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Talents & Trends

Composing Well-defined Stimulus-Responsive Materials through Postpolymerization Modification Reactions

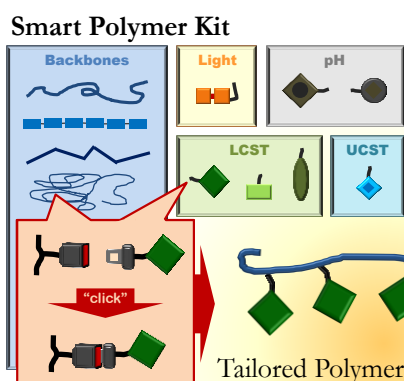
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Abstract. Postpolymerization modification—the installation of functional groups into a pre-made, reactive polymeric precursor—is emerging as an advantageous synthetic strategy toward tailored materials. In this review the preparation of environmentally sensitive, “smart”, polymers by virtue of postpolymerization modification is presented. The underlying fundamentals of different types of stimulus-responsiveness are highlighted with an emphasis on thermo-responsiveness, encompassing LCST and UCST behavior. Using a range of postpolymerization modifications as examples, properties imparted through incorporation of specific functional groups and their structure-property relations are discussed. Strategies for an appropriate choice of functionality in order to obtain well-defined materials with custom-made behavior are presented.



1. Introduction

The advent of reversible deactivation radical polymerization (RDRP) techniques and the thriving of robust and efficient modification reactions in the polymer chemistry arena have brought about an unprecedented control over design and functionality of macromolecular materials. As a consequence, well-defined polymers with tailored attributes have been spreading into other realms of science advancing interdisciplinary research, above all in the biomedical area.

An advantageous procedure to introduce functionality into polymers and to furnish the resulting material with specific properties is to install functional groups into appropriately reactive, pre-made macromolecular precursors. Such postpolymerization modification reactions offer several distinct advantages over a direct copolymerization of two, or more, functional monomers:^[1-4] (i) Postpolymerization modification is applicable to many functional groups that would not be stable under typical polymerization conditions or that would have adverse effects on the polymerization control. (ii) Modification of a single reactive precursor with a variety of reagents yields a (co)polymer library with identical degrees of polymerization, which may be challenging to achieve by other methods. (iii) Conversions can be performed with a mixture of modifying reagents, which is generally assumed to generate statistical copolymers, though, of note, studies on potential neighboring group effects on a non-statistical incorporation of functionality are, in fact, limited. (iv) Postpolymerization modification lends itself perfectly to constructing complex macromolecular architectures, for example for crosslinking reactions or for selective modification in combination with strategically positioned reactive handles within a polymer, e.g. for end group modification.

A commonly employed reactive functionality for polymer modification is the activated ester group such as the *N*-hydroxysuccinimide and pentafluorophenyl (PFP) esters of acrylic and methacrylic acid,^[5] though the concept has been expanded to include other polymerizable groups.^[6-10] The respective polymers, e.g. poly(pentafluorophenyl acrylate), pPFPA, and its

methacrylate sister polymer poly(pentafluorophenyl methacrylate), pPFPMA, show highly selective reactivity toward primary and secondary amines yielding the respective *N*-functional and *N,N*-difunctional poly(meth)acrylamides in typically quantitative yield. While the activated ester leaving group accrues as side product requiring removal, azlactone derivatives such as polymers based on 2-vinyl-4,4-dimethylazlactone (VDMA) undergo ring-opening addition reactions with amines producing bis-amide derivatives.^[11, 12] For amine reactive precursors prepared by RAFT polymerization, including pPFP(M)A and poly(VDMA) (pVDMA), care needs to be taken of the thiocarbonylthio end groups during conversion of the reactive side groups, since aminolysis is, in fact, the most common way to cleave RAFT end groups. A variety of procedures to avoid unwanted side reactions and to install further functionality into the end groups in the same step have been presented and the interested reader is referred to recent reviews on this subject.^[13-15]

Stimulus-responsive, “smart”, polymers respond reversibly to subtle changes of their environment (including physical and chemical stimuli) through drastic changes of their physical properties, prevalently solubility, in a given solvent typically resulting in a phase transition.^[16] From a mechanistic perspective, such behavior offers a wide scope of applicability: (i) Polymers that become insoluble by virtue of an applied stimulus will, in most cases, phase separate macroscopically, offering potential for purification/separation applications. (ii) Localized micro-phase separations can be exploited in amphiphilic AB diblock copolymers comprising one switchable block providing a means of stimulus-triggered self-assembly. (iii) The phase transition of a polymer will, in most cases, be accompanied by a change of polarity. This can be exploited in the production of surfaces with switchable wettability/adhesion. (iv) A crosslinked / gelled stimulus-responsive system can be expected to swell reversibly with the application of a stimulus, providing the basis for an actuator. (v) In most cases, the phase transition of a smart polymer will go along with a microscopic collapse of (single) polymer chains (which may, however, occur somewhat independently of

the macroscopic phase separation). Grafted onto a surface, polymer brushes would thus collapse on a surface, but also the collapse of single polymer chains may be exploited for specific 'nano-engineering' applications.

Whether or not a specific polymeric material is stimulus-responsive depends on its chemical composition. This review gives an overview of stimulus responsive materials and their preparation through postpolymerization modification reactions. The underlying fundamentals of different types of responsiveness are highlighted with an emphasis on thermo-responsiveness. Using a range of postpolymerization modifications from our group and others as examples, structure-property relations of various functional side groups and how they impart smart behavior are discussed, and guidelines for an appropriate choice of functionality are given in order to achieve smart materials with tailored properties. Not covered in this review are the production of responsive hybrid materials by means of grafting a stimulus-responsive *polymer* onto a non-responsive substrate, or cases where the stimulus itself causes postpolymerization modification (e.g. photo-dimerization, retro Diels-Alder reactions).

2. Thermoresponsive (Co)polymers with Lower Critical Solution Temperatures (LCSTs) in Water

2.1. LCST: Background

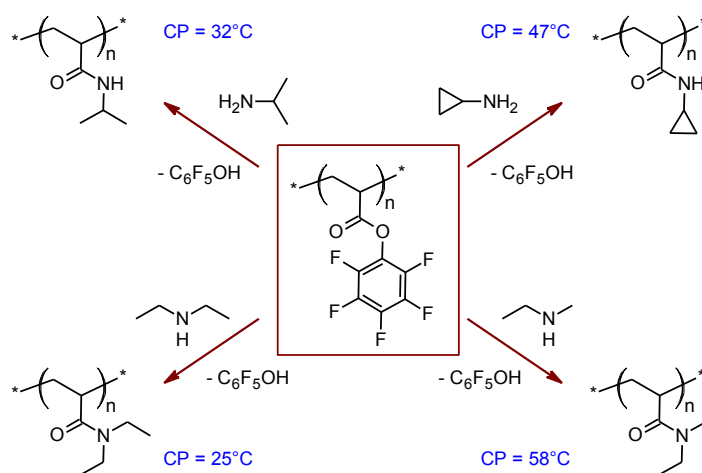
Mixtures displaying a lower critical solution temperature (LCST) are *miscible below* a critical temperature and phase separate above it. For a given system, this critical temperature is typically dependent on the composition of the mixture, with the LCST being the *lowest* critical temperature. LCST behavior is, perhaps, somewhat counterintuitive, but is, in fact, quite common for water-soluble (co)polymers^[17, 18] and is also known for certain small molecule mixtures, e.g. triethylamine–water.^[19] While molecules, including macromolecules, comprising mainly hydrophilic (or hydrophobic) fragments will be soluble (or insoluble) in water, LCST behavior can occur for molecules composed of an appropriate balance of hydrophilic and hydrophobic segments, for example polymers containing amide linkages (hydrophilic) connecting short alkyl side chains to a hydrocarbon backbone (both hydrophobic). The occurrence of soluble–insoluble transitions during heating of such (macro)molecules in water can be explained by the behavior of water molecules during their solvation. Not being able to hydrogen-bond to the hydrophobic segments of the solute (e.g., an LCST-type polymer), nearby water molecules will instead increase the hydrogen-bond efficiency to their water neighbors, forming a highly-structured ‘net’ around the hydrophobic group—a process called ‘hydrophobic hydration’. This hydration sphere is favored by energetic water–water and, though to a lesser extent, water–polymer interactions ($\Delta H < 0$), but is entropically unfavorable ($\Delta S < 0$) due to lower mobility of its water molecules. At a certain critical temperature T_c , the product $T_c\Delta S$ will outbalance the enthalpic interactions so that the Gibbs free energy $\Delta G = \Delta H - T_c\Delta S = 0$. Driven by a gain in total entropy, the hydration sphere ‘melts’ at this temperature, freeing its water molecules into bulk, which, in turn, means that the polymer loses hydration and becomes insoluble. Typically, a certain

amount of water will still be bound to the polymer, causing a separation into a polymer-rich and a water-rich phase (rather than separation of pure polymer). When studying novel (co)polymers with aqueous LCST it is generally advisable to determine the concentration dependence of the macroscopic (optically observable) phase transition since the resulting critical temperature–concentration phase diagram will provide equilibrium compositions for separated phases (as well as the LCST of the system), and may offer information on microscopic events during the phase transition. Phase diagrams with an extended flat region for example, as found for poly(*N*-isopropyl acrylamide) (pNIPAM), suggest sharp cooperative coil-to-globule collapses, while non-flat regions in a phase diagram suggest gradual microscopic transitions, either because different chains in a disperse system behave differently (common for LCST systems), or because chains are dehydrated gradually and will show different propensity to form aggregates when colliding with other partially collapsed chains (common for UCST systems).^[20]

Flory-Huggins solution theory can describe LCST behavior if the interaction parameter χ is allowed to increase with temperature, making the polymer solvophobic at higher temperature. A variety of lattice models have since been proposed to explain LCST as well as UCST behavior.^[21] LCST transitions were first measured in the 1960s on pNIPAM.^[22] A comprehensive study by Tailor and Cerankowsky published in 1975 detailed the need for an appropriate hydrophilic–hydrophobic balance within a range of polymers in order to achieve LCST behavior.^[23] In the following decades a large number of (co)polymers have been described to display soluble–insoluble phase transitions in water, with pNIPAM still dominating the field. Several recent reviews offer an excellent overview of (co)polymers with LCSTs in water,^[18] their applications^[24] and future directions.^[25]

2.2. Designing homopolymers with aqueous LCST through postpolymerization modification

Postpolymerization modification represents an excellent means of preparing (co)polymers displaying an aqueous LCST, designing novel LCST-type (co)polymers and for studying structure-property relations of LCST-type copolymers. To reiterate, LCST behavior occurs if a (co)polymer comprises an appropriate balance of hydrophilic and hydrophobic groups. The chemical nature of the backbone must therefore be taken into account, with a higher hydrophobic contribution typically expected to lower solubility (i.e. decrease the LCST). The unexpected case is, incidentally, found for the pair of pNIPAM and its methacrylamide sister polymer poly(*N*-isopropylmethacrylamide) (pNIPMAM), where the latter is more water soluble—an effect attributed to the methyl groups in the backbone restraining the intrachain collapse and producing looser aggregates.^[26] These two species also represent the, perhaps, simplest access to well-documented polymers with aqueous LCST through postpolymerization modification by virtue of the reaction of activated ester poly(meth)acrylates with isopropylamine.^[27-34] In a similar vein, the thermoresponsive species poly(*N*-cyclopropylacrylamide), poly(*N,N*-diethylacrylamide), and poly(*N*-ethyl, *N*-methylacrylamide) are available using cyclopropylamine, diethylamine and ethylmethylamine, respectively, see **Scheme 1**.^[27, 31, 35, 36] These conversions can be performed in one pot together with RAFT end group modification^[37] and represent a versatile platform for the investigation of simultaneously installed functionality responding to additional stimuli, see chapter 2.5.



Scheme 1. Synthesis of thermoresponsive species by reaction of an acrylamido activated ester (pPFPA shown) with aliphatic primary and secondary amines. Cloud points are taken from ref.^[18]

2.2.1. poly/oligo(ethylene glycol) functional (co)polymers

If there was a title for a “universal LCST effecting group” it would most likely go to poly/oligo(ethylene glycol), PEG/OEG. PEG itself is not thermally responsive in water between 0 and 100°C, but has a miscibility gap at elevated temperatures/pressures^[38, 39] and displays UCST behavior (insoluble below a critical temperature) in alcohols, albeit with large hysteresis.^[40, 41] Attached to (meth)acrylate backbones, OEG/PEG side chains of appropriate length impart well-defined, sharp LCST transitions in water^[42, 43] and sharp UCST transitions in alcohols with low hysteresis.^[44, 45] Their low toxicity, biocompatibility, simple synthesis through RDRP techniques, and predictable, easy tunable thermoresponsive behavior underpin the proliferation and prevalence of the entire poly(OEG (meth)acrylate), pOEG(M)A, family in a wide variety of synthetic and applied research fields. The OEG functionality has also lent itself perfectly to the construction of novel materials with LCSTs in water by means of grafting OEG chains onto a range of backbones in various postpolymerization modification reactions, see **Table 1**. In these instances, water solubility increases with both degree of OEG substitution and OEG side chain length.^[40, 46-50] In our studies, modification of pVDMA^[51]

and pPFPA^[40] even with the short OEG derivatives di/tri(ethylene glycol) methyl ether amine, on the other hand, was found to produce fully water-soluble homopolymers that, nonetheless, proved to be versatile biocompatible platforms^[40] and allow for LCST tuning via incorporation of hydrophobic co-amines, *vide infra*.

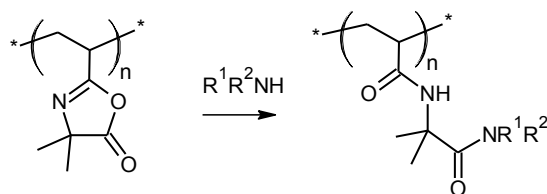
Table 1. Postpolymerization modification with PEG/OEG derivatives yielding (co)polymers with LCSTs in water

Reactive Backbone	Postpolymerization Modification Reaction	Modifying Reagent	Comments	Ref.
poly(γ -propargyl-L-glutamate)	CuAAC ^{a)}	di/tri(ethylene glycol) methyl ether azide	thermoreponsive polypeptides with cloud points between 22 and 74°C depending on MW	[46]
poly(γ -propargyl-L-glutamate)	CuAAC	di(ethylene glycol) methyl ether azide; di(ethylene glycol) azide; di(isopropyl)aminoethyl azide	thermo- and pH responsive polypeptides	[52]
poly(styrene- <i>bl</i> - γ -propargyl-L-glutamate)	CuAAC	di(ethylene glycol) methyl ether azide	self-assembled structures from thermoresponsive polypeptides containing diblock copolymers	[53]
poly(3,6-dipropargyl-1,4-dioxane-2,5-dione) and copolymers with lactide	CuAAC	tri(ethylene glycol) methyl ether azide, methoxy-PEG ₅₅₀ ^{b)} azide	degradable (lactide backbone) thermoresponsive polyglycolides	[48]
azide-functional polyester	CuAAC	methoxy-OEG propargyl ether (n = 6,7,8)	degradable (labile disulfide and ketal linkages in backbone) thermoresponsive polyesters	[49]
multiallylic dendronized polystyrene derivatives	radical thiol-ene	di/tri(ethylene glycol) methyl ether thiol	thermoreponsive dendronized polymers with shape anisotropy in solution	[54]
poly(dichlorophosphazenes)	nucleophilic substitution	OEG alkoxides	thermoreponsive poly(organophosphazenes) for stimuli responsive vesicles	[47]
poly(<i>p</i> -chloromethylstyrene)	nucleophilic substitution	methoxy-PEG ₁₁₀₀ alkoxide	thermoreponsive cylindrical molecular brushes	[55]
poly(<i>substituted</i> styrene- <i>alt</i> -maleic anhydride)	anhydride alcoholysis	methoxy-PEG ₃₅₀	alternating copolymer responsive to temperature (PEG), pH (acids from anhydride reaction) and salts (crown ether-like substituent on styrene monomers)	[56]
poly(pentafluorophenyl 4-ethynylbenzoate)	activated ester-amine acyl substitution	methoxy-PEG _{350/550} amine	thermoreponsive poly(phenylacetylenes)	[50]
poly(<i>n</i> -octyl methacrylate- <i>co</i> - <i>N</i> -hydroxy succinimide methacrylate)	activated ester-amine acyl substitution	tri(ethylene glycol) methyl ether amine	thermo-responsive vesicle-to-micelle transition of an amphiphilic random copolymer	[57]
poly(pentafluorophenyl methacrylate)	activated ester-amine acyl substitution	di/tri(ethylene glycol) methyl ether amine	thermoreponsive biocompatible OEG poly(methacrylamides)	[40]

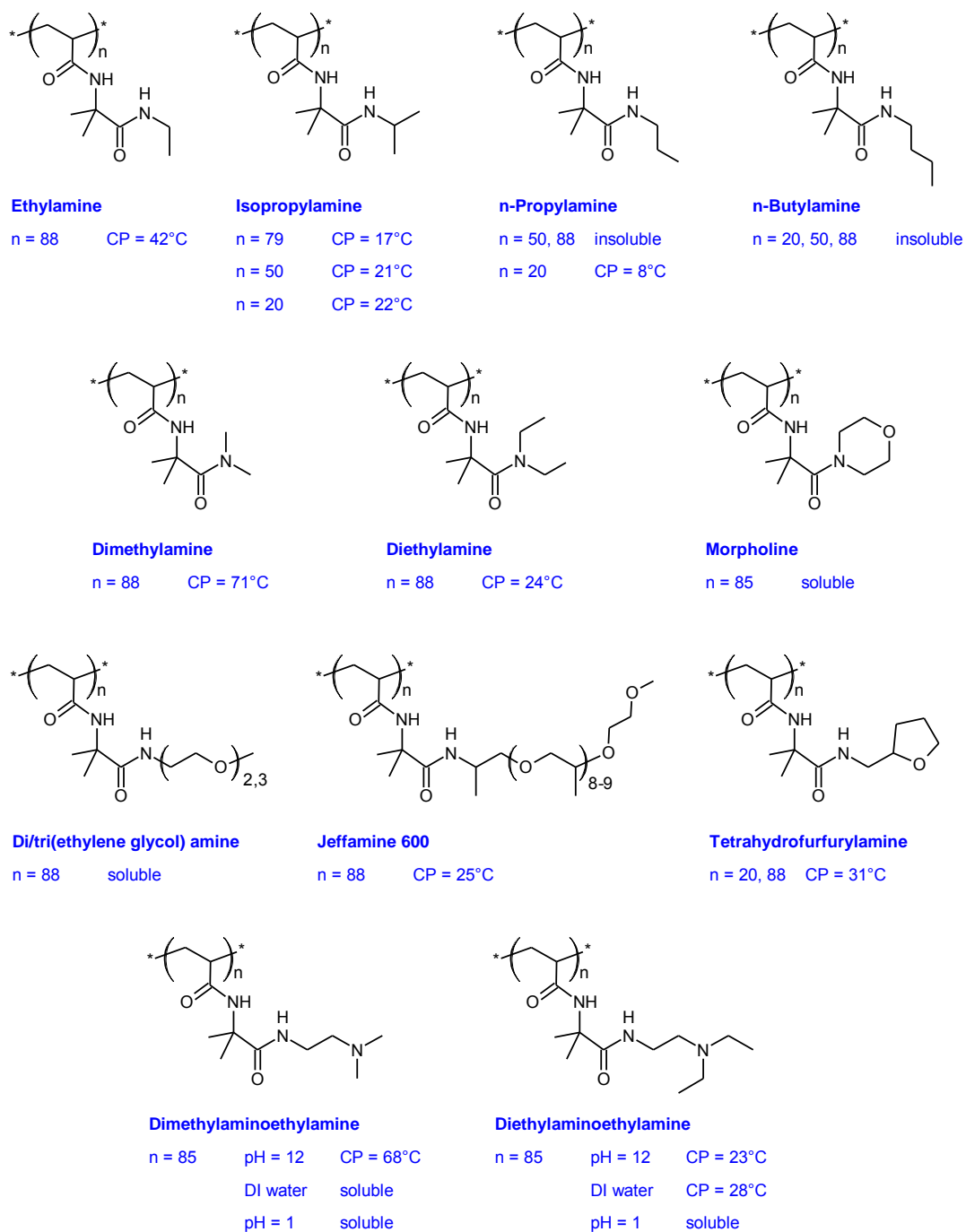
^{a)}copper catalyzed azide-alkyne cycloaddition; ^{b)} molar mass of PEG in g/mol

2.2.2 Thermoresponsive (co)polymers through postpolymerization modification of pVDMA

poly(2-vinyl-4,4-dimethylazlactone), pVDMA, is gaining increasing attention as a versatile scaffold for crafting advanced materials. Our group^[51] initially conducted a detailed study on transforming this reactive scaffold into thermoresponsive (co)polymers by reaction with amines of appropriate polarity, while a further report^[58] focused on temperature and pH responsive polymers prepared from pVDMA, see **Scheme 2**. In these studies, pVDMA precursors with degrees of polymerization ranging from 20 to 88 were reacted with a range of primary and secondary aliphatic amines and the resulting homopolymers were assessed for temperature-dependent water solubility. We identified several homopolymers with well-defined LCST cloud points. These poly(alkyl 2-acrylamido isobutyramide)s were less soluble than the corresponding acrylamido analogs. While PNIPAM, for example, has a well-documented LCST of 32°C, the homopolymer derived from pVDMA and isopropylamine, poly(isopropyl 2-acrylamido isobutyramide), had lower cloud points of 17–22 °C, depending on molar mass. Results of both studies^[51,58] are compiled in **Scheme 3**.



Scheme 2. Reaction of pVDMA with primary ($R^1 = \text{alkyl}$, $R^2 = \text{H}$) and secondary ($R^1, R^2 = \text{alkyl}$) amines yielding poly((bis)alkyl 2-acrylamido isobutyramide)s



Scheme 3. Compilation of results of two studies^[51, 58] on aqueous solution behavior of homopolymers derived from pVDMA by reactions with amines (given in bold; CP = LCST cloud point measured on solutions at a concentration of 5 g/L at a heating rate of 1 °C/min)

This overview serves as an expedient example to note several points that are applicable to most polymers with an LCST in water.

(i) Cloud points of thermoresponsive samples decrease with an increasing degree of polymerization. This behavior is typical for systems that show an influence of molar mass on the cloud point.

(ii) As to be expected from their increased hydrophobicity, longer alkyl substituents decrease solubility, i.e., lower cloud points. This is seen in the series of ethyl- *n*-propyl, *n*-butyl-substituted poly(2-acrylamido isobutyramide)s. Substituted with *n*-butyl or longer side chains, even poly(2-acrylamido isobutyramide)s with a low degree of polymerization were found to be insoluble. The same effect—lower solubility—is seen for the formal replacement of short OEG side chains ($n = 2,3$) (fully soluble homopolymers) with more hydrophobic oligo(propylene glycol) side chains (CP 25°C).

(iii) Branched side chains impart better water solubility compared to their constitutional isomers with linear chains. In the family of modified pVDMA homopolymers, for example, the *N*-isopropyl derivative (CP 21°C) was better soluble than the corresponding *N*-*n*-propyl species (insoluble) of the same degree of polymerization. Likewise, the *N,N*-dimethyl- (CP 71°C) and *N,N*-diethyl- (CP 24°C) derivatives were better soluble than their isomeric *N*-ethyl- (CP 42°C) and *N*-*n*-butyl- (insoluble) derivatives, respectively, although a cursory evaluation of their structures suggests that the additional H-bond donating capacity of the secondary amide NH group would improve water solubility of the linear side chain (ethyl, *n*-butyl) species. This observation can be attributed to a higher number of conformational/rotational isomers of a longer alkyl chain versus those of two half-length which creates a larger effective hydrophobic volume. It is therefore entropically less favorable for water to form a hydrating ‘net’ around longer alkyl chains which, in turn, means that a lower critical temperature in the term $-T_c\Delta S$ will suffice to outbalance energetic interactions. The ‘linear’ constitutional

isomers therefore have lower cloud points or are insoluble with theoretical cloud points below 0°C.

(iv) Some homopolymers featuring tertiary amines (see Scheme 3, bottom) displayed LCST behavior in basic medium and were fully soluble under acidic conditions when the amines were expected to be protonated, providing pH and temperature responsive materials.

Our group further presented modification of pVDMA with tetrahydrofurfuryl amine (THF amine) to yield homopolymers with largely flat phase diagrams featuring sharp, predictable LCST transitions close to body temperature that could easily be tuned.^[51]

2.3. Tuning of LCSTs by varying copolymer molar compositions

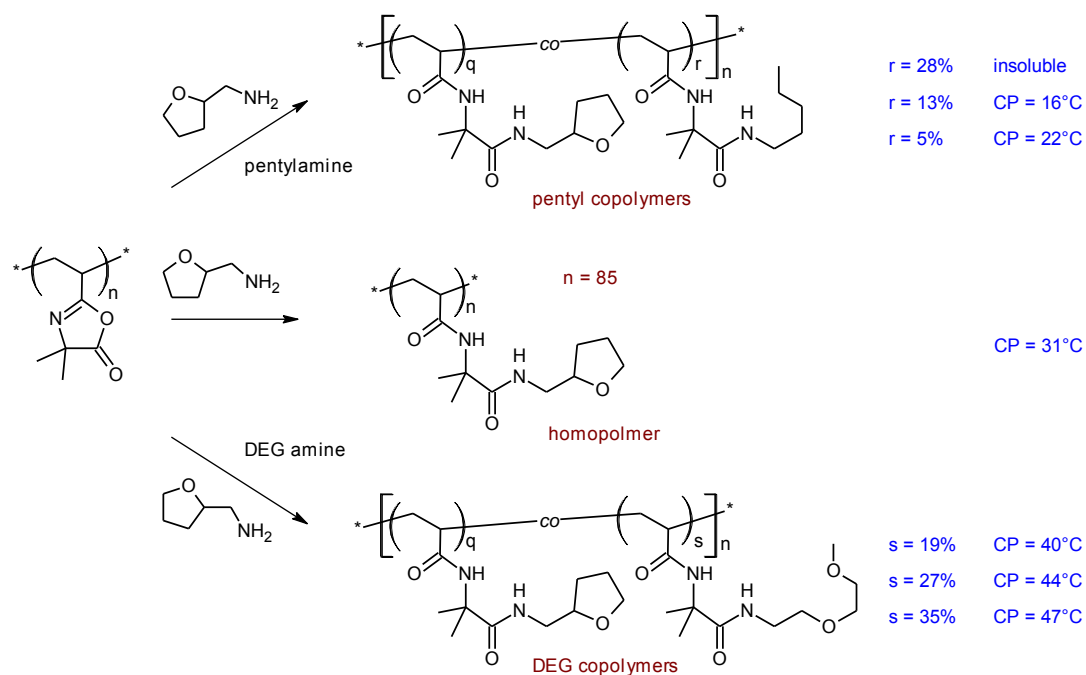
Installing one or more functional groups into a pre-made, well-defined polymer consisting, either wholly or partially, of reactive groups, allows a great amount of freedom in incrementally adjusting the molar composition of the resulting copolymers and thereby tuning the hydrophilic–hydrophobic balance, i.e. tuning the LCST transition.

Several statistical copolymers of (known) thermoresponsive polymers such as pNIPAM^[59-62] and pOEGA^[63] containing reactive monomer units, such as VDMA,^[60, 61] 2-isopropenyl-2-oxazoline (the ‘methacrylic’ analog of VDMA),^[62] sulfo-*N*-hydroxysuccinimide,^[59] and PFPA^[63] have been prepared. In these cases, the presence of hydrophobic reactive groups was found to—expectedly—lower the LCST transition.^[60-62] In a recent report, Beija et al.^[63] prepared statistical copolymers of PFPA with OEGA or di(ethylene glycol) ethyl ether acrylate to study copolymerization kinetics and the effect of reaction conditions on the conversion of the PFP esters. Modification of copolymers containing varying percentages of PFP comonomers with several hydrophilic and hydrophobic amines produced a library of copolymers with a range of LCSTs as well as soluble and insoluble species, depending on both the percentage of modification as well as the type of amine employed.

A further large and versatile class of thermoresponsive materials is constituted by poly(2-alkyl oxazolines) with varying alkyl side chain lengths which are available through living cationic polymerization and which span large ranges of LCST transitions in water and UCST transitions in alcohols and water–alcohol mixtures.^[64-68] Poly(2-isopropyl-2-oxazoline), pIPOx, a structural isomer of pNIPAM, for example, shows LCST transitions in water at ~ 37°C. Diehl et al.^[69] prepared copolymers based on pIPOx containing 3-butenyl-2-oxazoline comonomer units exhibiting double bond-functional side chains which were susceptible to radical thiol–ene reactions with thiols. The authors employed a variety of hydrophilic and hydrophobic thiols, including a glucose derivative, generating a library of copolymers with LCST transition temperatures ranging from 5–90 °C. The influence of comonomer units on the phase separation temperature was found to increase with comonomer content in a linear fashion. Kempe et al.^[70] prepared a novel sugar-substituted 2-oxazoline and copolymerized it with 2-(dec-9-enyl)-2-oxazoline similarly allowing for postpolymerization thiol–ene modification allowing for LCST tuning in the physiological range. In a similar vein, Brummelhuis and Schlaad^[71] prepared responsive star polymers from alkyne-functionalized 2-oxazoline copolymers by employing postpolymerization thiol–yne reactions for simultaneous modification and crosslinking.

Thermoresponsive copolymers with tunable LCST transitions are also easily accessible through postpolymerization modification of reactive homopolymers by employing a mixture of modifying reagents. Our group^[51] reacted pVDMA with THF amine (see Scheme 3; the homopolymer had a CP of 31°C) and either up to 35 mol % of (hydrophilic) di(ethylene glycol) methyl ether (DEG) amine or up to 28 mol % of (hydrophobic) pentylamine, **Scheme 4**. The molar composition of the resulting copolymers agreed well with the feed ratios of amines signifying the high level of control that postpolymerization modification offered in composing copolymers. Type and molar percentage of co-amines affected the thermal behavior of the copolymer species and enabled sharp, fully reversible LCST transitions from

16 to 47°C, see **Figure 1**. The cloud point was somewhat less sensitive to variations in the DEG content, with an increase of ~8 mol % of DEG side chains causing a cloud point increase of only 3–4 °C showing that a very precise tuning of the cloud point with varying DEG content was possible.



Scheme 4. Synthesis of statistical copolymers by postpolymerization modification of pVDMA with tetrahydrofurfurylamine and varying molar ratios of di(ethylene glycol) methyl ether (DEG) amine or pentylamine.

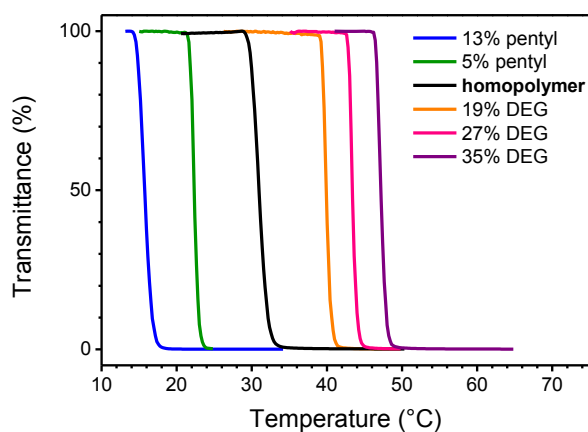
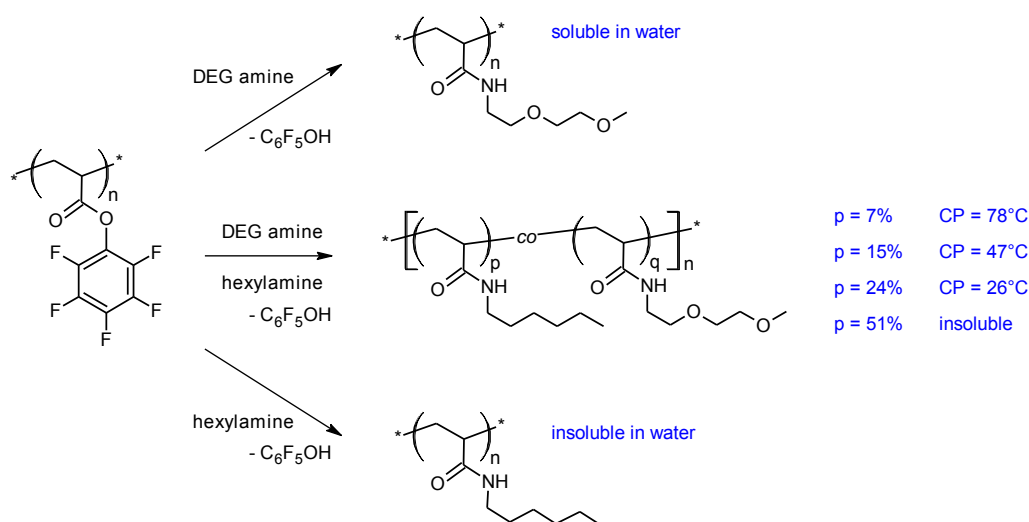


Figure 1. Transmittance curves of copolymers shown in Scheme 4. Reprinted with permission from reference.^[51] Copyright 2013 American Chemical Society.

Copolymers with an LCST in water can also be realized from a combination of hydrophilic and hydrophobic segments of which, in isolated form, neither is thermally responsive. Our group, for example, reacted pPFPA with mixtures of DEG amine and hexylamine. Notably, homopolymers formed from either amine are soluble (poly(DEG acrylamide)) or insoluble (poly(hexyl acrylamide)) in water (they may have theoretical cloud points above 100°C or below 0°C, respectively). At an appropriate ratio of the two amines, however—in this case 7–24 mol % of hexyl acrylamide comonomer units—the resulting copolymers showed sharp, fully reversible LCST transitions in water with low hysteresis, see **Scheme 5**.

A further illustration of combining segments of would-be soluble and insoluble homopolymers to form thermally responsive copolymers are hydrophobically modified poly(dimethylacrylamide) (pDMA)-based copolymers, which, unlike the soluble pDMA homopolymer, show LCST behavior. An example was realized by Jochum et al. who reacted pPFPA with dimethylamine and 4.4, 6.0, or 8.5 mol-% of *N*-(2-aminoethyl)-4-(2-phenyldiazenyl)benzamide, obtaining copolymers with cloud points of 80.5, 66.0, and 37.9 °C, respectively, indicating the large impact that this aromatic substituent had on pDMA. These two examples demonstrate that copolymers with sharp LCST transitions can easily be composed by the combination of an appropriate ratio of hydrophilic and hydrophobic groups, without the necessity of knowing structurally related thermoresponsive systems. There may, however, be limitations to the choice of hydrophilic and hydrophobic groups for this purpose. It is conceivable that functional groups with too disparate polarity may lead to self-assembled structures, which may or may not show the desired thermal response.



Scheme 5. Synthesis of copolymers with balanced hydrophilic/hydrophobic ratio through postpolymerization modification of pPFPA.^[40]

2.4. Tuning of LCSTs through postpolymerization end group modification

LCST transition temperatures can be tuned without altering the chemical composition of side groups or the molar composition within copolymers by way of modifying the end groups. For obvious reasons, end groups have the largest impact on the hydrophilic–hydrophobic balance for short (co)polymers. In fact, the molecular weight dependence of the thermoresponsiveness of pNIPAM has been discussed to be solely dependent on the influence of the end groups.^[72] Several groups, including ours, have investigated the influence of postpolymerization end group modification on the LCST transitions of a range of polymers.^[73-80] Examples include CuAAC-modification of azide-terminated pNIPAM prepared by ATRP,^[78] thiol–isocyanate click chemistry on thiol-terminated pDEAM obtained from RAFT polymerization followed by end group cleavage,^[77] a combination of PFP α -end groups^[81, 82] and ω -thiol–methanethiosulfonate chemistry^[15, 83-85] to introduce functional groups at both ends of RAFT-made pOEGMA,^[79] and a thiol–ene addition of functional thiols onto the methacrylate end groups of pOEGMA prepared by catalytic chain transfer polymerization.^[80] In all instances, introduction of hydrophilic end groups increased the

LCST cloud point. For the introduction of hydrophobic end groups, an LCST decrease is observed if the polymer chains remain unimerically dissolved, i.e. if the hydrophobic end groups interact with water. Above a certain critical length, hydrophobic end groups will, however, segregate into microdomains, forming micelle-like aggregates. For such morphology, a lower impact of the hydrophobic modification (or no change at all compared to an unmodified polymer) is observed, since interactions of the aggregated end groups and water is limited.^[73, 79, 86]

2.5. Tuning of LCSTs by means of an additional stimulus

As detailed above, postpolymerization modification of reactive scaffolds offers facile access to well-defined (co)polymers with LCST transitions in water. Especially pPFPA (and its modification with isopropylamine yielding pNIPAM) has therefore been employed as a versatile platform to create materials responsive to multiple stimuli. In these instances, a functional comonomer is installed that responds to an additional stimulus with a change of polarity (e.g. through isomerization), which affects the hydrophilic–hydrophobic balance of the copolymer and thus shifts the LCST.

Temperature and light-responsive copolymers, for example, have been realized by conversion of pPFPA with an LCST-affecting amine (such as isopropylamine) and amine-carrying light-responsive moieties such as azobenzene,^[28, 36, 76, 87] salicylidineaniline,^[27] or fulgimide.^[87] These molecules undergo reversible photoisomerization when irradiated at specific wavelengths causing a reversible change of polarity, affecting the LCST transition temperature of the copolymers. Further examples have included the production of redox-sensitive copolymers via introduction of ferrocene,^[88] or the *N*-oxyl species TEMPO^[89] into pPFPA and temperature and pH-sensitive copolymers via introduction of basic groups that are protonated at low pH.^[33, 52, 90-92] If the pKa of these pendant basic groups lies in the same order as that of carbonic acid CO₂ can be used as a gaseous (and easily removable)

stimulus^[93, 94] to affect switching the solubility of copolymers.^[33, 90] The interested reader is referred to a recent review by Schattling et al.^[95] that covers further developments in the area of multi-responsive materials.

3. Thermoresponsive (Co)polymers with Upper Critical Solution Temperatures (UCSTs) in Water

3.1. UCST: Background

Mixtures displaying upper critical solution temperature (UCST) behavior are *miscible above* a critical temperature and phase separate below it. In a critical temperature–composition phase diagram the UCST is the maximum of the coexistence curve. UCST behavior is common for solutes (including polymers) in organic solvents and also for small organic molecules and inorganic salts in water. A concentrated solution of sugar (sucrose) in water at high temperature, for instance, will phase separate upon cooling with pure sugar crystallizing from a saturated solution, thus displaying UCST behavior. Notably, the water-rich phase, i.e. the supernatant sugar solution, will still contain a considerable amount of sugar, even when cooled to the freezing point, suggesting that water would, perhaps, be a poor solvent choice for recrystallizing sugar. For this particular system, sucrose–water, the UCST incidentally lies above the boiling of water; full miscibility at all compositions is therefore not possible below 100°C.^[96] While a perfectly valid illustration of an aqueous UCST from a physico-chemical point of view, most polymer scientists would hardly consider this an appropriate example. This is because of several distinctions of the aqueous UCST paradigm in the materials arena. Firstly, and identical to the design of LCST-type systems, polymer chemists desire to develop materials that show very flat phase diagrams, i.e. instead of phase separating incremental amounts of solute while cooling over a large temperature range (as in the sucrose example), tailored polymers are intended to phase separate almost completely within a very narrow, largely concentration independent, temperature interval. Secondly, and needless to mention, polymer chemistry allows for a tailored modification of macromolecules and their crafting into complex architectural designs purposed for many applications. Finally, while virtually any other sugar, other reasonably well soluble small organic molecule, or inorganic

salt would have served as an example equivalent to sucrose, aqueous UCST transitions of polymers are, in fact, very rare and there has been an ongoing pursuit of developing and improving novel (co)polymers displaying the above-mentioned desired properties.

UCST behavior is easily explained. It relies on interplay between enthalpic solute–solute interactions (e.g., sugar–sugar or polymer–polymer) favoring phase separation and mixing entropy favoring dissolution of the solute. Weighed with absolute temperature, the entropy term will outbalance enthalpic attractions at the critical temperature. This concept also elucidates the sparseness of aqueous UCST transitions of polymers. While the above-mentioned small molecules and inorganic salts rely on their enthalpy of crystallization to eventually favor separation from solution during cooling, polymers, as largely amorphous materials, lack this driving force. Instead, polymers with aqueous UCST need to (i) be hydrophilic (otherwise hydrophobic hydration may cause LCST behavior); (ii) form very strong polymer–polymer interactions, stronger, in fact, than polymer–water interactions, able to replace an enthalpy of crystallization and to be broken by water only at elevated temperatures. Since water is generally an excellent solvent that forms strong bonds with hydrophilic solutes, the choice of even stronger polymer–polymer interactions is somewhat limited and typically results in aqueous UCST polymers being poorly soluble in most solvents other than hot water. Recent reviews by Seuring et al.^[97, 98] give a comprehensive overview of (co)polymers with aqueous UCST as well as a more detailed theoretical background.

3.2. Designing homo- and copolymers with aqueous UCST through postpolymerization modification

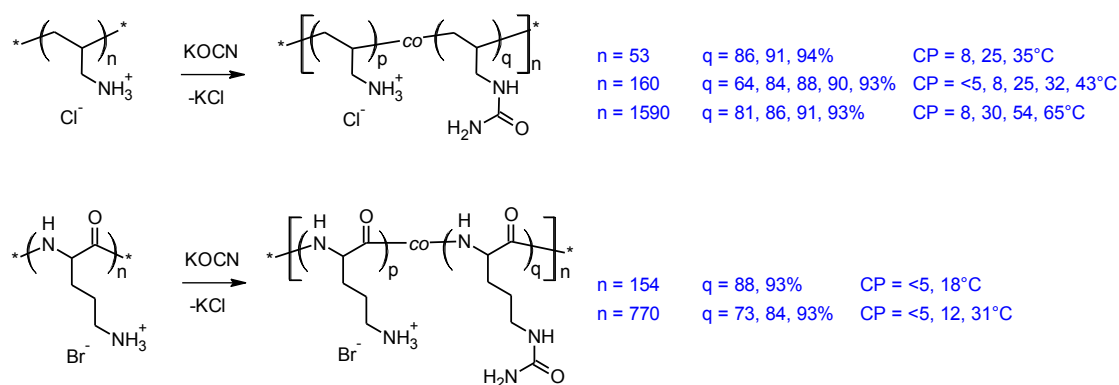
Several UCST systems have been synthesized through postpolymerization modification reactions. They fall largely into two classes, depending on the nature of the attractive polymer–polymer interactions—hydrogen bonding and electrostatic attractions.

3.2.1 Hydrogen bonding (co)polymers containing amido or ureido groups

In a recent study of our group^[99] we reacted poly(pentafluorophenyl acrylate), pPFPA, with varying amounts of ammonia and benzylamine forming hydrophobically modified acrylamide copolymers.^[100] Based on the strong attractions between amide groups in their capacities as H-bond donors and acceptors, a sample containing 13 mol-% of benzylacrylamide comonomer units was found to show a UCST transition in water at low temperature, while species containing less hydrophobic benzyl groups were fully soluble in water. With a higher content of benzylacrylamide comonomers, however, samples were insoluble in water suggesting that this system offered a poor control over UCST tuning which was attributed to possible PFP ester hydrolysis reactions producing minor amounts of acid side groups within the copolymers. Even minor amounts of charged moieties within (co)polymers have been shown to strongly interfere with UCST behavior within hydrogen-bonding-type UCST (HB-UCST) systems.^[101]

A more successful postpolymerization modification reaction to yield HB-UCST systems was presented by Shimada et al.^[102, 103] The authors modified the amine-functional polymers poly(allylamine) and, as a first example of a non-vinyl system displaying an aqueous UCST, poly(L-ornithine) with 64–94 mol-% of ureido groups using potassium cyanate, see **Scheme 6**. Owing to the excellent H-bonding potential of the urea-functional side chains, the copolymers showed UCST cloud points under physiologically relevant conditions (pH 7.5, 150 mM NaCl) that increased with an increasing molecular weight and an increasing ureido content.^[102] Subsequent modification of the remaining amino groups on the allylurea copolymers with acetyl anhydride (AA) or succinyl anhydride (SA) provided an additional handle of increasing (AA) or decreasing (SA) the UCST cloud points and of capturing specific proteins allowing for their separation under bio-friendly conditions.^[103] Mishra et al.^[104] recently proposed a series of postpolymerization modification reactions starting from poly(hydroxyethyl methacrylate), pHEMA, toward ureido-functional copolymers with tunable

UCST transitions in water. pHEMA was first coupled with 4-pentynoic acid and the resulting triple-bond functional polymer was then ‘clicked’ with an azide carrying urea functionality producing ureido-functional polymers with a UCST transition in water. Subsequent quaternization of the triazole rings with methyl iodide was presented as a means to lower the UCST transition temperature.



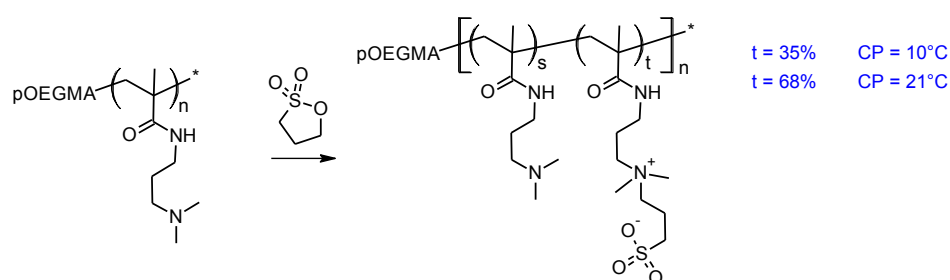
Scheme 6. Postpolymerization modification of the amine-functional polymer poly(allylamine) (top) and poly(L-ornithine) (bottom) with potassium cyanate yielding copolymers containing the ureido-functional segments allylurea (top) and L-citrulline (bottom) displaying UCST behavior in water under physiological conditions.^[102]

3.2.2 Electrostatically interacting zwitterionic (co)polymers

A main class of (co)polymers displaying UCST behavior in water is constituted of zwitterionic polysulfobetaines. Phase separation at low temperatures is driven through electrostatic interlocking of the zwitterionic side chains, which is typically limited to electrolyte-free water due to an antipolyelectrolyte effect that screens the zwitterionic charges from another.^[105]

Sulfobetaine units are easily prepared by means of quaternizing a tertiary amine with a sultone. Postpolymerization modification of poly(dimethylaminoethylmethacrylate), pDMAEMA, with propane sultone thus yields the zwitterionic species

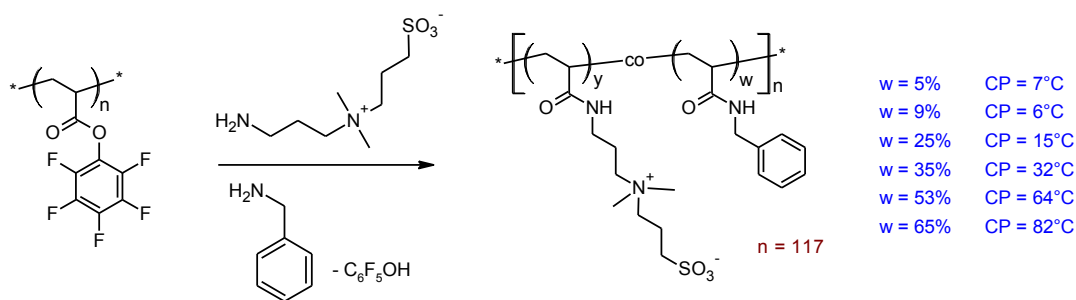
poly(methacroyloxyethyl dimethylammonio propanesulfonate) (pMAEPS),^[106, 107] which is, in fact, the most commonly described zwitterionic polymer with a UCST in water. The modification reaction is typically carried out in organic solvents from which the zwitterionic species precipitates. This synthetic route was used, for instance, in the production of a thermoresponsive ‘schizophrenic’ diblock copolymer in combination with a block displaying LCST behavior.^[108] Recently, Tian et al.^[109] demonstrated that incomplete quaternization of poly(dimethylaminopropylmethacrylamide) with propane sulfone provided a means of tuning the UCST transition of the resulting poly(methacrylamidopropyl dimethylammonio propanesulfonate) (pMAmPPS) containing species—the respective pMAmPPS homopolymer being a further well-documented species with UCST in water, see **Scheme 7**.^[105] UCST transition temperatures increased with an increasing content of zwitterionic side groups. The authors presented diblock copolymers comprising a selectively quaternized block with tunable UCST and a OEGMA-based block with an LCST tunable by virtue of the choice of comonomers with different OEG side chain lengths.



Scheme 7. Incomplete postpolymerization quaternization of a tertiary amine containing block as a means to tune the UCST transition of the resulting statistical zwitterionic copolymer block.^[109]

While an increasing amount of non-zwitterionic side chains in the previous example (Scheme 7) decreased the UCST cloud point, i.e., increased solubility, our group presented a straightforward synthetic technique to *increase* UCST cloud points of polysulfobetaines via

postpolymerization modification. In this study, pPFPA was reacted with mixtures of a zwitterionic amine, 3-((3-aminopropyl)dimethylammonio)propane-1-sulfonate, and hydrophobic amines (pentylamine, benzylamine, dodecylamine) in homogeneous solution using propylene carbonate as solvent, yielding well-defined statistical zwitterionic acrylamido copolymers comprising varying molar amounts of pentyl-, benzyl- and dodecylacrylamide comonomer units, **Scheme 8**. Whereas UCST transitions of polysulfobetaines are typically limited to higher molar mass samples, somewhat limiting practicality of this phase transition, we found the benzylacrylamide copolymer series with molar masses ranging from 26–35 kg/mol to display sharp reproducible UCST transitions that increased with increasing benzylacrylamide content, enabling UCST transitions up to 82°C. Incorporation of benzylacrylamide units was also found to counteract the antipolyelectrolyte effect, increasing the salt tolerance polysulfobetaines. A copolymer containing 35 mol-% of benzylacrylamide, for example, showed sharp reproducible UCST transitions decreasing with an increasing NaCl concentration of up to 76 mM, **Figure 2**. Surprisingly, the pentylacrylamide copolymer series was fully soluble over a wide composition range which was attributed to an increased entropic contribution of the flexible pentyl side chains. We expect this first example of tuning the UCST transition of polysulfobetaines over a wide temperature and salt concentration range to advance the applicability of polysulfobetaines as smart materials.



Scheme 8. Synthesis of hydrophobically modified sulfobetaine copolymers through postpolymerization modification of pPFPA employing a zwitterionic amine yielding copolymers with tunable UCST transitions.^[110]

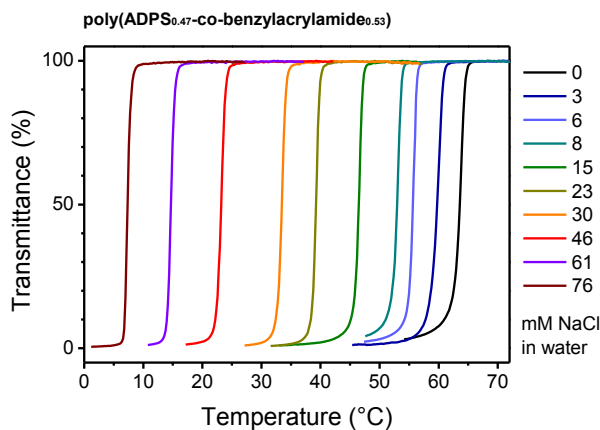


Figure 2. Transmittance curves of a copolymer of benzylacrylamide and acrylamidopropyl dimethylammonio propanesulfonate (ADPS) (structure shown in Scheme 8) in salt solutions showing increased solubility with an increasing salt concentration. Reprinted with permission from reference.^[110] Copyright 2014 American Chemical Society.

3.3 (Co)polymers with UCST transitions in water–alcohol mixtures

Several (co)polymers have been shown to exhibit UCST transitions in water–ethanol mixtures, with best solubility typically found at ~ 80 vol-% of ethanol. Examples include poly(methyl methacrylate) (pMMA),^[111, 112] various OEG-side chain methacrylates and (meth)acrylamides,^[40, 44, 45] and various poly(2-alkyl-2-oxazoline)s.^[65, 66] Tuning of the UCST transition of pMMA in water–ethanol was recently described by Zhang et al.^[113] by introducing reactive PFPMA comonomers into pMMA followed by postpolymerization modification with a variety of amines. Alkyl-modification was found to increase UCST cloud points (i.e. lower solubility) while modification with polar side groups (e.g. with ethanolamine or ethylene diamine) increased solubility in water–ethanol mixtures.

Surprisingly, at some ethanol fractions above or below the solubility maximum (~85 vol-% ethanol for this system), the hysteresis between heating (dissolution) and cooling (phase separation, typically at *lower* temperature than dissolution) was found to be reversed which was discussed in terms of mixed solvent structure and lower importance of water–polymer hydrogen-bonding at low water contents.

4. Outlook

Over the past decades, a large range of LCST-type polymers has been prepared and meticulously analyzed. In combination with postpolymerization modification, a wide variety of functional backbones has been endowed with thermoresponsive properties exhibiting LCST behavior in water. Known thermoresponsive polymers accessible through postpolymerization reactions serve as an expedient platform for the investigation of further stimuli. While especially the application of light as a physical stimulus has been advancing over the past years, several other stimuli remain largely unexplored, for example various mechanical stimuli, or tailored responses to very specific molecules, for example such of biological relevance. Polymers displaying a UCST in water, on the other hand, are sparse though recent postpolymerization approaches have provided access to ureido-functional copolymers with tunable UCST transitions and have improved the behavior of sulfobetaine copolymers making their smart behavior more accessible. No doubt, the advantages of postpolymerization modification in combination with robust and efficient modification reactions will further widen the scope of available smart materials and their usefulness in interdisciplinary fundamental and applied disciplines.

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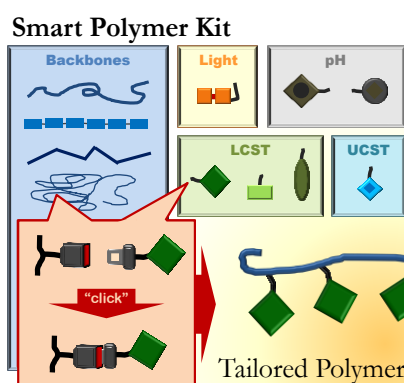
Keywords: LCST, UCST, RAFT polymerization, activated esters, click chemistry

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Peter J. Roth

Composing Well-defined Stimulus-responsive Materials through Postpolymerization Modification Reactions



Choosing the right building blocks is the key to designing novel smart materials. This review combines theoretical fundamentals of different types of stimulus-responsiveness, emphasizing LCST and UCST behavior, with a range of illustrations of postpolymerization modification in order to provide guidance on how to compose well-defined smart polymers with tailored properties.

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