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# Polymers with Upper Critical Solution Temperature in Aqueous Solution: Unexpected Properties from Known Building Blocks

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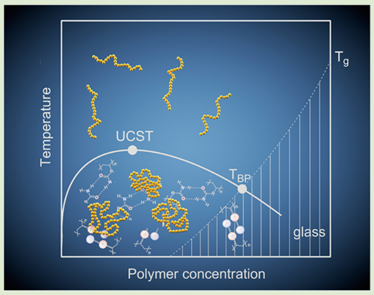
**ABSTRACT:** Polymers showing an upper critical solution temperature (UCST) in aqueous solution were not rare, but the UCST was rarely observed under practically relevant conditions. Recently, much progress has been made in the synthesis of polymer systems that display UCST behavior under mild and physiologic conditions. Current developments focus on polymers that rely on hydrogen bonding. This viewpoint explains the historical context, presents the major properties, and concludes with a discussion of the most recent examples.



Polymers with lower and/or upper critical solution temperature (LCST or UCST) in solution display a miscibility gap at high temperatures and/or low temperatures, respectively, and phase separation into a polymer-poor and polymer-rich phase is observed. During phase separation the polymer chains undergo a transition from the open coil state to the globule state. If the globules are not stabilized by surfactants or other means, subsequent aggregation to visible particles causes turbidity. Both UCST and LCST-type miscibility gaps are very common for polymer solutions.[1] In 1968 Heskins et al. showed for poly(*N*-isopropylacrylamide) (PNiPAAm) a LCST-type phase transition in water at around 32 °C with little change over a wide concentration range.[2] With progress in emerging water-based biochemical and medical sciences, the number of studies aiming to make use of the temperature-responsive behavior of PNiPAAm grew exponentially. Apart from PNiPAAm many other polymers with LCST behavior in water have been discovered, and to date numerous applications in the fields of tissue engineering, liquid chromatography, drug delivery, and bioseparation have been developed.[3] It was conspicuous that LCST polymers were exclusively chosen for these applications although polymers with UCST behavior would have been at least equally useful.

A recent review of the topic concluded that UCST behavior in water is not rare in general but was rarely observed under practically relevant conditions.[4] Whether UCST or LCST miscibilty gaps occurr depends on the free enthalpy of mixing which comprises enthalpic and entropic contributions. A detailed discussion about the nature of these contributions in the case of UCST polymers can be found elsewhere,[4] but it is agreed that an UCST arises from strong polymer−polymer and solvent−solvent interactions compared to weak polymer−solvent interactions. Additionally, the hydrophobic effect (entropic) is less dominant. Therefore, UCST behavior is called enthalpy driven. It can rely on hydrogen bonding (HB-UCST polymers) or Coulomb interactions (C-UCST polymers). This distinction is paramount when discussing the effects of ionic groups in the polymer and electrolytes in solution. Polymer−polymer interactions may be direct or bridged by water or ions, respectively. Commercially relevant HB-UCST polymers like poly(ethylene oxide) (PEO),[5−7] poly(vinylmethylether) (PVME),[8] modified pol(vinyl alcohol)-s,[9,10] and poly(hydroxyethyl methacrylate) (PHEMA)[11] show both LCST and UCST behavior with an UCST outside the 0−100 °C range. Polyacrylic acid and copolymers exhibit UCST behavior only at very high ionic strength (>400 mM NaCl) or low pH (pH < 4).[12,13] In contrast to poly(acrylic acid), C-UCST polymers like some zwitterionic polymers display UCST behavior exclusively in pure water and very low ionic strengths.[14−16] Finally, like-charged C-UCST polymers that require bridging interactions are polymeric ionic liquids[17] or function only in the presence of specific multivalent counter-ions.[18,19]

However, most applications require milder conditions with temperatures between 0 and 60 °C and ionic strengths between zero and physiological strength. Furthermore, to equal the omnipresence PNiPAAm achieved in the realm of LCST polymers, the phase separation should be extreme, sharp, and little dependent on concentration, ionic strength, ion type, and pH. For easy exploitation of thermoresponsive behavior by a wide range of users, the phase separation needs to be stable and accurately predictable under varying conditions rather than being influenced by a multitude of factors. For achieving these goals we strongly believe that HB-UCST polymers are more promising than C-UCST polymers. Research in our group

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focused on the development of HB-UCST polymers that approach the goals stated above and on answering the question why reports on such UCST polymers were almost unheard of. Drawing on the example of poly(*N*-acryloylglycinamide) (PNAGA), which has been known since 1967,[20] it was shown that PNAGA displays UCST behavior as long as ionic groups are absent.[21] Phase separation of PNAGA is triggered by the intra- and intermolecular formation of hydrogen bonds between the donor and acceptor sites of the primary amide groups. For instance, a 1 wt % solution of PNAGA in pure water displays a cloud point upon cooling of about 13 °C and a cloud point upon heating of about 22 °C when a heating/cooling rate of 1 °C/min is applied. (Note: Throughout this article mostly no cloud point temperature values are reported as this would always require us to state the concentration and heating/cooling rate at which the measurement was conducted. The polymer solutions compared had concentrations from 0.1 to 4 wt %, and the heating rate was typically 1 °C/min. However, the influence of various variables on the cloud points can be discussed qualitatively because the basic trends remain unaffected.) It is believed that the UCST of this polymer remained unknown in the past because the extreme effects of charges were underestimated and ionic groups can be introduced (un)intentionally in a number of ways: acrylate impurities in the monomer, hydrolysis, or usage of charged initiators or chain transfer agents. In the case of PNAGA just 0.2 mol % of acrylic acid (dissociation leads to the acrylate anion) is sufficient to suppress the UCST-type cloud point of a 1 wt % solution. LCST polymers like PNiPAAm are much less sensitive to ionic groups. An amount of 0.8 mol % of acrylic acid units raised the cloud point of PNiPAAm by just 3 °C[22] compared to the pure homopolymer. Ultrasensitive calorimetry of a PNAGA solution suggested that the much lower heat of the phase transition is responsible for the sensitivity to ionic groups.[4] Charged groups contribute strongly negatively to the enthalpy of mixing. Thus, these groups exert an extreme effect when the heat of transition is already small. The tolerance to ionic groups in the polymer improves with increasing ionic strength due to shielding effects. If a HB-UCST polymer is specifically intended for use in an environment with stable ionic strength, a higher content of charged moieties can be tolerated as will be discussed later.

As PNAGA is a prototypic example of HB-UCST polymers, subsequent research dealt with the exploration of basic influences on the cloud point, such as concentration, thermal history, end groups, molar masses, salts, and copolymerization with hydrophobic comonomers.[21,23−25] The observed trends agreed with theoretical expectations and complemented experiences made for LCST polymers. Polymers with different end groups were prepared by reversible addition−fragmentation chain transfer (RAFT) and atom transfer radical polymerization (ATRP) techniques over a range of molar masses.[23,24] Below molar masses of 15 kg/mol the hydrophobicity of a dodedyl end group derived from the RAFT reagent caused an upshift of the cloud points with decreasing molar mass. End groups derived from chloropropionamide using ATRP had less effect on the cloud point because of the similar hydrophilicity compared to the NAGA repeating units. Parallel to the investigations on PNAGA, Lutz et al. confirmed that derivatives of PNAGA carrying a second amide group also exhibit UCST behavior and that charged end groups cause cloud point depression with decreasing molar mass.[26] Similar to nonionic LCST polymers, PNAGA responded to salts according to the Hofmeister series of ions. Chlorides and thiocyanates caused a depression of cloud points, while sulfates increased the cloud points. In analogy to LCST polymers the cloud point of UCST polymers can be tuned by copolymerization.[25] Free radical copolymerization of NAGA with hydrophobic comonomers such as butyl acrylate or styrene increased the cloud point according to the comonomer content. From an application point of view, both comonomers proved to be unfavorable choices. Copolymers with butylacrylate had inferior hydrolytic stability due to the ester group. Copolymers with styrene were hydrolytically stable but showed very broad phase transitions. The large difference in monomer reactivities caused a compositional drift during polymerization, yielding a mixture of low-styrene−low-cloud-point-polymers and high-styrene−high-cloud-point-polymers.

Guidelines for the successful synthesis of new HB-UCST polymers were formulated. To obtain a polymer with a reversible, sharp UCST transition in pure water as well as physiological conditions, the polymer should ideally

- possess strong hydrogen donors and acceptors
- contain no or very few ionic groups
- be hydrolytically stable
- consist of chains with homogeneous copolymer composition

It became clear that these requirements can be fulfilled by simple, commercially available monomers. Indeed, copolymers from acrylamide (free of acrylic acid, e.g., electrophoresis grade) and acrylonitrile showed sharp and reversible UCST behavior with cloud points that were easily tuned by the copolymer composition.[25] PNAGA, its derivatives, and acrylamide copolymers possess a carbonyl group as a hydrogen bond acceptor and the amide hydrogen as the donor. The strong hydrogen bonding between amides is well-known from amino acids. The following examples demonstrate that different pairings are possible as well. However, the influence of the donor/acceptor pairing on the thermoresponsive behavior was not subject to study so far.

All polymers discussed above were based on the homo- or copolymerization of vinylic monomers. Simultaneously with these developments, Shimada et al. synthesized ureido-functionalized HB-UCST polymers by postmodification of poly(allylamine) and poly(L-ornithine).[27] The degree of functionalization was varied, resulting in different residual contents of amine groups which are in equilibrium with the protonated ammonium form. Although these polymers contained considerable amounts of ionic groups, they displayed UCST-type cloud points depending on residual amine content and pH. On first glance these results seem to contradict the previously propagated extreme effects of ionic groups, but it is important to note that turbidity measurements were performed in 150 mM sodium chloride. In this environment the repulsive effect of like-charged groups in the polymer is weakened by shielding effects. Under such conditions, however, Shimada et al. successfully demonstrated the application of HB-UCST polymers for bioseparation processes.[28]

Most recently Ritter et al. developed a wholly new copolymer system with tunable UCST, based on *N*-vinylimidazole and 1-vinyl-2-(hydroxylmethyl)imidazole.[29] Similar to the acrylamide/acrylonitrile system each of the homopolymers is either completely watersoluble or insoluble, so that copolymerization is necessary to properly adjust the hydrophilicity/lipophilicity balance. Compared to amines, imidazole is only mildly basic with a $\text{p}k_B$ value of 6.95, explaining why the reported copolymer system showed UCST behavior in pure water. In pure water the degree of protonization alpha can be approximated by $\alpha = \sqrt{[K_B/c(\text{Im})]}$. Turbidity measurements were performed at a quite high concentration of 4 wt % of polymer. According to this concentration the degree of protonization should be in the order of 0.0005. This corresponds to an ionic content that was found to be tolerable for the system NAGA/acrylic acid. Figure 1 compares the degree of ionization of some functional groups found in polymers with UCST capability. It is important to consider the difference between solutions in pure water and pH 7 buffered solutions. In buffered solutions the degree of ionization is approximated by $\alpha = K_A/[c(H^+) + K_A]$ or $\alpha = K_B/[c(OH^-) + K_B]$, respectively. Hence, buffer (with sufficient capacity) often forces ionization.

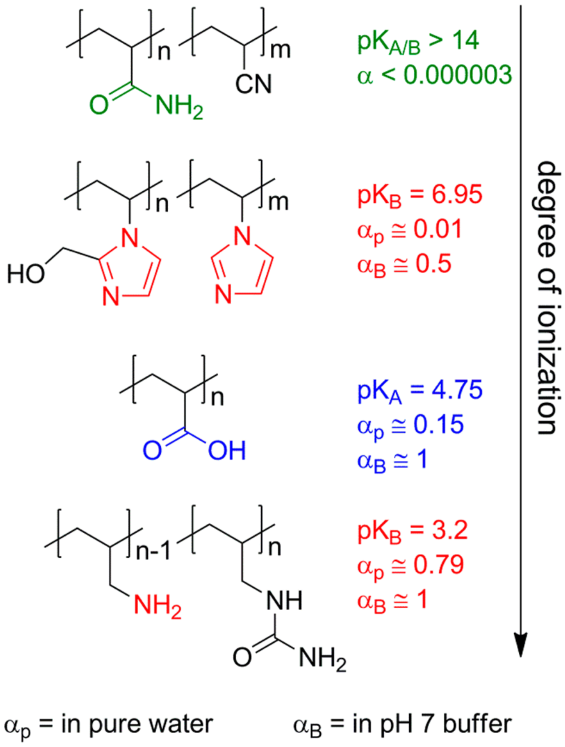

**Figure 1.** Approximate degree of ionization $\alpha$ in pure water or pH 7 buffer for different hydrogen bonding polymers. For the calculation of $\alpha_p$ the concentration of pH-sensitive groups was assumed to be 1 mmol/L.

While the mild basicity of these imidazole-based HB-UCST polymers introduces some complexity to the concentration, pH, and ionic strength dependencies, their immunity to hydrolysis is certainly a strong advantage compared to amide- and urea-based polymers. This is specifically relevant under basic or high-temperature conditions.

In the past few years significant advances have been made in the field of water-soluble UCST polymers. The most important but sometimes subtle influences on the phase transition have been unveiled. Still, careful balancing of the main parameters (Figure 2) is labor-intensive, but afterall the way is paved for the selective synthesis of many "new" polymer systems with UCST-type thermoresponse. Most intriguingly, current examples show that "new" properties do not require the use of new or exotic monomers. Instead, these new properties can be obtained by careful polymer design with old building blocks.

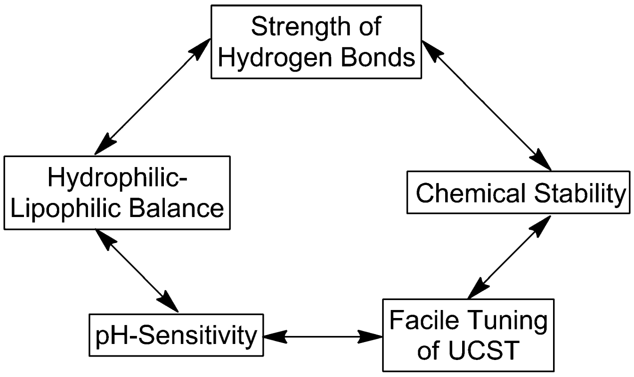

**Figure 2.** Balancing of the main parameters in the design of HB-UCST polymers.

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### Notes

The authors declare no competing financial interest.

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