**.

9) Amemori, S.; Kokado, K.; Sada, K. *J. Am. Chem. Soc.* **2012**, *134*, 8344-8347.

10) Moad, G.; Chiefari, J.; Krstina, J.; Postma, A.; Mayadunne, R. T. A.; Rizzardo, E.; Thang, S. H. *Polym. Int.* **2000**, *49*, 993.

11) Jansen, J. F. G. A.; Dias, A. A.; Dorschu, M.; Coussens, B. *Macromolecules* **2003**, *36*, 3861-3873.

12) Bouteiller, L. Colombani, O. Lortie, F. Terech, P. *J. Am. Chem. Soc.* **2005**, *127*, 8893-8898.

13) Tsierkezos, N. G.; Molinou, I. E. *J. Solution Chem.* **2007**, *36*, 153-170.

Chapter 5: Concluding Remarks

The polymers having thermo-sensitive behavior have been widely reported and exploited for numerous applications. Although molecular designs for the polymers have been extensively investigated, they are mostly active only in water. Especially, LCST-type thermo-sensitive polymers for organic solvents were hardly demonstrated. This is because that water molecules are regarded as the unique solvent interacting strongly with the polymer and structuring around the hydrophobic groups of the polymer chain. On the other hands, organic media except ionic liquids and high-polar solvents hardly act as these functions. In this thesis, in order to develop the thermo-sensitive polymers for non-aqueous media, small molecules so-called "effector" were utilized as the third components. The effectors act as a solubilizer for the polymer disrupting the polymer-polymer interaction in the similar manner to water molecules. The interactions between polymer and effectors govern the polymer solubility.

In Chapter 2, using the acceptor molecules as effectors and the polymer having pyrene group (**PPMA**), the author demonstrated LCST-type phase behavior in organic solvents such as 1,2-dichloroethane and toluene. It was revealed by evaluating the association degrees that charge transfer (CT) interaction between acceptors and **PPMA** governed the solubility of the polymer. Breaking the charge transfer interaction upon heating induced the aggregation of the polymer resulting in LCST-type phase behavior. Therefore, it is important for LCST-type phase behavior that relatively weak interaction such as CT interaction which showed large temperature dependence of association constants.

In Chapter 3, the author used the hydrogen bonding small molecules as effectors and the polymer having urea group **3.1**. Amazingly, thermo-sensitive behaviors of the polymer in 1,2-dichloroethane were controlled by type of the effectors. For example, UCST-type phase behaviors were caused by the addition of *N,N'*-butyloctylurea, and LCST-type phase behaviors were caused by the addition of 1-octanol. It is revealed that the hydrogen-bonding ability of the effector substantially governed the thermo-sensitivity by evaluating their association degrees. The effectors having high affinities for the polymer induced UCST-type phase behavior, because of breaking the interactions between the polymers, whereas those having low affinities cannot interact with the polymers at high temperature, providing LCST-type phase behavior. Utilizing the hydrogen bonds whose strength can be tuned easily instead CT interaction, precise controllable and chemo-selective thermo-sensitive behaviors were accomplished.

The chapter 2 and 3 showed molecular design for thermo-sensitive behavior in organic solvents.

The author proposes three requirements for LCST-type phase behavior in organic solvents as follows. (1) a polymer should contain the functional groups to provide an attractive interaction between the polymer chains, and show aggregation of the polymer due to high cohesive property in them. (2) Surrounding the polymers should be a small molecule “effector”, which interacts with the polymer chains through relatively weak polymer-effector interaction and then disturbs polymer-effector resulting in increase of the polymer solubility. And the polymer-effector interactions are easily broken by heating. (3) The solvents as a background medium are inert toward the polymer−polymer or polymer−effector bonds as far as possible. Therefore, inbalance of the interactions between polymer-polymer or polymer-effectors upon heating showed induce thermo-sensitive behavior.

In chapter 4, the author used incorporation of the lipophilic ion pair (TFPB) into the polymer **PUTFPBs** having urea groups in order to increase the solubility of the polymers instead of the addition of the effector. The increases of the solubility of the polymers in aprotic and non-polar solvent were observed with increasing the lipophilic ion contents. Moreover some of PUTFPBs showed UCST-type phase behavior in 1,2-dichloroethane and acetonitrile. The solubility of the polymers depended on the balance between the attractive force induced by hydrogen bonding among the urea groups and the repulsive force attributed to dissociation of the ionic groups. The author showed that this simple strategy for UCST-type phase behavior in some organic solvents and application for lipophilic ion pairs.

In this thesis, the author demonstrated thermo-sensitive phase behavior in organic solvents by utilizing the addition of the effectors or incorporation of the lipophilic ion pair. Researches in supramolecular chemistry by using non-covalent bonds have been extensively reported. Using other non-covalent interactions, it should be expected to molecular design of UCST-type or LCST-type thermo-sensitive polymers in other media. Since in water system, various applications of thermo-sensitive polymer such as sensor, temperature-sensitive chromatography, surface modifiers, and temperature-sensitive catalysts have been reported, the author’s strategy could contribute creating the applications can work in organic solvents.

Publication List

Chapter 2

Polymer Phase-Transition Behavior Driven by a Charge-Transfer Interaction

Shogo, A.; Kenta, K.; Kazuki, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 4174-4178.

Chapter 3

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

Shogo, A.; Kenta, K.; Kazuki, S. *J. Am. Chem. Soc.* **2012**, *134*, 8344-8347.

Chapter 4

Thermo-Sensitive Behavior of Lipophilic Polyelectrolyte Bearing Urea Units in Organic Solvents

Shogo, A.; Kenta, K.; Kazuki, S. *in preparation*.

Other publications not included in this thesis

Thiourea-tagged poly(octadecyl acrylate)gels as fluoride and acetate responsive polymer gels through selective complexation

Janakiraman, K.; Toshikazu,; O. Shogo, A.; Hiromu, K.; Seiji, S.; Kazuki, S. *Chem. Commun.* **2011**, *47*, 1571-1573.

Postscript

The studies presented in this thesis have been carried out under the direction of Professor Kazuki Sada through the two periods: Graduate School of Engineering, Kyushu University during April 2009 - March 2011, and Department of Chemistry, Graduate School of Science, Hokkaido University during April 2011 - March 2014.

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