Supramolecular control over thermoresponsive polymers

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Victor R. de la Rosa[1], Patrice Woisel[2] and Richard Hoogenboom[1,*]

[1] Supramolecular Chemistry Group, Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan 281-S4, B-9000 Ghent, Belgium
[2] Université Lille Nord de France, ENSCL, Unité des Matériaux et Transformations, UMR CNRS 8207, Equipe Ingénierie des Systèmes Polymères (ISP), F59655 Villeneuve d'Ascq Cedex, France

Thermoresponsive polymers facilitate the development of a wide range of applications in multiple areas spanning from construction or water management to lab-on-a-chip technologies and biomedical sciences. The combination of thermoresponsive polymers with supramolecular chemistry, inspired by the molecular mechanisms behind natural systems, is resulting in adaptive and smart materials with unprecedented properties. This work reviews the past advances on the combination of this young field of research with polymer chemistry that is enabling a high level of control on polymer architecture and stimuli-responsiveness in solution. We will discuss how such polymer systems are able to store thermal information, respond to multiple stimuli in a reversible manner, or adapt their morphology on demand, all powered by the synergy between polymer chemistry and supramolecular chemistry.

Introduction

In the past, the interest on materials was focused on the search of a composition that would confer the properties of interest (corrosion resistance, hardness, color, among others) to a certain device or machine, and would change as little as possible in time. If different properties were needed, then different materials were assembled together.

However, the paradigm is now evolving toward the search for materials that, far from being fixed and static, can actively perform tasks and adapt to the environment. The natural world around us is replete with examples of these responsive materials, such as the bacterial flagellum that drives the bacterium toward the nutrients, our muscles which contract on release of calcium ions from the nerve terminals, or the lens that changes its focal length when your gaze shifts from the page to the horizon. All these systems are, at least partially, based on a combination of polypeptide chains or proteins. This kind of materials, that are able to respond or adapt to changes in the environment, has been regarded to as intelligent or smart materials. The key difference with any other artificial material that responds to environmental changes (such as the thermal expansion of a metal) is that smart materials react to changes by design. Responsive polymeric materials that undergo a phase transition in response to external stimuli are perhaps the smart materials with most parallels with natural systems, and they have attracted much scientific interest [1,2].

The triggering event that induces the phase-changing event might be originated by a chemical or biological agent [3,4], the rise or fall in temperature [5–8], electromagnetic radiation [9–11], pH [12–14], ionic strength [15,16], the arrival of a magnetic [17,18] or electrical impulse [19,20], or the application of mechanical forces [21], to enumerate some examples. The specific response of the material can also be manifold, and changes can be induced in the surface properties of the material [4], its shape [22], its interaction with light [21,23], diffusivity [24], or its solubility properties [5,6]. In particular, thermoresponsive polymers, with the ability to respond to changes in temperature, have led to the development of a vast number of applications in areas spanning construction [25,26], water management [27], separation sciences [28,29], shape memory materials [30], and biomedicine [31], and allow the development of smart soluble materials or smart fluids. Most of such polymeric materials that undergo a solubility phase transition in response to a change in temperature exhibit a lower critical solution temperature (LCST) [32].

*Corresponding author:. Hoogenboom, R. (Richard.Hoogenboon@ugent.be)

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Lower critical solution temperature (LCST)

The behavior of a polymer in solution reflects the balance of positive and negative interactions with the surrounding solvent molecules. In aqueous solutions, the role of solvent-solvent interactions is particularly strong, as a result of the partially ordered structure of water. The particularities of this solvent [33] and its capacity to direct the conformation of the biological molecules are in fact responsible for the occurrence of life on Earth. Polymers exhibiting LCST behavior establish a network of hydrogen-bonds with surrounding water molecules, that arrange around the polymer polar groups forming clathrate-like structures. The established hydrogen-bonds result in a favorable exothermic enthalpy contribution ($\Delta H < 0$), driving the dissolution of the polymer. However, the clathrate structures formed also lead to an unfavorable entropy of mixing (negative ΔS), term that increases its importance along with rising temperature. Beyond a certain critical temperature value, regarded as the LCST, the entropic term predominates, and the difference in the Gibbs free energy (ΔG) becomes positive (Eq. (1)), resulting in phase separation [5].

$$\Delta G = \Delta H - T\Delta S \quad (1)$$

Because the phase transition temperature (the cloud point temperature, T_{CP}) depends on polymer concentration, a complete phase diagram of polymer concentration has to be measured to determine the LCST [5]; per definition, the lowest phase separation in the phase diagram. In addition, the phase transition temperature is also dependent on the polymer molecular weight, usually being lowered with increasing polymer length [34]. Nevertheless, in most cases polymer concentration is kept fixed, or varied within a small range, and therefore T_{CP} values are reported, being the phase separation temperature at a certain polymer concentration where the solution becomes turbid. Figure 1 shows an idealized representation of the temperature-induced phase transition of LCST polymers in aqueous solution.

Smart systems based on polymers and supramolecular chemistry

As defined by Jean Marie Lehn almost 25 years ago, supramolecular chemistry, that is, the chemistry beyond the molecule or the covalent bond, is the designed chemistry of the intermolecular bond, just as molecular chemistry is that of the chemical bond [35]. This relatively young area of science lays at the intersection of chemistry, physics and biology, and its wide horizons continue to be a source of challenges and inspiration for the chemist. Non-covalent interactions are indeed the primary driving force of nature to direct the self-assembly of biomacromolecules into the wide variety of architectures that configure the world of the living organisms at the nanoscale. The incorporation of non-covalent interactions in synthetic polymer systems therefore appears as a powerful approach to confer qualities and properties typical of natural systems to artificial structures. The specificity of the enzyme lock and key principle can be mimicked via supramolecular interactions via host–guest chemistry enabling the control on the polymer structure and properties in a reversible and adaptive manner [36–44].

In this contribution, we will discuss some of the recent advances of the combination of thermoresponsive polymers and supramolecular chemistry to obtain smart materials that benefit from interactions with other macromolecules resulting in responsive and adaptive materials. Although several recent reviews appeared on supramolecular polymer assemblies [45–50], this review will have special emphasis on thermoresponsive polymeric systems modulated by supramolecular host–guest interactions.

Modulating polymeric architectures by supramolecular interactions

The variation of a polymer structure by copolymerization or grafting allows the tuning of its solubility and self-assembly properties in solution. The incorporation of supramolecular host or guest moieties into a polymer offers a reversible handle for functionalization via non-covalent chemistry, affording adaptive structures. Inspired by nature's supramolecular systems, hydrogen-bonding, π–π stacking, dipole–dipole, Coulombic, metal–ligand coordination, or hydrophobic interactions have been utilized to direct the self-assembly of polymer chains in solution, and to modulate the polymer response to external stimuli [51–53]. In addition, the supramolecular information embedded in the

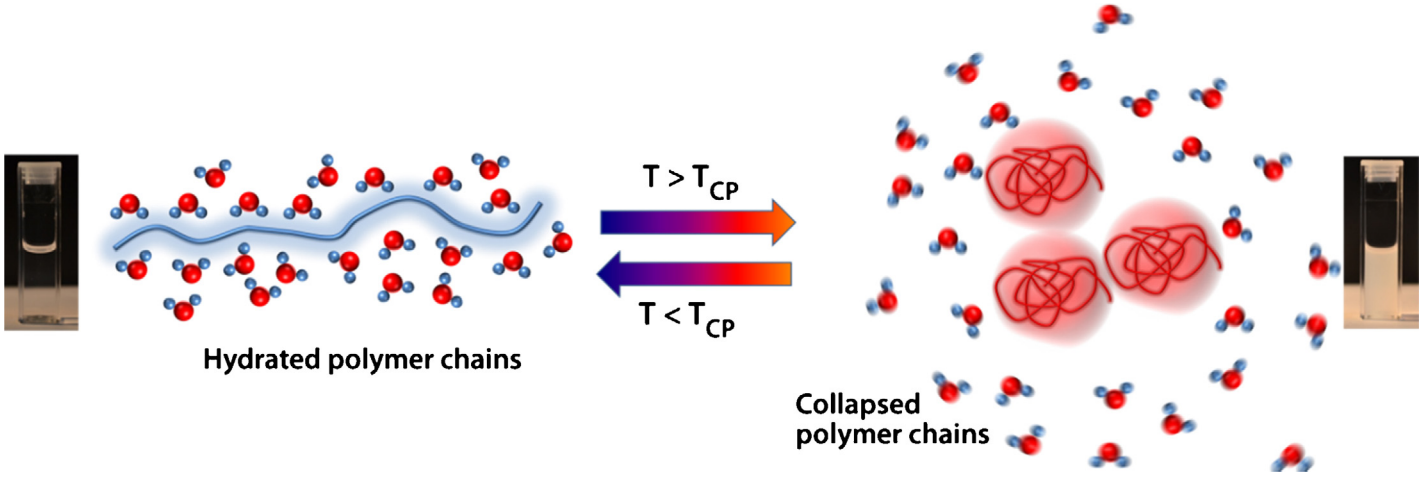

FIGURE 1

Schematic representation of the lower critical solution temperature (LCST) reversible demixing phase transition of polymers in water. Below the cloud point temperature, the polymer chains are hydrated, resulting in a clear solution (left). Heating beyond the T_{CP} causes the entropy-driven hydrophobic collapse and aggregation of the polymer chains and the release of the solvation water molecules to the bulk water, leading to a cloudy solution (right).

host/guest moieties attached to the polymer chain enables specific molecular recognition that can be governed, just as natural systems, by the temperature, ionic strength, pH or other stimuli in solution.

In virtue of the reversibility of intermolecular forces, besides offering a high level of control on polymer conformation, supramolecular chemistry also offers the ability to switch it on demand.

Controlling the helicity of polymers, in analogy to poly(nucleic acid)s or poly(amino acid)s, affords materials of interest in data storage, optical devices, and liquid crystals for displays, and nicely illustrates the potential of combining polymer and supramolecular chemistry [54,55]. An illustrative example was developed by Kakuchi *et al.*, who synthesized a poly(4′-ethynylbenzo-15-crown-5) conjugated polymer furnished with crown ethers that established host–guest interactions with several amino acids in a chloroform/acetonitrile (1/1, v/v) solvent mixture. These interactions directed the formation of a one-handed helical configuration of the polymer chains, as determined by circular dichroism, whose sense was dictated by the chirality of the amino acid guest. The formation of 2:1 crown-ether–amino acid host–guest complexes was shown to induce a conformational change in the polymer chain that modulates the binding affinity for further host–guest complex formation. This cooperative binding effect is directly related to the presence of multiple supramolecular moieties in a polymer chain, and reveals the interesting properties that arise when coupling polymers to supramolecular interactions. This recognition is manifested in this case by a sharp shift of the induced circular dichroism in the presence of the amino acid guest at −30°C, indicating host–guest complexation, and at 30°C, indicating host–guest disassembly (Fig. 2). Interestingly, varying temperature allows to modulate the strength of the host–guest complex [56] that, because of the cooperative nature of the binding, permits full on-off switching of the polymer chain chirality [57,58].

Other examples based on beta-cyclodextrin functionalized conjugated polymers have been reported, and allow for visual observation of the helicity changes with temperature, and in the presence of competitive guests [59].

The formation of graft and block copolymers through supramolecular chemistry represents a convenient methodology to modulate polymer self-assembly in solution, and to confer responsive properties to the nanostructures [60–62]. Woisel, Cook *et al.* have demonstrated the potential of specific host–guest interactions to control micelle formation of a tetrathiafulvalene (TTF) end-functionalized poly(*N*-isopropylacrylamide) PNIPAAm amphiphilic polymer [63]. Using Nile red as a molecular fluorescent probe, the formation of micelles containing a TTF core was confirmed by fluorescence studies. The micelles could be disassembled by oxidation of TTF and, interestingly, by the addition of a suitable host macromolecule such as randomly methylated beta cyclodextrin (RAMEB) or cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) that formed inclusion complexes with TTF rendering it hydrophilic. Micelles that were disrupted by the formation of TTF-RAMEB complexes could be reformed by addition of adamantanol as a competitive guest for RAMEB [64]. Similar examples of micelle formation/deformation by supramolecular interactions have been reported by Volet and Amiel based on poly(2-oxazoline)s terminated with an alkylic chain as guest and cyclodextrins as host [65,66].

A similar strategy was applied for the preparation of thermoresponsive double-hydrophilic diblock copolymers, by host–guest interaction between $CBPQT^{4+}$-terminated PNIPAAm and TTF-terminated PEG or poly(*N*,*N*-dimethylacrylamide) (PDMA). The formation of the supramolecular block copolymer was confirmed by 2D diffusion-ordered spectroscopy (DOSY) ^{1}H NMR spectroscopy, isothermal titration calorimetry. UV-Vis spectroscopy also proved the binding by the appearance of a green color and an absorption band at around 800 nm, both originating from the donor–acceptor interactions between the π-electron-deficient cavity of the $CBPQT^{4+}$ unit and the π-electron-rich TTF moiety. Interestingly, the host–guest complexes, and thus the diblock copolymer structure, remained stable upon the temperature-triggered collapse of the PNIPAAm thermoresponsive domain [67].

As seen in the aforementioned example, the incorporation of suitable host and guest units in the polymer chain ends allows the

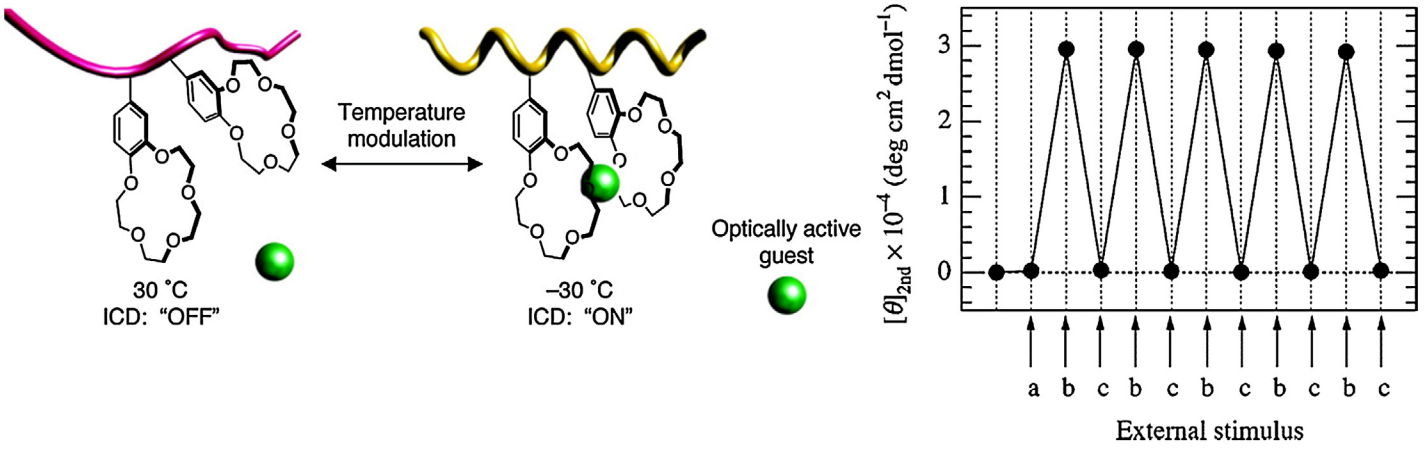

FIGURE 2

Left: Schematic illustration of the macromolecular helicity induction of poly(4′-ethynylbenzo-15-crown-5) driven by the host–guest complexation with an optically active guest (L-phenylglycine) and the thermoresponsive on–off switching of an induced circular dichroism (ICD) based on the construction and collapse of the one-handed helical structure. Right: Plot of the $[\theta]_{2nd}$ values of the polymer upon continuous external stimuli showing the $[\theta]_{2nd}$ value for a polymer solution in chloroform/acetonitrile (1/1, v/v) at 30°C. The stimuli (a–c) represent the addition of 1.0 equiv. of L-Pgly·$HClO_4$ at 30°C (a), changing temperature to −30°C (b), and changing temperature to 30°C (c). Reprinted from Ref. [58] by permission of the American Chemical Society (2006).

straightforward formation of supramolecular block and miktoarm copolymers [47,62,68,69]. As an illustrative example, multiresponsive double hydrophilic block copolymers were formed *via* host–guest complexation between terminal beta cyclodextrin (βCD) and adamantane (AD) moieties present in PNIPAAm (βCD-PNIPAAm) and poly(2-(diethylamino)ethyl methacrylate) (AD-PDEA) homopolymers, respectively. The two homopolymers orthogonally self-assembled into supramolecular PNIPAAm-*b*-PDEA copolymers, as confirmed by 2D nuclear Overhauser effect spectroscopy (NOESY). The supramolecular copolymer exhibited a ''schizophrenic'' self-assembly behavior in aqueous solution. Copolymers with a so called schizophrenic character self-assemble in solution producing two distinct micellar structures, as the individual blocks can become either hydrophilic or hydrophobic depending on subtle changes in solution temperature, pH, ionic strength, among others. [70]. Specifically, at room temperature and pH < 6, it existed as unimers, whereas it formed PDEA core micelles with PNIPAAm coronas at pH > 8 because of the deprotonation of the PDEA block. Furthermore, vesicular nanostructures with collapsed PNIPAAm bilayers and solvated inner/outer PDEA coronas formed at temperatures above the LCST of PNIPAAm at pH 4. The thermo- and pH-induced morphological transitions were fully reversible [71].

Yuan *et al*. added an extra layer of complexity by coupling PNIPAAm to adamantanol-initiated poly(e-caprolactone) (PCL) via thiol-ene Michael addition [72]. A supramolecular triblock copolymer could be formed by inclusion complex formation of this diblock copolymer with βCD end-functional poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA). The resulting ABC triblock copolymer formed vesicles in solution that swelled in the presence of CO_2, because of the protonation of the DMAEMA units. In addition, heating beyond the T_{CP} of the PNIPAAm block induced the formation of micelles (Fig. 3). The authors evaluated the *in vitro* cytotoxicity of the vesicles obtaining promising results for the use of this system in drug delivery applications.

In analogy to end-functionalized host/guest polymers, incorporation of supramolecular motifs across the polymer backbone render supramolecular graft copolymers with tunable micellization behavior [73–75]. In this context, a very recent report by Huang *et al.* describes the reversible switching between micellar and vesicular structures by the application of temperature or light stimuli [76]. The authors synthesized an amphiphilic copolymer based on polystyrene decorated with 12 mol% azobenzene units, that formed host–guest complexes with methoxy-tri(ethylene glycol) (mTEG) functionalized pillar[7]arene [77]. As seen in Fig. 4, the supramolecular ensembles formed vesicles at room temperature. Interestingly, the thermoresponsive character of the supramolecular host confers thermoresponsive properties to the polymer-cavitand ensemble. Because of the presence of the mTEG moieties, the pillar[7]arene cavitands exhibited an LCST behavior that was used to break the host–guest complexes upon heating the solution, resulting in a transition from vesicles to micelles. A similar transition was achieved by UV irradiation of the solution, which also induced the breakage of the azobenzene-pillar[7]arene complexes by shifting the azobenzene *trans* conformation to *cis*.

In addition, responsive hyperbranched polymeric structures and dendrimers can be realized by incorporation of multiple supramolecular moieties onto the polymer. Similarly as with other copolymer architectures, the assembly/disassembly of the hyperbranched structures can be controlled by the addition of a competitive guest [78–80], or other stimuli [81,82], making these responsive supramolecular systems of interest for the development of, for example, drug/gene delivery carriers.

Tuning polymer stimuli-responsiveness *via* supramolecular chemistry

Besides the impact on polymer morphology in solution, the combination of supramolecular hosts with thermoresponsive polymers allows to finely tune the polymer transition temperature. In addition, sensitivity toward additional stimuli can be introduced by using stimuli-responsive host–guest systems. Amphiphilic host molecules, such as cyclodextrins, featuring a hydrophilic outer shell and a hydrophobic cavity, can complexate with hydrophobic guests present in a thermoresponsive polymer, thereby increasing its hydrophilicity and T_{CP}. Many examples have been reported on complexation of cyclodextrins with end-group guest-functionalized thermoresponsive polymers, including PNIPAAm-azo dye [83], PNIPAAm-vinylcyclopropane [84], or poly(*N*,*N*-diethylacrylamide)-4-alkylphenol with methylated βCDs [85]. As expected, T_{CP} variations were found to be dependent on the excess of cyclodextrin host added, and typically increased by less than 5 K, although a T_{CP} increase of close to 10 K was observed in a *tert*-butyl phenyl-terminated poly(*N*,*N*-diethylacrylamide) (PDEAAm) thermoresponsive polymer in the presence of 2 equiv. of methylated-βCD. The addition of an excess of 1-adamantylamine as competitive guest reduced the cloud point temperature to an intermediate temperature between that of the free polymer and the polymer-cyclodextrin ensemble [86].

In another study, the T_{CP} of a 1,5-dialkoxynaphthalene-terminated PNIPAAm solution, could be tuned by the addition of $CBPQT^{4+}$ that forms a strong host–guest complex with the electron-rich dialkoxynaphtalene unit, similarly as seen previously with TTF. Upon addition of 1 equiv. of $CBPQT^{4+}$, the T_{CP} increased from *ca*. 28°C to 34°C, because of host–guest complex formation. By contrast with the behavior observed with TTF, in this case the dialkoxynaphtalene-$CBPQT^{4+}$ host–guest complexes were broken upon thermal collapse of the PNIPAAm chain. This was demonstrated by the disappearance of the purple color characteristic of the dialkoxynaphtalene-$CBPQT^{4+}$ donor-acceptor complex, and despite the large association constant of the host–guest couple ($K_a > 10^5\ M^{-1}$, as determined by ITC). The breakage of the host–guest complex was further confirmed by UV-Vis and ^1H NMR spectroscopy [87].

The disruption of the host–guest complexes upon the temperature-induced collapse of the copolymer was also observed for a thermosensitive cationic diblock copolymer composed of PNIPAAm-*b*-poly(3-acrylamidopropyl)trimethylammonium chloride ($PNIPAAm_{24}$-*b*-$PAMPTAM(+)_9$). Gamma cyclodextrin (γCD) was found to thread around the PNIPAAm polymer backbone forming pseudopolyrotaxanes. Increasing temperature to 40°C, beyond the PNIPAAm LCST, induced the dethreading of the γCD molecules, as observed by steady-state fluorescence spectroscopy [88].

The incorporation of hydrophobic units throughout the polymer backbone, acting as host moieties for suitable cavitands, multiplies the hydrophilicity gain upon host–guest complex for-

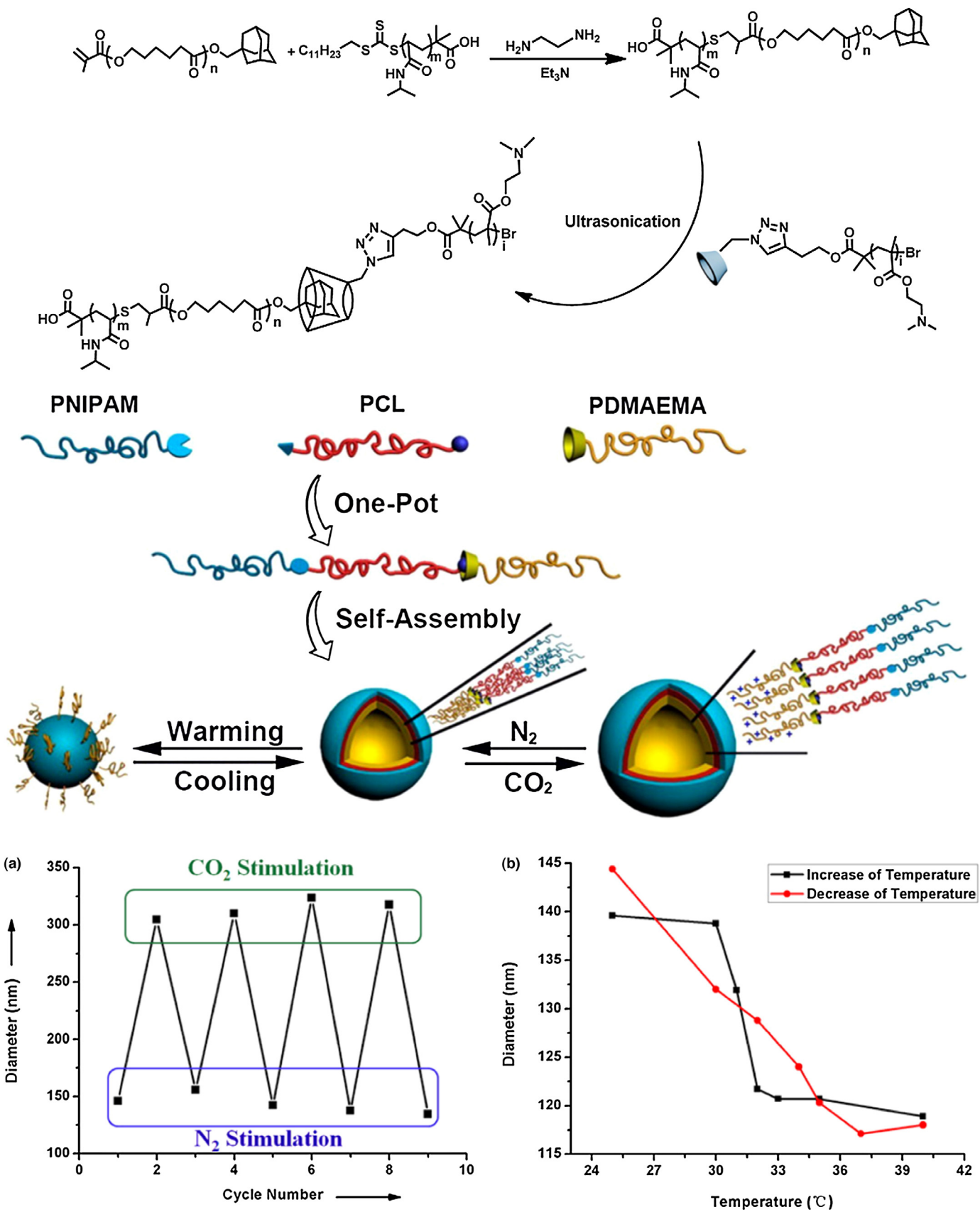

FIGURE 3

Top: Synthetic route toward the supramolecular triblock copolymer $PNIPAAm_{45}$-*b*-PCL_{40}-*b*-$PDMAEMA_{25}$. Center: Illustration of the self-Assembly of the supramolecular triblock copolymer PNIPAAm-*b*-PCL-*b*-PDMAEMA, and its CO_2-temperature dual stimuli-responsiveness. Bottom: Diameter change of PNIPAAm-*b*-PCL-*b*-PDMAEMA aggregates under alternating CO_2/N_2 stimulation (a) and as temperature increases and decreases (b), measured by dynamic light scattering. Adapted with permission from Ref. [72] by permission of the American Chemical Society (2014).

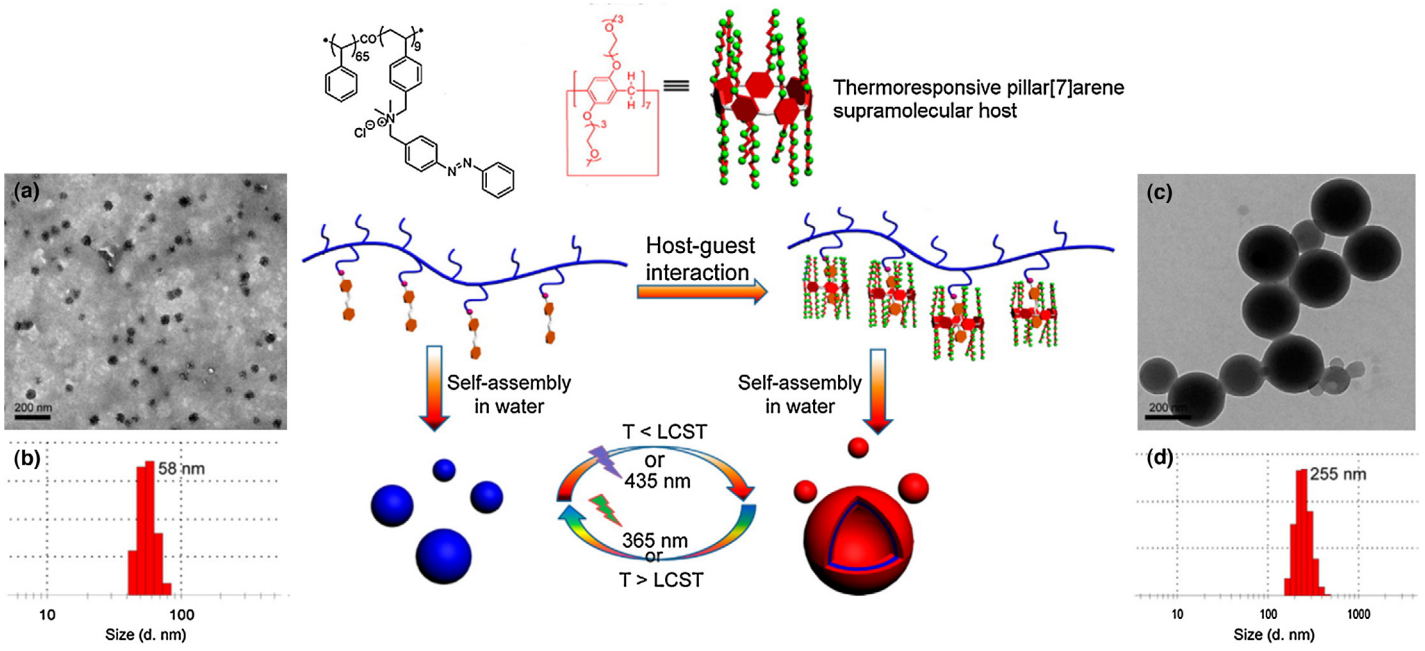

FIGURE 4

Schematic representation of the dual-responsive transition between micelles and vesicles, including chemical structures of the copolymers and the pillar[7]arene hosts. (a) TEM image of an aqueous solution of 7.00 mM of the copolymer and 1.00 mM of the pillar[7]arene upon heating to 60°C; (b) DLS result of (a); (c) TEM image of the same aqueous solution after further cooling to 25°C; (d) DLS result of (c). Adapted with permission from Ref. [76] Copyright (2015), American Chemical Society.

mation leading to larger increments in the T_{CP} of the polymer. Recently, Ritter *et al.* reported the thermoresponsive behavior of a copolymer containing 2-methacrylamido-caprolactam and *N,N*-dimethylacrylamide in a 0.7:0.3 molar ratio obtained by free radical copolymerization [89]. The copolymer T_{CP} was determined to be 34°C by turbidimetry, and increased to over 50°C upon addition of 1.5 equiv. of methylated-βCD (Fig. 5). The authors confirmed the cyclodextrin-caprolactam inclusion complex formation by 2D Rotating frame nuclear Overhauser effect spectroscopy (ROESY) NMR, and the 1:1 stoichiometry by a Job's plot. However, no correlation between host concentration and T_{CP} was given. Interestingly, the cyclodextrin complexation with the caprolactam units lowered the T_{CP} for the upper critical solution temperature (UCST) exhibited by this copolymer in short-chain alcohols solutions.

In another recent account [90], free radical polymerization of NIPAAm, *N,N*-dimethylacrylamide (DMAA), and a cholic acid-based methacrylate monomer (CA) resulted in a P(NIPAA$_{75}$-*co*-DMAA$_{25}$-*co*-CA$_2$) statistical copolymer with a $T_{CP} \approx 22$°C. Titration with different amounts of βCD produced an increase in the copolymer T_{CP} because of host guest complexation between the CA pendant groups and βCD. The authors studied the size of the aggregates formed upon collapse of the polymer chains, observing that the size of the aggregates was reduced when a large excess of βCD was present (200–300 nm), in relation with the aggregates formed upon collapse of the free polymer (>600 nm). This possibly indicates incomplete breakage of the host–guest complexes. When adamantane carboxylate (AD) was added as a competitive guest, the T_{CP} could be brought back to the original value of the free polymer. Although the T_{CP} of the copolymer-βCD ensemble increased with the concentration of βCD, up to 10 equiv. of the cavitand were necessary to increase the T_{CP} to 31°C. Similar results were obtained in another study performed on a copolymer comprising PNIPAAm and different levels of substitution with adamantane- and dodecyl-*N*-substituted acrylamide monomers [91]. As expected, the influence of the supramolecular host was larger on the polymers containing a higher content of alkyl substituents. The addition of 3 equiv. of hydroxypropylated-βCD (HPβCD) to a PNIPAAm-C12 copolymer containing 4.4% C12 side-chains produced an increase in the T_{CP} of 9 K.

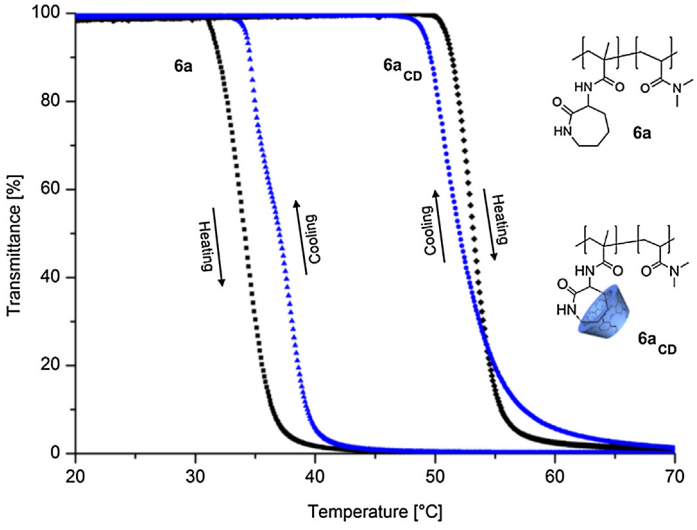

FIGURE 5

Turbidity curves upon heating and corresponding curves upon cooling of 10 mg mL^{-1} solution of a 2-methacrylamido-caprolactam and *N,N*-dimethylacrylamide copolymer with a 0.7:0.3 molar ratio. Heating/cooling rate of 1°C min^{-1}. Reproduced from Ref. [89] Creative Commons Attribution License, 2014 Burkhart and Ritter.

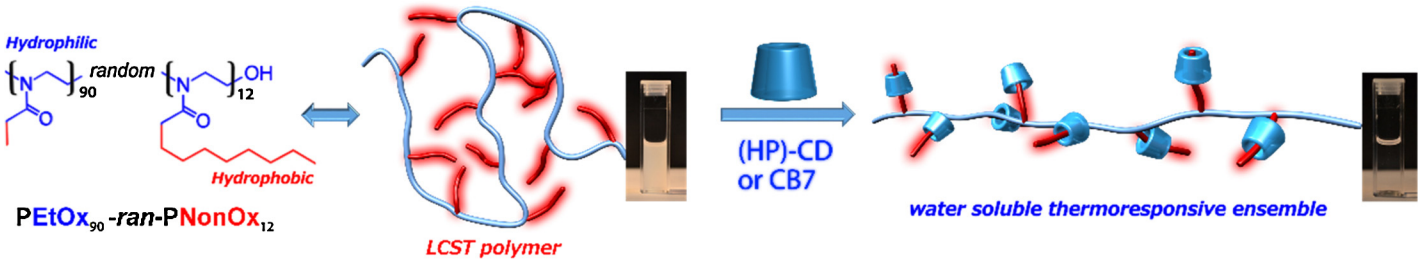

FIGURE 6

The solubility properties of an amphiphilic $PEtOx_{90}$-*ran*-$PNonOx_{12}$ random copolymer were evaluated in the presence of a range of supramolecular host molecules. The picture describes the supramolecular complexation of the $PEtOx_{90}$-*ran*-$PNonOx_{12}$ with cavitands resulting in the formation of thermoresponsive supramolecular complexes. Adapted from Ref. [92]. Copyright (2015) Royal Society of Chemistry.

Besides the increasing number of publications exploring the interactions between supramolecular hosts and thermoresponsive polymers, we identified a lack of systematic studies on the effect of cavitand type in the solubility properties of well-defined thermoresponsive polymers. Therefore, we recently reported a series of studies based on relatively simple, narrowly dispersed random copoly(2-oxazoline)s based on 2-ethyl-2-oxazoline (EtOx) (hydrophilic) and 2-nonyl-2-oxazoline (NonOx) (hydrophobic)

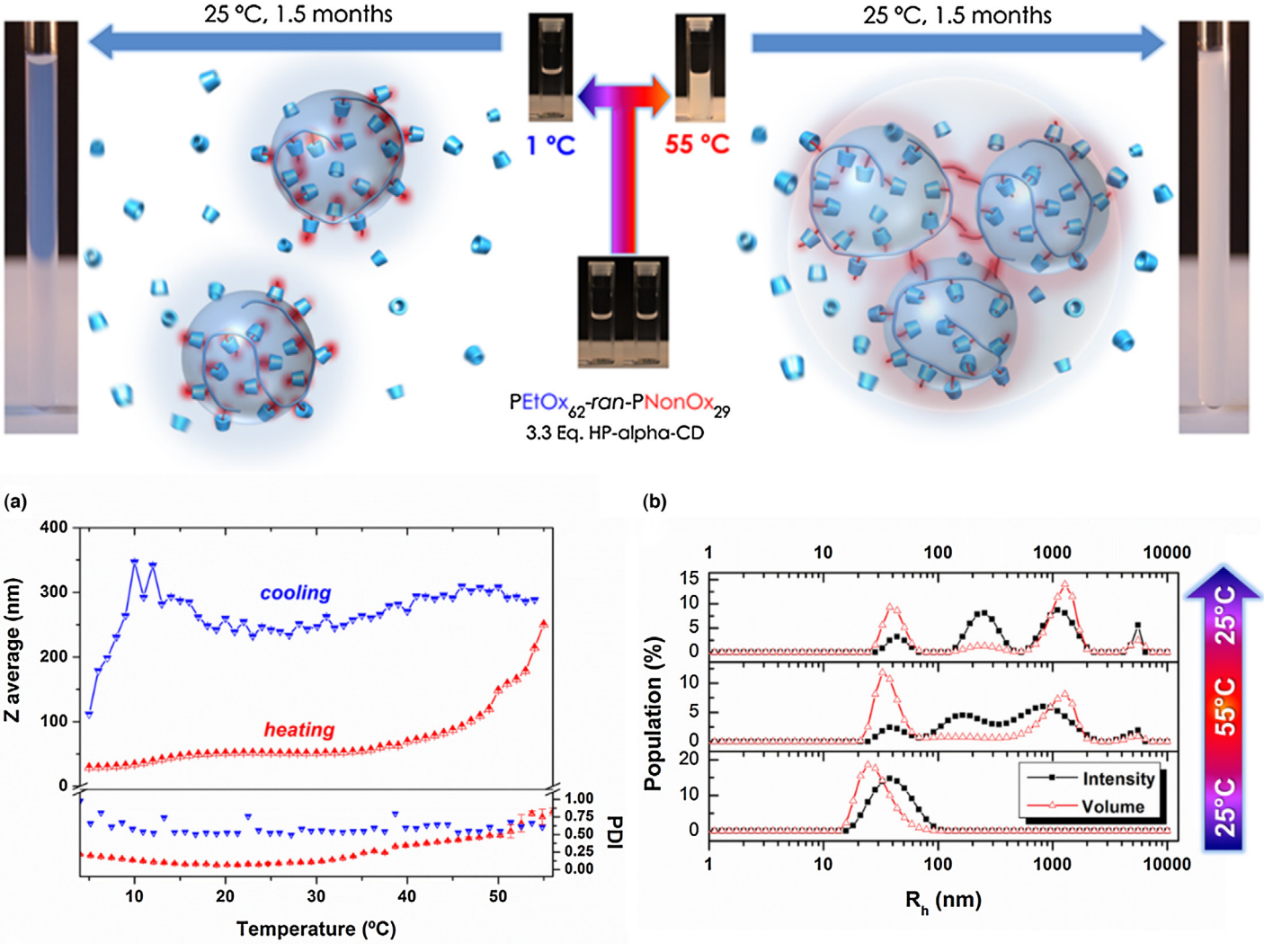

FIGURE 7

Top: Schematic representation of the supramolecular nanoparticles formed by host–guest complexation of the PEtOx-PNonOx copolymer and cyclodextrins, based on interpretation of the experimental data. Two aliquots of the same P[$(EtOx)_{62}$-*ran*-$(NonOx)_{29}$] solution containing 3.3 equiv. of HPαCD were, respectively, taken to 55°C and 1°C for 1 min. Subsequently, both samples were brought to room temperature and their appearance remained largely unvaried, even after 1.5 months. Bottom: (a) Temperature dependent dynamic light scattering data from the same solution showing a large hysteresis spanning ca. 40 K. (b) Size distribution of the sample at 25, 55, and back to 25°C. Well-defined (PDI 0.10) stable nanoparticles are observed at 25°C. Heating to 55°C leads to the appearance of larger particles and aggregates that remain stable when cooled back to 25°C. Rh = 230 nm. Adapted from Ref. [94]. Copyright (2015) Wiley-VCH Verlag GmbH & Co.

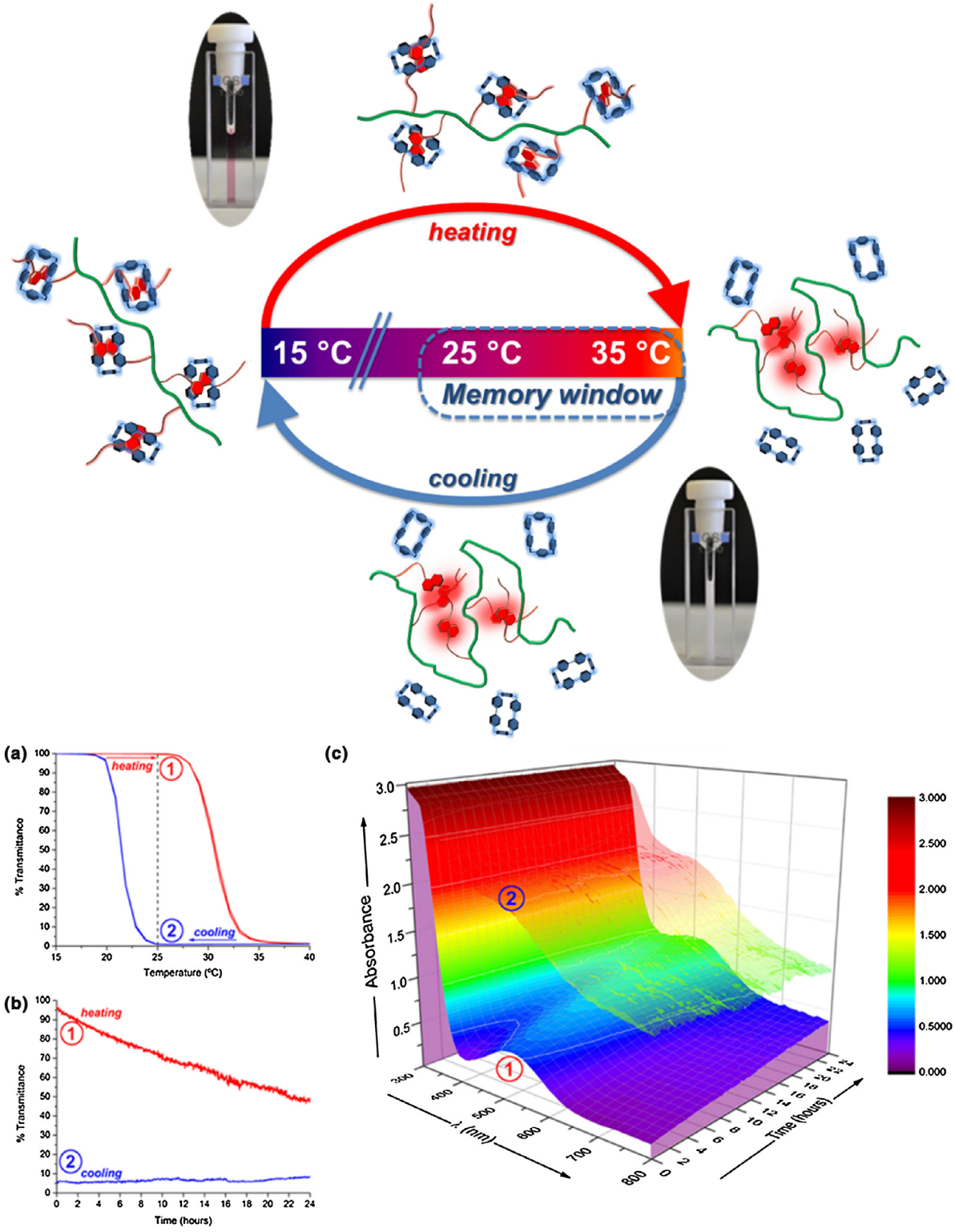

FIGURE 8

Top: Schematic representation of the temperature sensor with memory based on dialkoxynaphthalene-decorated PNIPAAm in combination with $CBPQT^{4+}$. (a–c) UV-vis experiments demonstrating the memory-stability. All the experiments were performed on aliquots from a solution containing the $PNIPAAm_{195}$-$naphtalene_5$ copolymer (5 mg mL^{-1}) and 5 equiv. of $CBPQT^{4+}$. (a) Transmittance versus temperature plot (2 overlapping heating/cooling cycles). The memory-stability experiments were performed at 25°C (dotted line), within the limits of the hysteresis window. Heating rate: 1 K min^{-1}, λ = 700 nm. (c) Evolution of transmittance at 700 nm at 25 °C for a sample that was cooled from 45°C to 25°C (label (1)) and a sample that was heated from 15°C to 25°C (label (2)). (c) Full UV-vis absorbance spectra of the solution at 25°C corresponding to the heated and cooled samples in b. The spectra were isothermally recorded over a period of 24 h (1 scan/1.4 min). Adapted from Ref. [95] Copyright (2014) Wiley-VCH Verlag GmbH & Co.

[92,93]. In particular, the combination of a thermoresponsive PEtOx-*ran*-PNonOx copolymer containing 12 mol% nonyl side-chains with a range of cyclodextrins and cucurbit[7]uril (CB7) hosts resulted in an unprecedented increase of the T_{CP} of 30 K with stoichiometric amounts of the cavitands (Fig. 6) [92].

The broad tunability of the T_{CP} achieved in this study is in line with the intuitive assumption that a higher content of hydrophobic guest units across the copolymer chain allow the incorporation of a larger number of cavitands therefore expanding the T_{CP} tunability of the copolymer. Later on, however, we will see that incrementing the copolymer's hydrophobicity can lead to less obvious results.

Essentially, in this study it was found that the power of a certain cavitand to modulate the solubility of the PEtOx-*ran*-PNonOx copolymer is mainly related to its affinity to the nonyl hydrophobic guest units, and not to its hydrophilicity. It thus seems that the solubility phase transition of the copolymer-cavitand ensemble is governed by the thermal-induced breakage of the cavitand-nonyl host guest complexes. Interestingly, analysis of the T_{CP} variation upon addition of different cavitands allowed to estimate the association constant for each cavitand, resulting in the following order of binding affinity: CB7 ($2200\ M^{-1}$) ≫ alpha-cyclodextrin ($440\ M^{-1}$) > hydroxypropyl-alpha-cyclodextrin ($220\ M^{-1}$) > hydroxypropyl-beta-cyclodextrin ($120\ M^{-1}$). In analogy to other reported systems, the addition of a competitive guest induced the phase transition of the copolymer, confirming the reversibility of the cavitand-nonyl host–guest complexes.

Temperature sensors with memory

As has been seen, increasing the content of hydrophobic guest units along the copolymer expands its T_{CP} tunability by combination with supramolecular hosts. However, further increasing the hydrophobicity of the copolymer progressively induces its self-assembly in solution, leading to the formation of polymer nanoparticles. This was recently found in water insoluble PEtOx-*ran*-PNonOx copolymers with a large NonOx content, that require the presence of an excess of cavitand in solution at low temperatures to be solubilized [93]. For example, when $PEtOx_{62}$-*ran*-$PNonOx_{29}$ was solubilized in the presence of 3.3 equiv. of HPαCD, stable kinetically trapped nanoparticles were formed. The solubility properties of these nanoparticles was highly unusual, as they remained stable in solution up to *ca.* 50°C, when a transition toward larger aggregates took place, turning the solution opaque. This thermoresponsive system exhibited a broad hysteresis, as the individual nanoparticles, and the transparent solution, could only be recovered by cooling to close to 0°C. Importantly, both the nanoparticles and their aggregates were stable for over 1.5 months at room temperature, thus allowing to record thermal information in the supramolecular structures (Fig. 7). In addition, the transition temperature and its reversibility could be tuned by the selection of the cavitand. The strength of the host–guest interaction thus dictated the stability of the nanoparticles [94].

Naturally, not only the number but also the nature of the hydrophobic units decorating the polymer needs to be considered to assess the influence of supramolecular complexation on the thermoresponsive properties of the copolymer. In a recent contribution, the LCST behavior of a P($NIPAAm_{195}$) copolymer bearing 5 dialkoxynaphthalene units across the polymer backbone was reported, and the effect of inclusion complex formation with $CBPQT^{4+}$ evaluated (Fig. 8) [95]. The polymer T_{CP} could be varied from ≈20°C to ≈32°C upon addition of stoichiometric amounts of $CBPQT^{4+}$ in relation to dialkoxynaphthalene moieties. Interestingly, a hysteresis spanning the whole solubility range was found for the copolymer – $CBPQT^{4+}$ stoichiometric mixture. Because of the high hydrophobicity of the dialkoxynaphthalene side chains, this large hysteresis was found to be stable in time, and applicable to the development of temperature sensors with memory. The complete disappearance of the purple color upon heating beyond the T_{CP} indicated the disassembly of the naphthalene–$CBPQT^{4+}$ donor-acceptor complexes.

Multi stimuli-responsive systems

As introduced earlier, the incorporation of responsive guests or hosts in the polymer structure enables the modulation of their interactions with host macromolecules in solution, affording multi-stimuli responsive systems [96,97]. A nice illustration of this multi-stimuli responsiveness is provided by the alpha cyclodextrin (αCD)-azobenzene host–guest couple, while the association constant between αCD and *trans*-azo derivatives is high ($K_a \approx 10^4\ M^{-1}$) [98], the *cis*-azo obtained by UV irradiation of the *trans* form yields relatively weak complexes with $K_a \approx 10^1\ M^{-1}$ [99]. The ability to control the host–guest complexation of αCD and azobenzene-functional polymers has been extensively investigated by Harada for the preparation of supramolecular hydrogels with a reversible sol-gel transition controlled by UV irradiation and for other supramolecular systems, including a photoresponsive artificial muscle [46,100–102].

One example of modulation of a polymer T_{CP} by light irradiation has been realized in a system comprising a poly(*N*,*N*-dimethylacrylamide-*co*-*N*-4-phenylazophenyl acrylamide) (PDMAA-*co*-PAPA) thermoresponsive copolymer and αCD. The copolymer containing 11.3 wt.% of azo groups, exhibited a T_{CP} of 29°C, that increased up to 45.5°C upon addition of 1 equiv. of αCD. Irradiation with 365 nm UV light for 40 min reduced the T_{CP} to ≈40°C as a consequence of the *trans* to *cis* conversion of the azo groups, and the consequent breakage of the azo-αCD inclusion complexes. The relatively small drop in T_{CP} upon irradiation was ascribed to the lower hydrophobicity of the *cis* azo derivative, that has a higher dipole moment than the trans form, leading to an increase in T_{CP} in relation with the *trans* form [103]. The dependence of the azo group conformation with T_{CP} has also been found in PNIPAAm-based copolymers where it is highly affected by the solvent composition [104].

A similar strategy based on a NIPAAm and paraquat-functional styrene thermoresponsive copolymer was recently reported by Huang *et al.* [105,106], in which the LCST transition of the copolymer could be tuned in a wide range of nearly 20 K by addition of different carboxy-functionalized water soluble pillararene hosts. In this case, the strong red coloration of the solution was maintained upon thermal collapse of the polymer-pillararene ensemble, indicating that most host–guest complexes remained stable, and thus the transition was mediated by the polymer phase transition (pictures in Fig. 9a). In addition, the protonation of the pillararene cavitands in acidic medium lowered their hydrophilicity, allowing to modulate the T_{CP} also by changing the pH of the solution (Fig. 9).

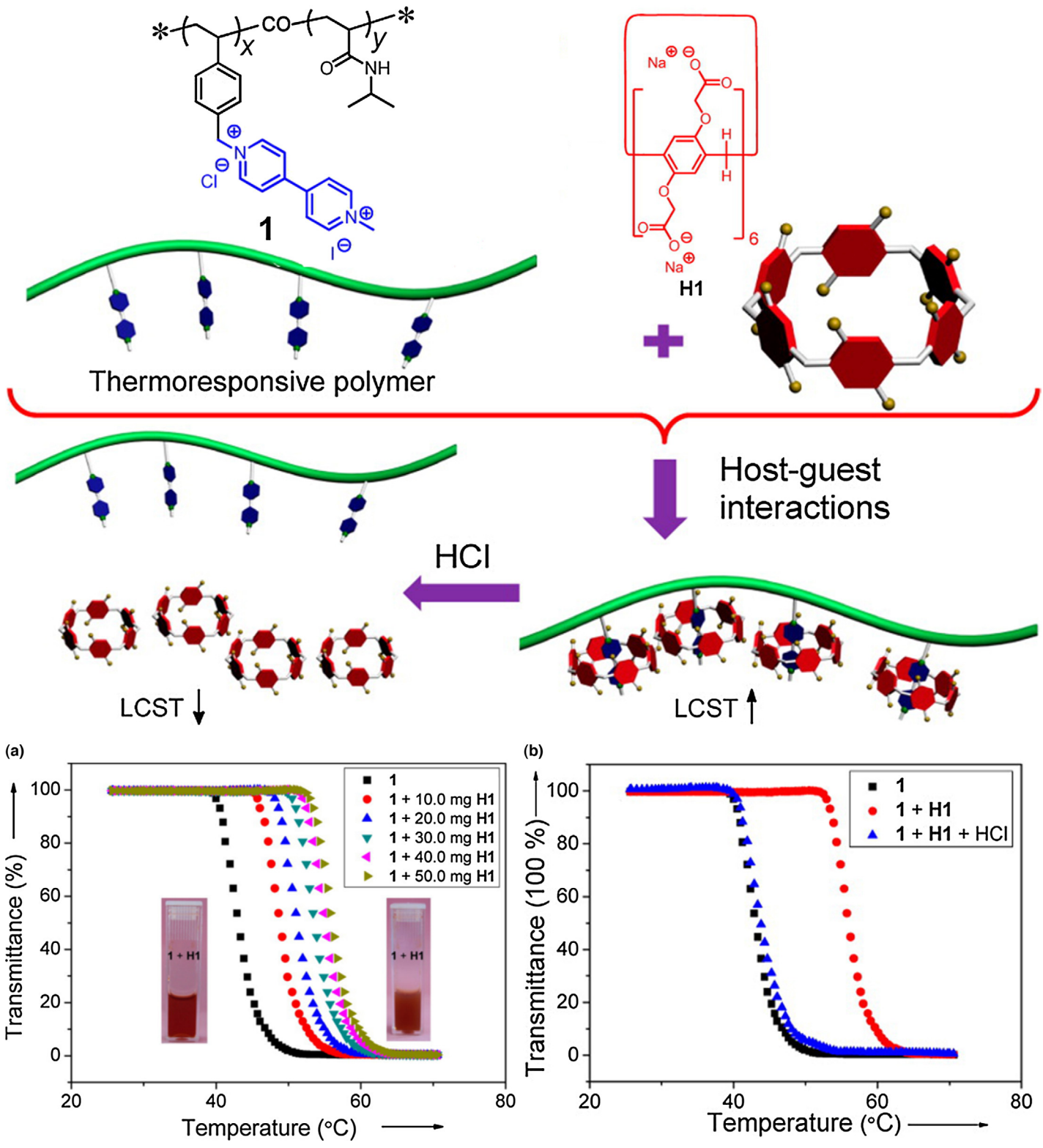

FIGURE 9

Top: Representation of thermoresponsive copolymer $PNIPAAm_{216}$-*co*-$(PS\text{-}paraquat)_{17}$ 1 and the water-soluble pillar[6]arene host H1. (a) Transmittance changes (550 nm) of copolymer 1 (1.11 mM) with the addition of different amounts of H1 (3.80, 7.60, 11.4, 15.2, and 19.0 mM). (b) Transmittance changes (550 nm) of copolymer 1 (1.11 mM) and upon addition of H1 (19.0 mM), or a mixture of H1 (19.0 mM) and HCl aqueous solution (42.0 μL). Adapted from Ref. [106] by permission of the American Chemical Society (2014).

Alternatively, the T_{CP} can be controlled by using a pH sensitive supramolecular guest, as was very recently reported in a system comprising diaminonaphthalene end-functionalized PNIPAAm in combination with $CBPQT^{4+}$ [107]. The donor-acceptor host–guest complex formation between the electron rich aminonaphtalene group and $CBPQT^{4+}$ resulted in a green coloration of the solution, and increased the T_{CP} from 29°C to 34°C. In addition, when the pH of the solution was lowered below 4.5 by the addition of HCl_{aq},

protonation of the aminonaphtalene group led to the disassembly of the complex because of repulsive Coulombic interactions with the $CBPQT^{4+}$ cationic host. Both thermal and pH triggers resulted in the loss of the solution coloration, indicative of dissociation of the host–guest complex.

Conclusions

Thermoresponsive polymers constitute a polymer type with a wide range of applications, as they bring together structure and function, therefore resulting in smart-materials of interest in applications ranging from construction, to microfluidics, lab-on-a-chip technologies or biomedical sciences. The polymer morphology in solution and its response to temperature can be tuned by combining different hydrophilic and hydrophobic units in the polymer composition.

In addition, supramolecular chemistry has recently emerged as a valuable strategy to modulate the conformation of polymer chains and their self-assembly behavior in solution resulting in complex adaptive structures strongly inspired by Nature. Moreover, the transition temperature of thermoresponsive polymers can be finely tuned in a reversible and adaptive manner by the incorporation of suitable supramolecular host molecules. The potential of host–guest interactions to modulate the LCST behavior of amphiphilic polymers constitutes a fascinating field of research that is blooming in the past years. The appropriate combination of copolymer composition and supramolecular host is allowing to tune the T_{CP} of the thermoresponsive polymers across a temperature range well beyond what had been recently envisioned. These phenomenological studies have established a solid background that serves as basis for more profound analyses on the temperature hysteresis and kinetic effects associated with these supramolecular systems. The importance of these kinetic effects is manifested in recent findings showing the ability of thermoresponsive polymers in combination with supramolecular hosts to remain in the collapsed state upon temperature-triggered aggregation. This kinetic control over the polymer phase transition is leading to temperature sensors able to store thermal information. Future research is needed to further expand the memory time-scales of these systems and the ability to program the transition temperature on demand, where more in-depth analyses of the kinetic effects related to the host–guest interactions are needed.

As this research area is still in its infancy, many fundamental questions remain unanswered and require further in depth studies, such as the interplay between phase-transition temperature and host–guest association constant, and whether the breakage of the host–guest complexes generally induces the thermal collapse of the polymer or vise versa or does this depend on the specific host–guest system evaluated.

As has been seen throughout this article, among all possible supramolecular hosts available, there is a clear prevalence of cyclodextrins, especially because of their good water solubility and capacity to form host–guest complexes with a wide range of hydrophobic guests in combination with commercial availability. This very limited variety of host–guest systems in combination with polymers should nevertheless be expanded in the future. The arousal of new research covering new pillar[n]arene or cucurbit[n]uril based supramolecular systems indicates a promising future in this regard. New host–guest systems may afford a higher level of control on the kinetics of the transition, while allowing to further expand the temperature range tunable by supramolecular interactions.

Finally, the introduction of stimuli-responsive supramolecular guests along the polymer side-chain or alternatively responsive supramolecular hosts is allowing to develop multi-stimuli responsive systems. These systems will furnish new molecular logic-gates, highly sensitive detection and diagnosis for lab-on-a-chip technologies, or drug/gene delivery carriers with improved targeted release. The hydrophobic nature of most potent active pharmaceutical ingredients, together with the inherent capability of supramolecular hosts to complexate hydrophobic guests, will definitely open the way to new therapies benefiting of these responsive systems. In all, considering the youth of both polymer and supramolecular chemistry, and all the achievements already realized, their combination will certainly bring us novel materials with unprecedented properties in the near future. Therefore, besides the need for further fundamental research in this field, future research should also aim to develop applications based on these versatile materials, that are especially promising in biomedicine.

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