Supramolecular control over thermo-responsive systems with lower critical solution temperature behavior

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Abstract

Lower critical solution temperature (LCST) is the critical temperature below which the solution is miscible for all compositions and above which the solution becomes a suspension. The study of LCST properties has become a central research topic due to its profound impact on the applications of stimuli-responsive materials. Inspired by the marriage between materials science and supramolecular chemistry, the introduction of supramolecular pairs and interactions into polymeric LCST systems is increasingly practiced. Especially, supramolecular interactions provide precise control over LCST behavior in both water and organic solvents. Furthermore, supramolecular interactions not only control or adjust LCST behavior (supramolecular interaction controlled LCST), but also induce LCST phase behavior in species lack of thermo-sensitive properties (supramolecular interaction induced LCST). In this review, we summarize the applications of supramolecular interactions in LCST systems. By examining the relationship between supramolecular interactions and LCST changes, we further discuss the differences between supramolecular interaction controlled LCST and supramolecular interaction induced LCST. We hope this review will give our readers a snapshot on how the supramolecular interactions influence the LCST behavior in various systems, and benefit them with different applications.

KEYWORDS

host–guest interactions, lower critical solution temperature, molecular recognition, phase separation, supramolecular chemistry

1 | INTRODUCTION

Thermo-responsiveness is one of the most common phenomena¹ and has been widely introduced into artificial materials.² Lower critical solution temperature (LCST) phase behavior, a type of unique thermo-responsiveness, is a significant research topic.³ In LCST systems, solutes are miscible with solvents below the critical temperature, while phase separation only occurs above this temperature. The inherent essence of this reversible single phase-two phase transition is the competition between solutes and the solvent.⁴ At low temperatures, solute molecules are stabilized and solvated due to intermolecular interactions (hydrogen bonds in most cases) between solute and solvent molecules; above the critical temperature, these interactions deteriorate dramatically, thus solute molecules favor aggregation and expel solvent molecules (from a swollen state to a shrunken state), leading to the formation of aggregates of large sizes and the occurrence of macroscopic phase separations. In contrast, upper critical solution temperature (UCST) systems show a transition from a swollen (soluble) state to a shrunken (insoluble) state upon cooling.

From a thermo-dynamic viewpoint, the occurrence of LCST behavior is an unfavorable entropy effect.⁵ The

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relationship between decreased solubility or solvation and increased temperature is related to a negative exothermic enthalpy contribution, and above the critical temperature, the unfavorable entropy term begins to dominate, leading to phase separation. This phase separation phenomenon is also partially associated with hydrophobic hydration, especially in low molecular weight species involving LCST systems.

LCST is a well-known phenomenon related to traditional polymer systems. Diverse artificial systems, including nonpolar polymers, polymeric systems, poly(ionic liquids), complicated copolymers, and small molecules are discovered to display LCST behavior under appropriate conditions. Currently, overwhelming attention on this topic remains limited to polymer solutions. Considerable effects have been made to realize programmable and controllable LCST phase separation behavior. Nowadays, with the aim of adjusting LCST, researchers have turned their attention from general factors, such as concentration, solvent, salt, and pH, to supramolecular interactions. With the aid of supramolecular interactions, various external stimuli can be introduced into LCST systems. New stimuli give rise to increased flexibility in the control of LCST behavior, and the combination of LCST and supramolecular chemistry can direct the design of function-oriented soft materials. Compared with commonly employed methods, supramolecular interactions represent a powerful tool for controlling LCST behavior. Based on the complexity and diversity of supramolecular interactions, LCST systems can be reversibly regulated and precisely controlled.

As noncovalent interactions, supramolecular interactions are affected by multiple factors, which thus indirectly influence LCST behavior. This feature implies that LCST behavior is not only adjustable by supramolecular interactions directly, but can be controlled indirectly by additional factors, provided these factors can affect supramolecular interactions. Although LCST behavior and supramolecular interaction controlled LCST systems are invariably associated with polymeric systems, the study of small molecule-based LCST behavior has attracted increasing attention.

In this review, the topic of supramolecular interaction controlled LCST behavior is surveyed, providing comprehensive and direct information on the relationship between supramolecular interactions and LCST behavior. After a brief overview of thermo-responsive species and supramolecular interactions, LCST phase separation properties modulated by supramolecular interactions are discussed, with classification into two sections: polymeric LCST systems and small-molecule LCST systems. Supramolecular interaction induced LCST-type phase behavior will then be introduced, followed by a discussion on the challenges of supramolecular chemistry as it pertains to LCST systems.

2 | THERMO-SENSITIVE SPECIES AND SUPRAMOLECULAR INTERACTIONS IN SUPRAMOLECULAR INTERACTION CONTROLLED LCST SYSTEMS

Although thermo-responsive properties have been widely investigated and utilized in diverse applications, the study of the combination of supramolecular interactions and LCST remains restricted to a relatively narrow area. For polymeric systems, poly(N-isopropylacrylamide) (PNIPAM) and its derivatives are the most commonly used thermo-responsive species, while for small molecules, ionic liquids and glycol oligomers are principally employed for the realization of LCST behavior (Scheme 1).

1. PNIPAMs: As the largest class displaying LCST properties in aqueous medium, PNIPAMs are the most well-known examples. The prevalence of PNIPAMs is due to two aspects: (a) critical phase separation occurs at approximately 25–35°C in water, which is close to physiological temperature; and (b) the LCST behavior of PNIPAMs is relatively insensitive to external stimuli.

2. Ethylene glycols, including ring-closed derivatives thereof, such as crown ethers and short glycol chains with alkyl terminal groups can be readily attached to small molecules to realize LCST phase behavior in water. In recent years, an increasing number of crown ethers have been used to display thermo-responsiveness in water and act as cation binders to achieve control over LCST behavior.

3. Ionic liquids: This new type of thermo-responsive species and ionic liquids based poly(ionic liquids) likewise display LCST behavior. One feature of these compounds is that they display LCST in water as well as in organic solvents.

Compared with the diversity of thermo-responsive systems used for supramolecular interaction controlled LCST, supramolecular interactions are predominantly limited to macrocycle-based host-guest chemistry. Pillar[n]arenes, cucurbit[n]urils (CBs), crown ethers, and cyclodextrins (CDs) together with complementary guest compounds, namely organic molecules or metal cations, are applied to control/induce LCST behavior, due to their good solubility and molecular recognition in

\[ R = \text{Parquat, adamantane cholic acid, crown ether} \]
water. In addition to macrocycle-based host–guest interactions, charge transfer and metal coordination interactions are also employed in LCST systems.\cite{23–26}

LCST phenomenon can be easily identified by naked eyes. To quantitatively investigate LCST behavior, the most commonly used characterization method is UV/Vis spectroscopy. Dynamic light scattering, temperature-dependent NMR spectroscopy, cryo-TEM and simulation are frequently used to monitor the aggregation process of LCST systems.\cite{11}

\section{3 \ SUPRAMOLECULAR CONTROL OVER POLYMERIC LCST SYSTEMS}

CD/adamantane is one of the most well-known supramolecular pairs used to control the LCST behavior of PNIPAM.\cite{27}

In a classical strategy, adamantyl groups are connected to the backbones of PNIPAM; then, CDs are added to adjust LCST phase behavior.\cite{28} After modification of thermo-responsive polymers by adamantyl groups, the critical transition temperature ($T_{cloud}$) of PNIPAM is chiefly controlled by the competition between the hydrophobic and steric hindrance effects.\cite{29}

Ritter et al. found that although different linkers were employed to connect adamantyl units with PNIPAM, both 1 and 2 exhibited similar LCST behavior (Figure 1).\cite{27} I/CD and 2/CD systems behave similarly, displaying higher $T_{cloud}$. The increase in critical temperature is attributed to the inclusion of hydrophobic adamantyl units by hydrophilic CD. As the entire system becomes more hydrophilic, more energy is necessary to destroy the complexes and give rise to LCST behavior. They further studied the role of CD structures in controlling LCST behavior. When the concentrations of CD were identical, 1/3 (14.0 °C) and 2/3 (15.7 °C) presented $T_{cloud}$ that was 20°C lower than those of 1/CD and 2/CD systems (35 °C), respectively. The rationale behind the lowering of $T_{cloud}$ upon the addition of dimer-type 3 is straightforward. Compared with the CD monomer, the addition of the CD dimer led to the formation of a dense polymer network with low mobility and solubility, enabling the aggregation of polymer/CD dimer systems to create a more hydrophobic environment (the concentrations of CD units are the same; hence, the hydrophilic effect of CD units is comparable).

Meanwhile, the study from Zhao et al. demonstrated that CD-based host–guest complexation not only altered the $T_g$ of LCST systems, but also exerted significant influence on the transition window shape.\cite{30}

Not all supramolecular interactions in LCST systems are responsible for the changes of LCST behavior. Yuan et al. designed and prepared star-branched poly((caprolactone)-star-(poly(2-N,N dimethylamino)ethylmethacrylate) (star-PCL-(PDMAEMA)), which was connected by adamantane/CD pairs via host–guest interactions. In this study, supramolecular interactions acted only as linkers and were not harnessed for controlling LCST behavior. With the introduction of ionic interactions between opposite charges in star-PCL-(PDMAEMA), they successfully realized a dramatic transition from LCST to UCST behavior.\cite{31}

Supramolecular polymerization between traditional polymers and small molecules enables access to thermo-responsive copolymers with tunable LCST properties. Zhang et al. synthesized a linear polymeric CD (poly-CD) and two oligo(ethylene glycols) (OEGs)-adamantyl group-based dendrons. After mixing poly-CD with various dendrons, they successfully prepared two copolymers with LCST properties (originating from OEGs). They found that the terminal groups in OEGs significantly affected LCST properties: the methyl-bearing poly-CD/Dendron exhibited higher $T_{cloud}$ than its ethyl-bearing counterpart.\cite{32}

In addition to adamantane, various guest molecules are capable of binding CDs with the aim of controlling the LCST behavior of thermo-responsive polymer systems. The addition of CD to PNIPAM containing cholic acid pendants 4 effectively increased $T_{cloud}$, analogously to the reported CD/adamantine-linked PNIPAM.\cite{33} This supramolecular interaction controlled LCST behavior can be dramatically affected with the use of potassium 1-adamantylcarboxylate. Potassium 1-adamantyl carboxylate exhibits a stronger binding affinity for CD than cholic acid (Figure 2); therefore, CD/cholic acid complexes were destroyed to release uncomplexed PNIPAM. Photo-sensitive azobenzene has likewise been employed to adjust the LCST behavior combination with CD.\cite{34} In CD/azobenzene systems, LCST behavior can be controlled by the reversible cis-trans isomerization of azobenzene.\cite{35}

Metal coordination interactions have also been introduced to PNIPAM systems to develop thermo-responsive materials by Yang et al.\cite{24–26} In these systems, the existence of organoplatinum(II) metallacycles exerted a slight influence.
on the LCST behavior of PNIPAM, and no obvious changes in $T_{\text{cloud}}$ were observed.

Although LCST behavior is an important factor in thermo-responsive materials, upper critical solution temperature (UCST), an opposite phenomenon, is likewise crucial. Fan et al. designed a supramolecular system exhibiting both LCST and UCST behavior. When solutions of 5 and 6 were mixed together at an appropriate concentration and temperature (Figure 3), a turbid mixture instead of a transparent solution was observed, which can be ascribed to the complexation between CD and naphthalene units. A competitive experiment using sodium adamantyl carboxylate proved the existence of host–guest complexation. Upon heating, the majority of the complexes were destroyed, liberating 5 and 6, leading to the formation of a transparent solution (UCST behavior). Continued heating led to the occurrence of LCST, chiefly ascribed to poly(ethylene glycol) (PEG) units. However, compared with individual 6, the 5/6 system exhibited higher $T_{\text{cloud}}$ (1 mM, 44.5°C for 6, and 57°C for 5/6 complexes). This unusual phenomenon may be caused by the partial complexation between CD and naphthalene at high temperatures and the introduction of hydrophilic components (CD units).[36]

In general, supramolecular interactions are sensitive to temperature.[37] High temperatures are applied to weaken or destroy molecular recognition. From the perspective of supramolecular interactions, the PNIPAM-based macroscopic phase separation temperature is not high (25–35°C). Thus, only minor weakening of supramolecular interactions has been observed in this temperature range. Based on this information, Li et al. designed a simple but effective system to accomplish LCST phase separation-induced gelation. First, star-shaped PNIPAM-CD polymer 7 and adamantyl-terminated 8-arm PEG 8 were prepared (Figure 4). After mixing the above two compounds in water at low concentrations, $T_{\text{cloud}}$ of 37.5°C was attained, owing to the existence of host–guest complexation between CD and adamantane. A 1:1 host–guest mixture at a concentration of 12 wt% formed a clear solution at 25°C, while heating to 37°C resulted in an obvious transition from a transparent solution to a turbid hydrogel (simultaneous LCST and gelation processes). Upon heating, the PNIPAM chains gradually collapse and shrink to form more compact particles. During this process, PNIPAM chains from adjacent CD units twist together and act as cross-linkers to connect host–guest complexes. Considering the existence of multiple PNIPAM chains in a single CD unit, the star-shaped complexes can be connected to form three-dimensional network structures. These structures ultimately became hydrogels by entrapping the surrounding water molecules. Ordinarily, supramolecular interactions are manipulated to adjust LCST properties in solution. This example represents a fascinating attempt to combine supramolecular interactions and phase separation for the assembly of bulk materials.[38]

Li et al. developed a novel temperature-sensitive hydrogel system. In this system, CD-grafted alginate and ferrocene-modified OEGs were synthesized separately. At low temperatures, OEGs existed as freely extended polymer chains. When the temperature was raised to $T_{\text{cloud}}$ of OEGs, they began aggregating into spherical micelles (microscopic phase separation). Due to the strong binding ability between CD and ferrocene, micelles were cross-linked together to form hydrogels.[39]

In the above two examples of LCST-induced gelation, it is evident that supramolecular interactions and supramolecular pairs do not govern LCST properties, although the introduction of CD units alters the LCST behavior of PNIPAM or OEG. However, their presence is crucial to the formation of hydrogels. Employing a similar gelation strategy, water-sensitive hydrogen bonds have also been used to prepare hydrogels. The LCST behavior of PNIPAM creates a relatively hydrophobic environment for the formation of hydrogen bonds.[40]

Another macrocycle widely used in supramolecular controlled LCST systems is pillar[n]arenes (Scheme 2). Pillar[n]arenes have been applied for adjusting LCST behavior in two ways: (a) pillar[n]arenes are used to adjust the LCST behavior of functionalized PNIPAM when guest molecules are linked to the backbones of PNIPAM; (b) thermo-responsive units are directly connected to pillar[n]arenes to form new LCST systems, and complementary guests are introduced to modulate LCST behavior via pillar[n]arene-based host–guest chemistry. We will discuss the second strategy in the small-molecule LCST systems section (vide infra).
Paraquat derivatives are commonly used as binding sites in PNIPAM to complex water-soluble pillar[n]arenes. Functionalized PNIPAM derivatives generally exhibit similar LCST behavior, including comparable critical transition temperatures, narrow transition windows, and the absence of or minimal hysteresis during heating-cooling cycling.[41] These newly paraquat-appended copolymers display higher $T_{\text{cloud}}$ (40.5°C), compared with that of pure PNIPAM (32–35°C).[19] This is attributed to the changes of hydrophilic environment and electrostatic repulsion. Pillar[5]arene and pillar[6]arene were examined in the initial strategy of pillar[n]arene used in supramolecular controlled PNIPAM systems. After the gradual addition of water-soluble pillar[5]arene or pillar[6]arene, increasing $T_{\text{cloud}}$ trends were observed, indicating strong suppression effects of supramolecular interactions in LCST behavior. For example, when the concentration of pillar[6]arene was increased from 0 to 50 mg ml $^{-1}$, $T_{\text{cloud}}$ increased by approximately 12°C. This can be rationalized by two aspects: (a) the introduction of pillar[n]arenes units increases the hydrophilic environment of PNIPAM; and (b) supramolecular complexes also increase electrostatic repulsion and steric hindrance, which have a negative effect on the formation of large-scale aggregates.[19]

Subsequently, in order to expand the application scope of the pillar[n]arene family, pillar[n]arenes with a higher number of repeating units were applied.[41] Pillar[7]arene and pillar[10]arene display comparable suppression effects on the LCST properties of PNIPAM copolymers. Based on the differences in cavity sizes, the pillar[n]arene family shows selective host-guest interactions with paraquat and diquat. Competitive guests were applied to confirm that the complexation had induced LCST changes. Upon the addition of competitive guests, such as diquat, a lower $T_{\text{cloud}}$ trend was realized, indicating that the pillar[10]arene/paraquat interactions in tuning LCST behavior had been dramatically weakened.[42]

Supramolecular interactions between cyclophane and naphthalene have likewise been applied to control the LCST properties of PNIPAM. Woisel et al. developed a convenient method for controlling LCST behavior of a naphthalene-appended PNIPAM derivative via supramolecular interactions between cyclophane and naphthalene. The mixture of cyclophane and 1,5-dialkoxy naphthalene-functionalized PNIPAM is purple, as a result of the formation of the cyclophane/naphthalene complex. $T_{\text{cloud}}$ of the complex is comparable to that of the naphthalene-appended PNIPAM, as are their LCST curves. However, DLS experiments indicated somewhat different data. Above $T_{\text{cloud}}$, cyclophane/naphthalene-appended PNIPAM complexes exhibited significantly smaller diameters (ca. 1460 nm), compared with naphthalene-appended PNIPAM (ca. 4850 nm). This result clearly demonstrates the effect of supramolecular interactions in controlling aggregate dimensions. From this study, we can conclude that supramolecular interactions do not always alter $T_{\text{cloud}}$ at times changing only the micro-phase separation behavior.[43]

By introducing supramolecular interactions and supramolecular pairs, it is possible to kinetically control the LCST phase behavior of naphthalene-appended PNIPAM (Figure 5). The addition of 9 to a solution of 10, not only led to higher $T_{\text{cloud}}$, but also endowed the supramolecular system with thermal hysteresis. Compared to the $T_{\text{cloud}}$ obtained in the heating process, the $T_{\text{cloud}}$ of the cooling process was 10°C lower. This obvious hysteresis can be ascribed to the formation of a metastable soluble state of supramolecular complexes.[44]

Crown ethers are good candidates for controlling the LCST behavior in water. Small crown ethers, such as 15-crown-5 and 18-crown-6, are introduced to PNIPAM to act as cation binders.[21,45] $T_{\text{cloud}}$ of 11 shifted to lower temperatures after the addition of alkali metal ions (Na$^+$, K$^+$, and Cs$^+$), due to the formation of 2:1 crown ether/cation sandwich superstructures (Figure 6).[21] In such superstructures, cations act as linkers to connect surrounding PNIPAM chains, facilitating the aggregation of PNIPAM chains (the cross-linking of PNIPAM chains by the sandwich structures), akin to the role of CD-dimer in.[27] Once the binding mode between crown ether and cation is 1:1, no cross-linking behavior is possible and cation-induced LCST phenomena are different. For example, the combination of polysilsesquioxane with 15-crown-5 gave rise to entirely distinct LCST changes. Upon the addition of various metal ions to a solution of polysilsesquioxane, an increased $T_{\text{cloud}}$ was observed, due to the formation of hydrophilic crown ether/ion complexes. Moreover, the crown ether-appended LCST systems were sensitive to cations, but relatively insensitive to anion species.[46]

Owing to the limitation of the boiling point of water, $T_{\text{cloud}}$ measurements are invariably conducted below 100°C ($<$80°C in most studies). Hawker et al. used sealed cuvettes to investigate the role of cation/crown ether molecular recognition in adjusting LCST behavior. $T_{\text{cloud}}$ about 100°C was recorded when various salts (LiCl, NaCl, and KCl) were added to crown ether systems.[47]

In the above-mentioned LCST systems containing crown ethers, the crown ether units are connected to PNIPAM. Because crown ethers can display LCST behavior in the absence of PNIPAM, the complexity of thermostresponsiveness will increase.[17] Metal cations are used to execute control over LCST behavior. Hence, the addition of metal cations will lead to a typical and strong salting-out effect, resulting in $T_{\text{cloud}}$ lowering. The salting-out effects of different metal cations are distinct. Without the consideration of both the salting-out and salting-in effects in crown ether-based LCST systems, identifying the role of supramolecular interactions becomes arduous, especially when no binding results are available. Dong et al. studied the competition between the cation-induced salting-out effect...
and molecular recognition-induced salting-in effect. They found that the concentration of cations exerted a significant influence on $T_{\text{cloud}}$. At low salt concentrations, $T_{\text{cloud}}$ is primarily dominated by the salting-in effect. High salt concentrations lead to the domination of the salting-out effect (decreased $T_{\text{cloud}}$). Such occurrences were observed in crown ether-based LCST systems with or without polymeric backbones. By the introduction of theoretical models (such as Langmuir adsorption model), the effects of ion identity and concentration can be quantitatively calculated.

Supramolecular interactions not only effectively modulate the macroscopic LCST phase behavior, but exert significant effects on the morphology of assemblies. Scherman et al. reported supramolecular polymeric peptide amphiphilic vesicles with tunable LCST behavior and controllable vesicle sizes (Figure 7). In the absence of CB, a mixture of pyrene-appended peptide 12 and paraquat-functionalized PNIAPM 13 exhibited analogous LCST behavior to that of pure PNIPAM. After the addition of CB, a ternary complex system, containing CB, paraquat, and pyrene, was formed, leading to the quenching of LCST properties arising from PNIPAM units. Due to complexation, aggregate size increased from 10 nm (unimers) to 180 nm (vesicles), with an increase in temperature from 25 to 35°C. This study represents a classical strategy for the control of aggregate morphology.

In the majority of studies, changes in both the critical transition temperature and macroscopic phase behavior are observed after the introduction of supramolecular interactions. In other words, supramolecular pairs and supramolecular interactions can effectively control or modulate the LCST behavior of thermo-responsive species. However, Tam et al. found that PEG/CD interactions presented a very weak effect in the control of the LCST behavior of PNIPAM, although the addition of CD changed the polymer configuration and possibly additionally introduced a higher degree of...
4 | SUPRAMOLECULAR CONTROL OVER SMALL-MOLECULE LCST SYSTEMS

For small-molecule LCST systems, short glycol chains with terminal methyl groups are the most commonly utilized thermo-responsive moieties. However, a significant drawback of these systems is that only one or two glycol chains result in high critical transition temperatures and very broad transition windows, dramatically restricting their further applications. With the aid of supramolecular interactions and chemical self-assembly, multiple glycol chains can be readily introduced into supramolecular structures to effectively decrease $T_{\text{cloud}}$.

For example, Huang et al. utilized metal coordination to connect 14, comprising six short glycol chains, and 15 together to form a discrete amphiphilic organoplatinum(II) metallacycle (Figure 8). The metallacycle displayed LCST behavior at a relatively low temperature range (26–30°C), when the concentrations were in the range between 3.0 and 0.5 mM. No sign of fatigue was observed during the heating/cooling cycles, and the LCST transition was completely reversible, indicating the integrity of supramolecular structures at both low and high temperatures. After the addition of potassium hexafluorophosphate, a decrease in $T_{\text{cloud}}$ was observed instead of an increment, which was ascribed to host–guest interactions between the glycol chains and potassium cations. In this approach, supramolecular interactions (metal coordination) function as linkers to gather multiple thermo-responsive components together to achieve phase separation at low temperatures.

Rivera et al. disclosed the generation of nonpolymeric thermo-sensitive supramolecules by the self-assembly of small molecules with the assistance of potassium cations. These LCST supramolecules contained central, relatively hydrophobic cores, surrounded by hydrophilic groups. High temperatures (above 55°C) were needed to illicit LCST behavior in aqueous phosphate-buffered solutions (pH 7.1, 2 M KI). DLS experiments revealed a sudden transition from small supramolecules to large aggregates. Furthermore, at low temperatures, monodispersed discrete self-assembled hexadecamers (4.4 nm) were obtained, while above $T_{\text{cloud}}$, large hydrated globules (above 1000 nm), and subsequently shrunken globules (400 nm), were formed. Further heating...
can induce the formation of larger polydisperse aggregates (800 nm).

The above two examples in this section illustrate the application of supramolecular interactions in the realization of LCST behavior in water: the enrichment of thermo-sensitive compounds into supramolecules.

Another method for obtaining lower $T_{\text{cloud}}$ is to introduce short glycol chains to pillar[n]arenes, as pillar[n]arenes possess 10 or more reactive sites. Ogoshi et al. successfully prepared two thermo-responsive pillar[n]arenes, pillar[5]arene 16 with 10 glycol chains, and pillar[6]arene with 12 glycol chains (Figure 9).\cite{53,54} They then focused on the supramolecular control of LCST behavior via pillar[n]arene-based host–guest chemistry. For example, the addition of paraquat to 16 effectively suppressed the LCST behavior, with the elevated $T_{\text{cloud}}$ being a salient feature. This observation is the result of the formation of additional hydrophilic host–guest complexes between 16 and paraquat. An effective competitor, CB,\cite{7} which exhibits a higher binding affinity toward paraquat, can destroy 16/paraquat complexation and decrease $T_{\text{cloud}}$, further confirming supramolecular controlled LCST behavior. Due to the size selectivity of pillar[n]arenes, reversible control over the transparent solution-turbid mixture transition of pillar[6]arene was accomplished using a photo-responsive host–guest system.\cite{54} In this system, photo-induced conformation changes effectively realize the reversible transition between threeding and dethreading states of supramolecular complexes, thus affect the thermo-responsive nature of pillar[n]arenes. Ionic liquids were also used as guests to regulate the LCST behavior of 16.\cite{55}

The introduction of short glycol chains to larger pillar[n]arenes, such as pillar[7]arene and pillar[10]arene, is likewise beneficial for the preparation of thermo-responsive systems. Interestingly, at equimolar concentration (2 mM), pillar[n]arenes with different sizes (5, 6, 7, and 10 repeated units) have comparable $T_{\text{cloud}}$ (40–42°C). The formation of pillar[7]arene/or pillar[10]arene/paraquat complexes results in the same suppression effect on LCST behavior. Complexation between pillar[10]arene and diquat likewise results in higher $T_{\text{cloud}}$.\cite{41,56,57}

From several above-mentioned examples of pillar[n]arene-based small-molecule LCST systems, it is evident that for supramolecular control over thermo-responsiveness, pillar[n]arenes play a consistent role of increasing the hydrophilicity environments by complexation. The formation of pillar[n]arene/guest complexes leads to strong suppression of LCST behavior (higher $T_{\text{cloud}}$).

A similar strategy was used to design LCST systems from various macrocycles.\cite{58,59} For example, oxatub[4]arenes are new macrocycles with a range of interesting host–guest properties.\cite{58} Jiang et al. introduced short glycol chains into oxatub[4]arene to prepare thermo-sensitive 17, resulting in an increase in $T_{\text{cloud}}$ from 35 to 55°C. Rapid responsive behavior (1°C) and relatively small hysterias (1.4°C) were observed. Based on the interactions between oxatub[4]arene and ammonium salt, they found that the addition of guest salt effectively suppressed LCST behavior, as confirmed by the increased $T_{\text{cloud}}$ and broader transition windows. In order to introduce additional stimuli, they utilized nitro group-appended guests, which can be converted into neutral molecules via the reduction of the nitro group by H$_2$S. Indeed, the addition of NaHS to a mixture of oxatub[4]arene and nitro group-appended ammonium salt led to the re-occurrence of LCST phase separation (Figure 10).\cite{58}

Ionic liquids exhibit unique thermo-dynamic properties, including LCST behavior, in aqueous solutions or organic solvents.\cite{22a,81} For example, Ritter et al. developed a series of amino acid-appended ionic liquids, which displayed typical LCST behavior in water, with relatively low $T_{\text{cloud}}$. However, supramolecular control was not applied to adjust their thermo-responsiveness.\cite{22a} Schalley et al. found that 1,3-dimethylimidazolium based ionic liquid displayed obvious phase separation in acetone at high concentrations.\cite{14a}

Considering the favorable host–guest properties between ionic liquid and macrocycles, they used dibenzo-24-crown-8 (DB24C8) and pillar[5]arene, respectively, to control LCST behavior in acetone. Generally, the manifestation of supramolecular complexation leads to higher $T_{\text{cloud}}$. In this ionic liquid-based system, DB24C8 and pillar[5]arene behaved in a contrasting manner: the addition of DB24C8 results in an increasing trend of $T_{\text{cloud}}$, and a high concentration of DB24C8 was observed to completely quench the phase separation (DB24C8 concentration and $T_{\text{cloud}}$ were

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**Figure 9** Pillar[n]arene-based LCST behavior and its supramolecular control over thermo-responsiveness. Reproduced from [53]. Copyright (2012) American Chemical Society

**Figure 10** An oxatub[4]arene-based LCST system and its supramolecular control over thermo-responsiveness. Reproduced from [58]. Copyright (2017) American Chemical Society
proportional); while for pillar[5]arene, an evident decreasing trend in $T_{\text{cloud}}$ was observed (pillar[5]arene concentration and $T_{\text{cloud}}$ were inversely proportional). In pillar[n]arene/ionic liquid mixtures, this contradictory trend may be attributed to the presence of complexes with diminished solubility and changes in solvent properties caused by the OH-rich pillar[n]arene.

5 | HOW SUPRAMOLECULAR INTERACTIONS CHANGE LCST BEHAVIOR IN SUPRAMOLECULAR CONTROLLED LCST SYSTEMS

Supramolecular interactions, whether weak or strong, can readily and effectively affect LCST properties, including $T_{\text{cloud}}$ and macroscopic phase changes, without tedious work on the chemical structure modification of thermo-responsive polymers. Supramolecular interactions control LCST properties in two ways: by altering the hydrophilic/hydrophobic environment and through the influence of the size/shape of supramolecular complexes (steric hindrance, before and after complexation).

In general, after complexation, the newly formed supramolecular complexes (as parts of PNIPAM structures, in most cases) are more hydrophilic, as the introduced small molecules are hydrophilic. However, changes in the hydrophilic environment only partly rationalize supramolecular control over LCST. Macrocycles, including pillar[n]arenes and CDs, are rigid molecules; hence, the complexation of supramolecular pairs in polymeric LCST systems leads to an obvious difference in size and/or shape of the thermo-responsive species before and after complexation. The role of supramolecular interactions in controlling LCST behavior involves the combination of the above two factors, with the hydrophilic/hydrophobic effect being dominant. In certain systems wherein molecules with multiple charges are present, electrostatic repulsion should be considered.

6 | A BRIEF DISCUSSION OF SUPRAMOLECULAR INTERACTION CONTROLLED LCST BEHAVIOR AND SUPRAMOLECULAR INTERACTION INDUCED LCST BEHAVIOR

For the majority of supramolecular interactions involving LCST systems, supramolecular interactions only act as external stimuli to adjust the LCST behavior of thermo-responsive species; we generally define this as supramolecular interaction controlled/adjusted LCST behavior. These species definitively exhibit LCST phase behavior without the introduction of supramolecular interactions, which only alter the already existing LCST behavior.

In supramolecular interaction induced LCST systems (Scheme 3), none of the components are capable of LCST behavior, that is, they are not thermo-sensitive. Only the combination of several components together via supramolecular interactions can realize LCST behavior (macroscopic phase separation, reversible one phase-two phase transition). In supramolecular interaction induced LCST systems, the only driving force for thermo-responsiveness is supramolecular interactions. LCST properties cannot exist in the absence of supramolecular interactions. Compared with the plethora of studies on supramolecular interaction controlled LCST systems, only a limited number of supramolecular interaction induced LCST systems have been reported, with the majority being serendipitously discovered. The main reason is that it is difficult to design thermo-responsive systems to fulfill all the criteria (Scheme 3).
7 | SUPRAMOLECULAR INTERACTION INDUCED LCST BEHAVIOR

Imidazolium-based ionic liquid 19 shows LCST behavior in acetone (Figure 11); however, it does not possess any thermo-responsiveness in other organic solvents, such as chloroform. A mixture of 19 and chloroform exhibited typical phase separation at room temperature as well as at high temperatures, with the ionic liquid layer residing at the bottom. Considering the supramolecular interactions between pillar[5]arene and 19, Huang et al. added pillar[5]arene 18 to a mixture of 19 and chloroform. The addition of 18 led to the elimination of macroscopic phase separation, and yielded a transparent solution, which can be ascribed to the formation of chloroform-soluble supramolecular complexes. Because pillar[5]arene-based supramolecular interactions (hydrogen bonding and CH–π interactions) are sensitive to temperature, elevated temperatures can effectively destroy the chloroform-soluble complexes, to release uncomplexed 19 into chloroform, and ultimately lead to the aggregation of 19. With sufficient free and chloroform-insoluble 19 in the mixture, macroscopic phase separation occurred. Cooling such a mixture to room temperature resulted in a transparent solution once again due to the reformation of chloroform-soluble pillar[5]arene/ionic liquid complexes. As a typical feature of supramolecular interaction induced LCST systems, the molar ratio of pillar[5]arene and ionic liquids effectively influences the LCST behavior. This supramolecular interaction induced phase separation can be used to isolate components from mixtures.

For the establishment of polymeric LCST systems, water is the most commonly used solvent. Based on deliberate design, organic solvents are also available for the induction of LCST behavior. Sada et al. selected a ternary system containing 1,2-dichloroethane and supramolecular pairs involving charge transfer interaction (Figure 12). As 1,2-dichloroethane is a poor solvent for poly((1-pyrene)methyl acrylate) (PPMA) with pyrene groups, PPMA derivative 20 displayed macroscopic phase separation. After the addition of 21, the suspension became transparent owing to the existence of charge transfer interaction. This transparent solution exhibited typical LCST behavior during heating.

Ma et al. designed a supramolecular amphiphilic system containing naphthalene unit 22 and sulfonatocalix[4]arene 23 (Figure 13). Although neither the macrocycle nor the naphthalene exhibited LCST behavior in water, the mixture of 22 and 23 displayed classical LCST behavior due to the supramolecular interactions between sulfonatocalix[4]arene and naphthalene. The combination of sulfonatocalix[4]arene and naphthalene favored to the formation of water-soluble supramolecular micelles, which transformed into an insoluble cross-linked network at high temperature and resulted in the appearance of macroscopic phase separation. As the driving force for LCST behavior is supramolecular interactions, this system presents typical monomer ratio-based thermo-responsiveness. The higher sulfonatocalix[4]arene/naphthalene ratio, the higher T_{cloud}. Ritter et al. reported many pioneering studies both in supramolecular interaction controlled LCST and supramolecular interaction induced LCST systems. They investigated imidazolium-based poly(ionic liquids) with bis(trifluoromethylsulfonyl)imide (Tf_2N^-) anions. These polymers were water-insoluble at room temperature. However, after the addition of randomly methylated CDs, a transition from turbid mixtures to transparent solutions occurred, due to the formation of water-soluble CD/Tf_2N^- complexes. After heating the solutions from 20 to 70 °C, a near tenfold decrease in the binding capacity of CD/Tf_2N^- complexation was observed (from 10,200 to 1170 M^{-1}), explaining the occurrence of turbid mixtures. A remarkable factor is that hysteresis was evident (48°C at the heating round, and 38°C in the cooling round) during the heating–cooling process. This hysteresis can be attributed to the dynamical equilibration of supramolecular complexation,
because at high temperature, relatively strong interactions between CD and TF$_2$N$^-$ remain.\cite{61} Complexation between CD and other bulky groups, such as the 2-bromoisobutyryl group, likewise effectively induced LCST from water-insoluble polymers.\cite{2}

\section*{8 How the Supramolecular Interactions Change LCST Behavior in Supramolecular Interaction Induced LCST Systems}

In supramolecular interaction induced LCST systems, one component of the supramolecular pair is poorly soluble. The addition of the other component results in the formation of soluble supramolecular complexes at low temperatures. As supramolecular interactions are weakened at elevated temperatures, the complexes will be destroyed to release uncomplexed components. Because of their poor solubility, these components aggregate together to expel solvent molecules, leading to the formation of macroscopic aggregates and the occurrence of phase separation. Owing to temperature-induced reversible supramolecular complexation and decomplexation, the solution-immiscible mixture transition is reversible.\cite{15}

In these systems, supramolecular interactions are first utilized to achieve thermo-responsiveness by the reversible complexation and decomplexation of supramolecular complexes.\cite{62} Then by controlling the concentration of supramolecular complexes or the ratio of supramolecular pairs, the same interactions will modulate induced LCST behavior. Essentially, the role of supramolecular interactions is to achieve a balance between insoluble species and soluble complexes. Additional supramolecular interactions are ordinarily introduced to further control the induced LCST behavior. These additional interactions affect LCST behavior in an indirect way.

\section*{9 Future and Outlook}

The development of new materials not only exerts a significant influence on scientific research and industry, but also changes the way we live and work.\cite{63} Thermo-responsive materials with LCST properties exhibit unique phase transitions and have thus received considerable attention in the field of adaptive materials. The introduction of supramolecular interactions to thermo-sensitive materials with LCST properties represents a versatile and effective strategy for obtaining desired functions. By rational design of molecular structures,
various supramolecular interactions can be introduced into LCST systems. Based on the features of supramolecular interactions, supramolecular-controlled/induced LCST behavior provides additional opportunities to obtain programmable thermo-responsiveness. With the understanding of the role of supramolecular interactions in phase transition behavior, the study of supramolecular interaction controlled/induced LCST systems is expected to result in the design and fabrication of function-oriented smart materials.

The investigation of supramolecular interaction controlled/induced LCST properties not only provides the basis and evidence for understanding thermo-responsiveness and supramolecular interactions but also expands polymer chemistry and materials science applications. Though the application of supramolecular interaction induced LCST systems has not been widely investigated, this thermo-sensitive behavior can be used as a new strategy for separation.

Although supramolecular interactions play an increasingly important role in the control of LCST behavior, significant challenges still remain. Most studies are focused on the solution state, and only limited number of bulk materials with LCST behavior and supramolecular properties are designed and prepared. For small-molecule LCST systems, a big problem is that the critical transition temperature is relatively high (above 40°C, some are over 50°C).

To realize supramolecular control, supramolecular pairs (host and/or guest molecules) should be attached to polymer structures or used molecules. The co-existence of these host and/or guest molecules may restrict the potential application of supramolecular interaction controlled LCST systems in biological systems. For example, several currently employed guest molecules are highly toxic paraquat/diquat derivatives. Furthermore, the removal of these molecules from a solution is challenging, following their use as chemical stimuli. In future studies of supramolecular interaction controlled/induced LCST, the supramolecular pairs should not be limited to macrocycles and their complementary guests. Supramolecular systems with hydrogen bonding, metal coordination, and charge transfer can be used as good candidates to provide supramolecular control over LCST systems.[64] Moreover, more efforts should be devoted to the transition from single molecules to aggregates in the design of supramolecular interaction controlled systems.

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