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Thermoresponsive poly(2-oxazoline)s, polypeptoids, and polypeptides

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This review covers the recent advances in the emerging field of thermoresponsive polyamides or polymeric amides, *i.e.*, poly(2-oxazoline)s, polypeptoids, and polypeptides, with a specific focus on structure–thermoresponsive property relationships, self-assembly, and applications.

1. Introduction

Natural systems are governed by adaptive and responsive behavior to survive, which is mostly driven by conformational changes and catalytic actions of proteins. These perfectly defined polyamide structures take on defined folded structures to get very sophisticated response behavior. Inspired by such

systems, polymer scientists have developed a wide range of synthetic responsive polymer materials that respond to a wide range of stimuli (pH, temperature, ionic strength, molecules, *etc.*) with various changes in the polymer materials, including phase transition, color change, and shape transformation.¹

Thermoresponsive synthetic polymers that undergo a temperature induced solubility phase transition in aqueous solutions have received significant interest as mild temperature changes provide an easy way to trigger the solubility.^{2–8} Furthermore, such systems are highly appealing for development of drug delivery systems if the transition temperature is close to body temperature, allowing to prepare formulations that are soluble at room temperature and gel upon injection,

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polymeric sensors as well as switchable surfaces.^{9–14} Two different types of thermoresponsive polymers exist, namely those that undergo a demixing phase transition upon heating and those that demix upon cooling.

Polymers that are fully soluble at low temperatures and phase separate upon heating are so-called lower critical solution temperature (LCST) polymers, whereby the LCST represents the lowest phase transition temperature in the entire binodal phase diagram. Most commonly, the cloud point temperature (T_{cp}) is reported as the phase separation temperature at a specific concentration, determined by turbidimetry. The LCST phase transition is driven by the entropy-loss due to interaction of water molecules with the polymer and upon heating this entropy-loss becomes dominant eventually leading to dehydration of the polymer and phase separation.

Polymers with opposite behavior are known as upper critical solution temperature (UCST) polymers and such behavior is much more rare as it is mostly based on the enthalpic attraction between the polymer chains.⁵ Such enthalpic attraction is based on supramolecular interactions, such as electrostatic interactions or hydrogen bonding. A second type of UCST polymer phase transition is more commonly observed in alcohol–water mixtures, which is driven by the non-ideal mixing of the solvent mixture leading to a significant drop in solvent polarity upon heating, thereby increasing the polymer solubility.⁷

Within this review, we provide an overview of recent work on synthetic thermoresponsive polyamides, or polymeric amides, that closely resemble the (random coil) structure of proteins, namely poly(2-oxazoline)s, polypeptoids, and polypeptides (Fig. 1). Synthetic polypeptides are analogues of natural peptides that are prepared by ring-opening polymerization of the corresponding amino acid *N*-carboxyanhydrides,¹⁵ which are obviously not limited to the use of natural amino acids but allow the introduction of other functionalities to tune the thermoresponsive behavior. Polypeptoids are the tertiary amide analogues of polypeptides that can also be prepared by similar methods. Poly(2-oxazoline)s, prepared by living cationic ring-opening polymerization of 2-oxazolines,^{16,17} are polymers having tertiary amides units too, albeit with a slightly different configuration as only the nitrogen is part of the main chain and the carbonyl is part of the side chain. These three classes of polymers have in common that they have a hydrophilic main chain (partially) consisting of the repeating amide groups. As such, the introduction of slightly

hydrophobic side chains allows accurate tuning of the hydrophilic–hydrophobic balance to obtain thermoresponsive polymers.

In the following, the recent developments in the areas of thermoresponsive poly(2-oxazoline)s (section 2.1), polypeptoids (section 2.2), and polypeptides (section 2.3) will be discussed mostly focusing on work from the past five years.

2. Thermoresponsive polyamides or polymeric amides

2.1 Poly(2-oxazoline)s

Poly(2-oxazoline)s are a synthetic class of polyamides, or polymeric amides, that are obtained by (living) cationic ring-opening polymerization of 2-oxazoline monomers yielding the corresponding ring-opened polymers that have a tertiary amide structure of which just the nitrogen is incorporated in the polymer backbone.^{17–21} The 2-substituent of the monomer can be varied allowing accurate control over the hydrophilic–hydrophobic balance of the resulting poly(2-oxazoline)s.^{22–25} If the hydrophilic tertiary amide bond of the polymer backbone is complimented with small hydrophobic side chains, this leads to thermoresponsive poly(2-oxazoline)s with lower critical solution temperature (LCST) behavior. In this regard, the boundaries are set by poly(2-methyl-2-oxazoline), which is very hydrophilic and does not show LCST behavior in water, and by poly(2-butyl-2-oxazoline), in which the hydrophobic butyl side chains dominate the behavior making the polymer insoluble in water. Obviously, larger hydrophobic aliphatic or aromatic side chains also result in hydrophobic poly(2-oxazoline)s. Poly(2-oxazoline) homopolymers bearing side chains with intermediate hydrophobicity will lead to thermoresponsive polymers with LCST behavior in water. An overview of the poly(2-oxazoline) homopolymers that have been reported to exhibit LCST behavior is shown in Fig. 2.

2.1.1 Homopolymers. Poly(2-ethyl-2-oxazoline) (PEtOx; Fig. 2) was the first poly(2-oxazoline) analogue that was reported, in 1988, to be thermoresponsive. Lin and coworkers reported T_{cp} values in between 61 °C and 69 °C, depending on the molar mass and concentration of the polymer in water for rather high molar mass polymers.²⁶ This study was extended to lower molar mass PEtOx by Du Prez *et al.*²⁷ and later Schubert *et al.*²⁸ who demonstrated that PEtOx with minimal 100 repeat units is required to observe a T_{cp} below 100 °C. It was also demonstrated that PEtOx follows classical Flory–Huggins type 1 behavior, that is the T_{cp} decreases with increasing molar mass. The LCST of PEtOx, defined as the lowest T_{cp} in the polymer–water phase diagram has been reported to be around 60 °C to 63 °C.²⁶ The architecture of the PEtOx also has a significant impact on the thermoresponsive behavior as enforcing a higher local polymer concentration, by attachment of short PEtOx fragments to a compact core structure, leads to a significant drop in T_{cp} . This effect has been demonstrated by Dworak *et al.* for star-shaped PEtOx, which had a T_{cp} 62 °C while a linear analogue had a T_{cp} of 75 °C.²⁹

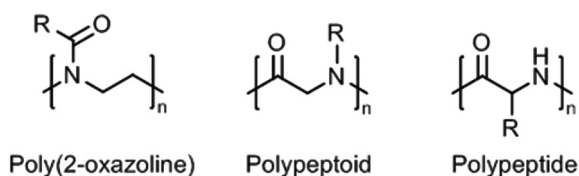


Fig. 1 General chemical structures of (partially) main-chain polyamides: poly(2-oxazoline), polypeptoid, and polypeptide; R = organic substituent (usually alkyl).



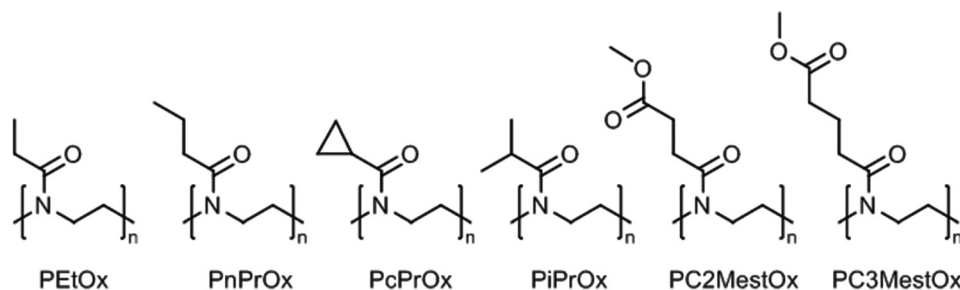


Fig. 2 Thermoresponsive poly(2-oxazoline) homopolymers with the abbreviated names.

A recent report by Grayson described the straightforward synthesis of cyclic poly(2-oxazoline)s,³⁰ and albeit no thermo-responsive properties have been reported yet, it may be anticipated that cyclic poly(2-oxazoline)s will have different thermo-responsivity compared to their linear analogues as has been reported for poly(*N*-isopropylacrylamide) (PNIPAM).³¹ The high local concentration of PETox in amphiphilic block copolymer micelles also leads to a drop in T_{cp} to around 60 °C,³² while PETox-functionalized peptide nanotubes had a T_{cp} of 70 °C and the degree of polymerization (DP) of PETox was only 40.³³ Similarly, a comb-shaped polymer having short PETox with DP of five in the side chain of a polymethacrylate backbone was reported by Schubert to have a LCST of 75 °C based on determination of the complete coexistence curve.³⁴ Furthermore, the effect of both Hofmeister salts and ions has been demonstrated as tool for tuning of the T_{cp} in the entire range from 0 °C to 100 °C by Hoogenboom *et al.*,³⁵ Demirel *et al.*,³⁶ and Schlaad *et al.*³⁷ Even though, it is generally accepted that the temperature induced LCST phase transition of poly(2-oxazoline)s has little to no hysteresis, in contrast to the widely studied PNIPAM,³⁸ Demirel has demonstrated that prolonged annealing of an aqueous solution of PETox above the T_{cp} leads to irreversible crystallization and formation of nanofibers.³⁹

Poly(2-isopropyl-2-oxazoline) (PiPrOx; Fig. 2) was first reported to be thermoresponsive by Uyama and Kobayashi in 1992.⁴⁰ As the LCST of PiPrOx is close to body temperature, being 26 °C to 34 °C depending on polymer molar mass indicative of type 1 Flory–Huggins behavior,⁴¹ this polymer has developed into the most studied and most popular thermoresponsive poly(2-oxazoline) derivative.^{42–44} Similar to PETox, Filippov and coworkers demonstrated for PiPrOx that the T_{cp} decreases for star-shaped polymers compared to linear analogues due to enhanced local polymer concentration and polymer–polymer interactions.⁴⁵ PiPrOx comb-shaped polymers were demonstrated by Jordan to have T_{cp} 's of 28 °C to 31 °C with side chain graft lengths down to DP 4 units indicating that the high local concentration induces the thermo-responsive behavior since linear PiPrOx with DP 17 has been reported to have a T_{cp} of 73 °C.^{42,46} Furthermore, the T_{cp} of PiPrOx has been demonstrated to strongly depend on the end-group, especially for shorter polymer chains where the effect of the end-group is more dominant. Winnik *et al.* reported

that the T_{cp} of PiPrOx with DP 57 decreased from 48.1 °C with methyl and hydroxyl end-groups to 32.5 °C with *n*-octadecyl and hydroxyl end-groups and 31.6 °C with two *n*-octadecyl end-groups (all at 0.1 mg mL⁻¹ in water).⁴⁷ A detailed investigation by high sensitivity differential scanning calorimetry revealed that both polymers with one and two *n*-octadecyl end-groups organized into micellar aggregates, thereby leading to similar enhanced polymer–polymer interactions and similar T_{cp} values. Similar results were reported by Jordan who demonstrated that the T_{cp} of PiPrOx with DP 27 decreased from 47 °C to 28 °C and 32 °C by introduction of one or two *n*-nonyl end-groups, respectively (all at 20 mg mL⁻¹), tentatively ascribed to micellization.⁴⁸ Furthermore, it was demonstrated that introduction of short hydrophilic PMeOx outer blocks with DP 3 increased the T_{cp} to 53 °C while introducing short hydrophobic poly(2-*n*-nonyl-2-oxazoline) outer blocks with DP 1 or DP 2 decreased the T_{cp} to 15 °C and 11 °C.

Even though all the early reports on the LCST behavior of PiPrOx demonstrated fully reversible phase transitions without significant hysteresis, Schlaad and coworkers were the first to report irreversible crystallization driven self-assembly of PiPrOx upon continued heating above the T_{cp} .^{49–51} In 2012, Winnik and coworkers demonstrated by a combination of optical spectroscopy and solution vibrational spectroscopy and molecular dynamics simulations that heating of PiPrOx aqueous solution leads to an irreversible change in the chain conformation to a more regular all-*trans* conformation (Fig. 3).⁵² Despite this change in chain conformation, the LCST phase transition remains fully reversible upon repetitive heating-cooling cycles. However, prolonged heating leads to crystallization facilitated by the more regular chain conformation. This hypothesis was more recently confirmed by the work of Wu based on temperature variable ¹H NMR, Fourier-transform infrared and Raman spectroscopy, including two-dimensional correlation spectroscopy.⁵³

Only 15 years after the first report on the LCST behavior of PiPrOx, Kataoka and coworkers reported that poly(2-*n*-propyl-2-oxazoline) (PnPrOx; Fig. 2) also exhibits LCST behavior with a T_{cp} around 25 °C.⁵⁴ The T_{cp} of PnPrOx revealed much smaller molar mass and concentration dependence than PETox as may be attributed to its more hydrophobic character that facilitates dehydration.²⁸ The third possible C₃ side chain,



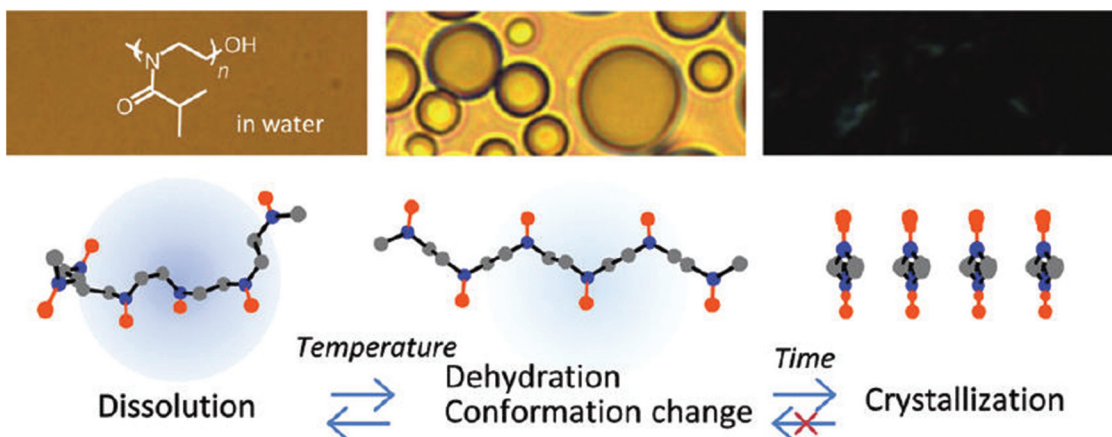


Fig. 3 Proposed mechanism for the irreversible crystallization of PiPrOx upon annealing of aqueous solutions above the cloud point temperature. Reprinted with permission from ref. 52. Copyright 2012 American Chemical Society.

namely cyclopropyl, was reported by Schubert *et al.* to lead to poly(2-cyclopropyl-2-oxazoline) (PcPrOx; Fig. 2), which is also thermoresponsive and has a T_{cp} that is intermediate to PiPrOx and PnPrOx.⁵⁵ For both PnPrOx and PcPrOx it has been demonstrated that incorporation as side chains in comb polymers leads to a decrease in T_{cp} .^{46,55}

Poly(2-oxazoline)s with methyl ester side chains were first reported by Litt in 1968,⁵⁶ but it was only reported in 2015 by Hoogenboom that such polymers exhibit thermoresponsive LCST behavior in aqueous solution.⁵⁷ In fact, poly(2-methoxycarbonyl-ethyl-2-oxazoline) (PC2MestOx; Fig. 2) has very similar solution behavior as PEtOx with a T_{cp} around 100 °C for a polymer with DP 100 while poly(2-methoxycarbonylpropyl-2-oxazoline) (PC3MestOx; Fig. 2) has very similar behavior as PnPrOx with a T_{cp} around 25 °C.

2.1.2 Homopolymer mixtures. A rather recent trend in tuning of thermoresponsive behavior of polymers is by mixing (also referred to as blending) of polymers, sometimes leading to cooperative behavior.^{58–61} Wu and coworkers reported a study on mixing of PiPrOx with PNIPAM and poly(*N*-vinylcaprolactam) (PNVCL).⁶² Rather strikingly it was observed that mixtures of PiPrOx and PNIPAM undergo two distinct phase transitions that are slightly affected by the presence of the other polymer, while mixtures of PiPrOx and PNVCL undergo one cooperative phase transition. This difference in behavior upon mixing was ascribed to the strong intramolecular hydrogen bonding of PNIPAM that does not allow interactions with PiPrOx. On the other hand PiPrOx and PNVCL are both polymers with only hydrogen bond accepting amide groups and upon heating water bridges are formed between the two polymers leading to cooperative phase separation and the formation of a high concentration phase containing both polymers. However, Zhang and coworkers reported that mixtures of poly(methyl vinyl ether) and PEtOx also revealed two distinct phase transitions while both polymers only contain hydrogen accepting groups,⁶³ indicating that the rationale between cooperative LCST behavior is not yet well understood. Further

work of Trzebicka and coworkers on mixtures of PNIPAM and PiPrOx revealed the influence of heating rate on the thermoresponsiveness.⁶⁴ Slow gradual heating, as is commonly applied during turbidimetry, indeed confirmed two distinct phase transitions of the individual polymers. In contrast fast sudden temperature increase above the T_{cp} of both polymers led to the formation of mixed phase separated mesoglobules, a term used to describe the high concentrated dispersed polymer phase that is formed upon crossing the phase transition temperature of dilute polymer solutions. A study on mixing of poly(2-oxazoline)s bearing a hydrophobic lipid chain that self-assemble into micelles in water was reported by Morandi *et al.*⁶⁵ Both PEtOx and PiPrOx were synthesized using a tosylate functionalized lipid initiator and the resulting polymers with T_{cp} of 35 °C and 76 °C, respectively, were subsequently mixed at different ratios in aqueous solution. Up to addition of 52% of lipid-PEtOx, the T_{cp} gradually increased from 35 °C to 42 °C, but at higher lipid-PEtOx content two distinct phase transitions were observed, one corresponding to cooperative behavior and one corresponding to pure lipid-PEtOx. The authors did not yet unravel whether this behavior results from the presence of mixed micelles and pure PEtOx micelles already below the T_{cp} or that demixing of PEtOx and PiPrOx occurred during the LCST phase transition.

2.1.3 Statistical copolymers. The previously discussed mixing approach is an interesting and straightforward way of tuning T_{cp} , albeit it is hard to predict whether or not cooperative behavior will be obtained. A more robust way of accurately tuning the T_{cp} of poly(2-oxazoline)s is by copolymerizing different monomers to accurately control the hydrophilic–hydrophobic balance of the copolymer chains. T_{cp} values are adjustable between 0 °C and 100 °C by incorporation of inert more hydrophobic or more hydrophilic comonomers into one of the discussed thermoresponsive homopolymer, respectively. Specific examples of copolymers with tunable T_{cp} include copolymers of PEtOx with PnPrOx,^{22,54} PiPrOx,⁶⁶ PcPrOx,⁶⁷ and poly(2-*n*-nonyl-2-oxazoline) (PNonOx),^{68,69} copolymers of



PiPrOx with PEtOx,⁶⁶ PnPrOx,^{54,68} poly(2-*n*-butyl-2-oxazoline) (PButOx),⁶⁸ and PNonOx⁶⁸ as well as copolymers of PnPrOx with PMeOx,⁷⁰ PEtOx,^{22,54} and PiPrOx.^{54,68}

In recent years, some more exotic comonomers have been explored to tune the T_{cp} of poly(2-oxazoline)s in aqueous solution. Volet and coworkers reported copolymers of PMeOx and poly(2-(5-azidopentyl)-2-oxazoline) that have T_{cp} values in between 0 °C and 100 °C depending on the comonomer composition.⁷¹ Schubert *et al.* reported the synthesis of copolymers of PEtOx and poly(2-(4-Boc-aminobutyl)-2-oxazoline) (Boc = *tert*-butyloxycarbonyl) that after removal of the Boc group yielded copolymers of PEtOx and poly(2-(4-aminobutyl)-2-oxazoline).⁷² Even though the amino group is more hydrophilic in water due to protonation leading to fully water-soluble copolymers that do not show LCST behavior in neutral water, it was demonstrated that at pH 14, where the amino-group is in its free base form, the copolymers had T_{cp} values in between 25 °C and 65 °C, depending on the copolymer composition and the polymer concentration. Copolymers of PEtOx, PnPrOx, PC2MestOx and PC3MestOx were also shown to have tunable T_{cp} values in between 25 °C and 100 °C.⁵⁷ Interestingly, copolymers of PEtOx and PC3MestOx revealed a linear relationship between composition and T_{cp} while copolymers of PnPrOx and PC2MestOx cover exactly the same range of T_{cp} values, but with a strong non-linear correlation. This difference in behavior is not yet understood, but may be related to the size of the side chains and their exposure to the aqueous phase. Hydrolysis of PcPrOx-PC2MestOx and PnPrOx-PC2MestOx copolymers was demonstrated to lead to dual responsive polymers that are sensitive to both temperature and pH resulting from (de)protonation of the carboxylic acid units.^{73,74} Similarly, direct amidation of the PC2MestOx with ethylene diamine led to an amine functional copolymer showing temperature and pH sensitivity based on (de)protonation of the amino groups.^{73,75} Schlaad and coworkers reported dual responsive poly(2-oxazoline) micelles containing carboxylic acid or amine groups in the core, prepared by post-polymerization modification of core-crosslinked micelles using thiol-yne radical coupling.³² These ionically modified crosslinked micelles were demonstrated to not only respond to changes in temperature and pH, but their T_{cp} values were also strongly dependent on the presence of salts following the Hofmeister series.³⁷

These latter examples already indicated that post-polymerization modification is another popular strategy to control the T_{cp} of poly(2-oxazoline)s. The popularity of this strategy is based on the possibility to modify the side chains of (co)polymers without affecting the polymer chain length and molar mass distribution allowing direct interpretation of the effect of the side chain on the T_{cp} . Schlaad *et al.* introduced poly(2-butenyl-2-oxazoline) (PButenOx) as a robust scaffold for post-polymerization modification using radical thiol-ene chemistry.^{76,77} This methodology was then applied for post-polymerization modification of PiPrOx-PButenOx copolymers to tune the T_{cp} providing a versatile platform in which the T_{cp} could be tuned by copolymer composition as well as by

post-polymerization modification.⁷⁸ As expected, introduction of hydrophobic side chains such as acetyl-protected thioglucose and 1-octanethiol led to a decrease in T_{cp} , whereas introduction of hydrophilic side chains such as 2-mercaptoethanol and 1-thioglycerol increased the T_{cp} . Similarly, deprotection of the acetyl-glucose side chains led to significant increase in T_{cp} . Schubert and coworkers reported a very similar strategy for the post-polymerization modification of PEtOx-poly(2-(9-decenyl)-2-oxazoline) (PEtOx-PDecenOx) copolymers.⁷⁹ However, the presence of the long hydrophobic alkyl side chain led to a decrease in T_{cp} when unprotected thioglucose was attached to the terminal double bonds by thiol-ene coupling.⁸⁰ This difference in behavior between the PButenOx and PDecenOx can be ascribed to the formation of hydrophobic pockets that favor hydrogen bonding between the glucose and the amide groups of the polymer backbone in the case of PDecenOx,⁸¹ thereby enhancing the polymer-polymer interactions and decreasing the solubility. A final example of tuning the T_{cp} by post-polymerization modification of poly(2-oxazoline)s was reported by Meier and Hoogenboom *et al.* making use of Passerini and Ugi multicomponent side chain modification of an acid-containing copolymer obtained by hydrolysis of PEtOx-PC3MestOx.⁸² By variation of the small molecule reagents for these multicomponent reactions, the T_{cp} of the acid-functionalized copolymer (T_{cp} = 78 °C) could be lowered to 15 °C while intermediate transition temperatures could also be achieved.

2.1.4 Block copolymers. As mentioned previously, adding short hydrophilic or hydrophobic blocks to a thermo-responsive poly(2-oxazoline) can be exploited to modify the T_{cp} of the polymer.⁴⁸ A longer hydrophilic block can also be utilized to develop thermoresponsive micelles that are fully soluble below the T_{cp} and assemble into micellar nanostructures upon heating. This concept has been utilized by Hruby and coworkers by developing a triblock copolymer consisting of hydrophilic PMeOx outer blocks and middle thermo-responsive block consisting of a statistical copolymer of PiPrOx and PButOx.⁸³ Upon increasing the temperature, this triblock copolymer self-assembled into defined micellar structures. Kataoka and Jang prepared a block copolymer consisting of a poly(benzyl ether) dendron with carboxylic acid moieties at the periphery as one block and PiPrOx as thermo-responsive second block.⁸⁴ This system showed intricate self-assembly behavior that could be controlled by both temperature and pH to lead to unimolecularly dissolved chains at high pH below T_{cp} , vesicular structures at high pH above T_{cp} , cylindrical micelles at low pH below T_{cp} and macroscopic aggregates at low pH above T_{cp} . A block copolymer consisting of PiPrOx as thermo-responsive block and poly(3-acrylamidopropyltrimethylammonium chloride) as permanently charged hydrophilic block was reported by Winnik *et al.*⁸⁵ Upon increasing the temperature of an aqueous solution of this block copolymer above the T_{cp} of PiPrOx of 40 °C the block copolymer self-assembled into vesicular structures. However, depending on the heating rate, the pathway to form these structures was found to vary. Fast heating from room temperature to 60 °C



led to initial assembly into cylindrical micelles that rearranged into vesicles, while slow heating led to the initial formation of small spheres that slowly grew in size upon further heating until diffusion of the hydrophilic charged block to the center leads to the formation of the vesicles.

A double thermoresponsive PEtOx-*b*-PnPrOx block copolymer was reported by Hoogenboom and Kjoniksen *et al.*⁸⁶ The thermoresponsive behavior of this block copolymer was studied by a combination of static and dynamic light scattering and turbidimetry revealing that below the T_{cp} of both blocks the polymer is present as unimers and in loose aggregates (Fig. 4). When passing the T_{cp} of the PnPrOx block, large aggregates are formed that upon further heating undergo a transition to defined micellar aggregates with a PnPrOx core and a PEtOx corona. Further heating beyond the T_{cp} of PEtOx led to the formation of large macroscopic aggregates as the entire polymer becomes insoluble in water. A related study on PEtOx-*b*-PiPrOx block copolymers was reported by Sato and Winnik *et al.*⁸⁷ Upon heating the block copolymer solution in water to 50 °C, which is in between the T_{cp} of both individual blocks, the initial formation of star-like micelles was observed that further aggregate to induce macroscopic phase segregation. This is in contrast to the PEtOx-*b*-PnPrOx block copolymer micelles that remained stable in time, which may be ascribed to the smaller difference in T_{cp} of PEtOx and PiPrOx leading to more cooperative behavior compared to PEtOx and PnPrOx. Similarly, PiPrOx-*b*-PNIPAM block copolymers were also reported to undergo one cooperative phase separation rather than individual collapse of the blocks.⁸⁸

2.1.5 UCST-type polymers. In contrast to this large amount of work on LCST-type poly(2-oxazoline)s, only a limited number of studies reported UCST-type poly(2-oxazoline)s in alcohol-water solvent mixtures and no poly(2-oxazoline) has been reported with UCST behavior in pure water. Such UCST-type solubility in alcohol-water mixtures can be obtained by increasing the hydrophobicity of the side chain resulting in insolubility in water as well as alcohol-water solvent mixtures. However, these latter solvent mixtures will become less polar upon heating allowing dissolution of the polymer as has been demonstrated by Schubert and Hoogenboom *et al.* for PButOx,

being the least hydrophobic water-insoluble poly(2-oxazoline).⁸⁹ While PButOx revealed UCST behavior in 50 : 50 wt% ethanol-water solvent mixtures, more and more ethanol was required to get such behavior if the side chain length was increased up to PNonOx.⁸⁹ A broad screening of the effect of poly(2-oxazoline) side chain on the LCST and UCST behavior in ethanol-water solvent mixtures revealed a general correlation between hydrophobicity and required amount of ethanol to gain UCST behavior (Fig. 5). Besides control over the UCST behavior by variation of the 2-oxazoline monomer structure, it can also be controlled by copolymerization of different monomers as was demonstrated for PEtOx-NonOx random copolymers.⁶⁹

Annealing of poly(2-isobutyl-2-oxazoline) (PiBuOx) and PNonOx below their UCST in ethanol-water solvent mixtures was demonstrated by Schlaad and coworkers to lead to isothermal crystallization leading to nanosized hierarchically organized structures.⁹⁰ Furthermore, the UCST behavior of PPhOx in ethanol-water solvent mixtures was exploited by Schubert *et al.* for the preparation of thermoresponsive micelles consisting of PMeOx or PEtOx as hydrophilic part and PPhOx as UCST-switchable part.⁹¹ The resulting micelles that are formed below the UCST phase transition temperature dissolve into unimolecularly dissolved polymer chains upon heating. Another example of UCST-switchable micelles was reported by Hoogenboom *et al.* based on copolymers of PNonOx and PPhOx.⁹² By variation of the solvent system, one single copolymer was found to form UCST switchable micelles with either PNonOx as switchable core or PPhOx as switchable core.

2.1.6 Applications. Temperature responsive poly(2-oxazoline)s are already known since 1988 and in recent years their application potential is being explored more and more. In the following, some recent application directed studies based on responsive poly(2-oxazoline)s will be discussed. The temperature induced self-assembly of poly(2-oxazoline)s has most frequently been used to exploit the size and shape of the formed mesoglobules or micelles in the case double hydrophilic diblock copolymers are used that contain a permanently soluble block and a thermoresponsive block. Hruby and

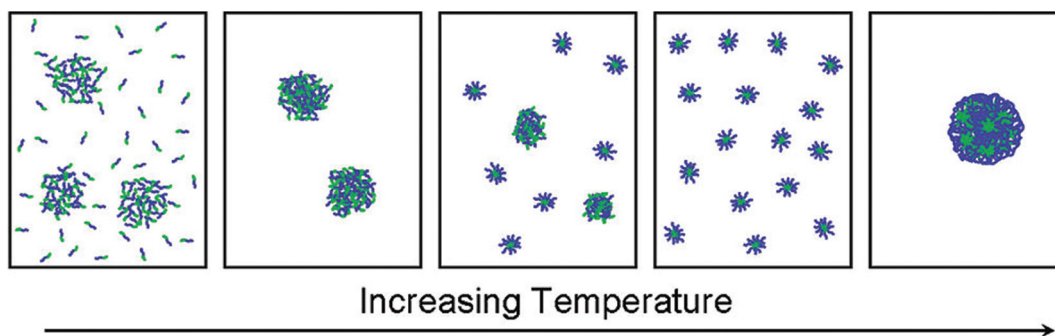


Fig. 4 Schematic representation of the temperature induced self-assembly of PEtOx-*b*-PnPrOx going from a mixture of unimers and loose aggregates below T_{cp} to large aggregates that fall apart in discrete and defined micelles with a PnPrOx core and PEtOx corona until finally macroscopic aggregation when passing the T_{cp} of PEtOx. Reprinted with permission from ref. 86. Copyright 2012 American Chemical Society.



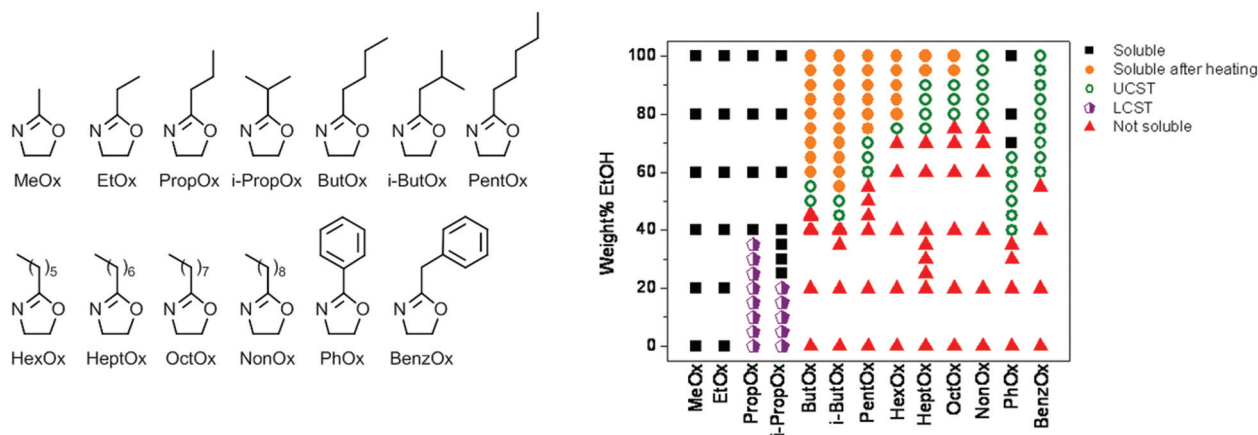


Fig. 5 Screening of solubility behavior of a wide set of poly(2-oxazoline)s (monomer structures shown) (left) in different ethanol–water solvent mixtures (right). Reprinted with permission from ref. 89. Copyright 2010 MDPI AG.

coworkers used this feature in PMeOx-*b*-(PiPrOx-*stat*-PButOx)-*b*-PMeOx triblock copolymers that were labeled with ^{125}I as radionuclide.⁸³ Upon increasing the temperature, radionuclide loaded micelles are formed due to collapse of the middle block that could benefit from the enhanced permeation and retention effect for passive targeting of nanocarriers to tumors. It was also demonstrated the PiPrOx-PButOx copolymers are more stable against small doses of β -radiation than other potential thermoresponsive polymers for therapeutics, including PNIPAM and PNVCL.⁹³

In a related context, Osada and Kataoka *et al.* reported a triblock copolymer consisting of PETox, PnPrOx as middle thermoresponsive block and polylysine as cationically charged block.⁹⁴ The polylysine could be exploited for complexation with DNA resulting in cylindrical micelle self-assembled structures. Increasing the temperature of the solution then led to collapse of the PnPrOx block onto the DNA-polylysine core, thereby providing a barrier to stabilize the polyplex on the one hand and to protect the DNA against degradation on the other hand. This novel strategy was demonstrated to lead to enhanced transfection efficiency.

The formation of defined mesoglobules upon increasing the temperature of an aqueous solution of PiPrOx was utilized by Rangelov *et al.* as template for the construction of hollow capsules.⁹⁵ The collapsed mesoglobules of PiPrOx were utilized as seeds for the radical polymerization of NIPAM and a crosslinker above the T_{cp} of both PiPrOx and PNIPAM. Subsequent lowering of the temperature below the T_{cp} of both polymers allowed extraction of the non-crosslinked PiPrOx core by diffusion through the cross-linked PNIPAM layer leading to hollow thermoresponsive PNIPAM capsules.

A last example where the thermoresponsive behavior of a poly(2-oxazoline) homopolymer was exploited to control assembly processes was reported by Hoogenboom and De Geest *et al.* for layer-by-layer (LBL) assembly of PnPrOx and tannic acid.⁹⁶ It was demonstrated that LBL assembly of alternating layers of PnPrOx and tannic acid led to much faster

growth of the multilayer film thickness when performed above the T_{cp} of PnPrOx due to adsorption of mesoglobules rather than individual PnPrOx chains as is the case below the T_{cp} .

Since the LCST phase transition of poly(2-oxazoline)s is accompanied by a transition from a hydrophilic to a hydrophobic polymer, this feature can be utilized to obtain temperature control over adsorption and desorption processes. Claesson *et al.* demonstrated that the adsorption of a block copolymer of PiPrOx as thermoresponsive block and poly(3-acrylamidopropyltrimethylammonium chloride) as charged block to adsorb onto a negatively charged silica substrate is indeed temperature dependent.⁹⁷ Upon increasing the temperature, the PiPrOx is partially dehydrated and becomes more hydrophobic which favors the adsorption process leading to an increase in adsorbed mass. This process was found to be reversible and decreasing the temperature led to partial desorption of the block copolymer. The design of such an adsorption–desorption system can also be reversed by attaching the thermoresponsive polymer to a substrate. Dworak and coworkers demonstrated that a PiPrOx or PETox-PNonOx thermoresponsive polymer modified glass substrate can be used for temperature controlled cell-culture surfaces.⁹⁸ Cells can be grown and cultured at 37 °C on the collapsed and dehydrated poly(2-oxazoline) layer. After growth of the cells, it was demonstrated that the cell sheet can easily be removed by simply lowering the temperature below the T_{cp} of the poly(2-oxazoline). The hydration and swelling of the polymer layer leads to spontaneous detachment of the cell layer. In an improved system, the PiPrOx polymer layer was modified by deposition of PiPrOx crystallites that were formed by annealing of PiPrOx above its T_{cp} .⁹⁹ This modified system enhanced proliferation of the human dermal fibroblast cells while facilitating their detachment from the substrate. A very recent example of temperature controlled adsorption and desorption with thermoresponsive poly(2-oxazoline)s was reported by Maskos and Bertin *et al.*¹⁰⁰ PiPrOx coated rhodamine labeled polyorganosiloxane were prepared and their interaction with serum



proteins was studied. It was demonstrated that the adsorption of serum proteins is significantly enhanced upon heating beyond the T_{cp} while subsequent cooling below the T_{cp} led to release of the proteins indicating the reversible nature of this process.

A final application area where thermoresponsive poly(2-oxazoline)s are receiving significant attention is as sensors and molecular logic gates. The most straightforward sensor with a thermoresponsive polymer is as temperature sensor, whereby the polymer phase transition induces clouding of the solution which can be the output signal. Hoogenboom has recently shown that PETox-PNonOx copolymers are ideal for this application as the exact phase transition temperature that is 'sensed' can be accurately tuned by addition of different amounts of α -cyclodextrins that form host guest complexes with the nonyl side chains, thereby altering the hydrophilic–hydrophobic balance of the copolymer and hence the T_{cp} .^{101,102} Furthermore, it was demonstrated that introducing a large content of hydrophobic PNonOx leads to a widening of the phase transition hysteresis in presence of α -cyclodextrins, that is upon heating the clouding of the solution takes place at 50 °C while upon cooling the solution only turns transparent when cooled below 10 °C.¹⁰³ This hysteresis originates from the supramolecular host–guest complexation that results in the formation of a meta-stable soluble phase. Once collapsed, reformation of the host–guest complexation only takes place at the original phase transition temperature of the non-complexed polymer. It was shown that this large hysteresis can be exploited as memory function for the molecular thermometer. A solution of the copolymer and α -cyclodextrin will remember whether it has been heated beyond 50 °C or not for more than 1.5 months at room temperature.

A similar sensor concept was developed by Jang, although employing a much more sophisticated fluorescence output signal.¹⁰⁴ PiPrOx was prepared with a tetraphenylethene end-group that translated the polymer phase transition in a fluorescent output signal. This system acts as a sensor for the

polymer concentration as well as the presence of γ -cyclodextrin. Moreover, the polymer γ -cyclodextrin host guest complex acts as temperature sensor as collapse of the polymer upon heating releases the γ -cyclodextrin to the aqueous solution, thereby inducing a change in fluorescence of the tetraphenylethene end-group. Very recently, Jang and coworkers reported PiPrOx end-modified with blue (pyrene), green (boron-dipyrromethene) and red (porphyrin) emissive dyes.¹⁰⁵ Even though the same PiPrOx polymer was used, the T_{cp} values were tuned by variation of the polymer chain length and by making star-shaped polymers. As such, the three emissive polymers all had different T_{cp} s and each of the individual polymers acts as a temperature sensor. However, by careful optimization of the concentration of the three polymers in one solution it was possible to design systems with different emission color in response to variations in temperature as shown in Fig. 6.

The final two examples describe the use of multiresponsive poly(2-oxazoline)s for molecular logic gate operations. Hoogenboom *et al.* reported the preparation of poly(2-oxazoline) coated gold nanoparticles that aggregate and change color from red to purple upon increasing the temperature above the T_{cp} of the polymer coating and in presence of sodium chloride.¹⁰⁶ It was demonstrated that the system operates as AND logic gate and that only a color change occurs when both triggers are present. Variation of the poly(2-oxazoline) from PiPrOx to PETox allowed tuning of the temperature required for the input. A triple responsive poly(2-oxazoline) was developed by Ju and Jang as AND-OR logic gates with the solution being opaque or transparent as output signal.¹⁰⁷ PiPrOx was prepared having two azobenzene end-groups, whereby the PiPrOx induces thermoresponsivity while photoisomerization of the azobenzene governs host–guest complexation with either α -cyclodextrin in the *trans*-form and with β -cyclodextrin in the *cis*-form. The AND-OR logic gate operation is based on photoirradiation for isomerization of the azobenzene, presence of cyclodextrin and the temperature as input signals.

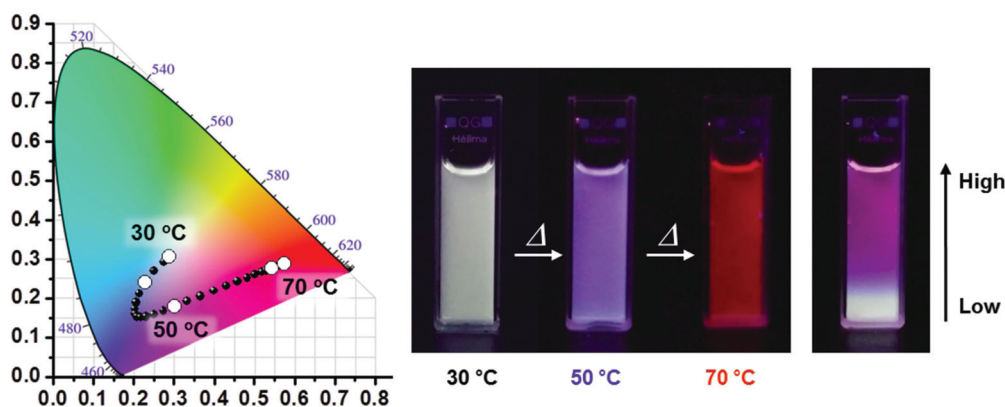


Fig. 6 Temperature-dependent fluorescence emission changes of three-component mixtures of PiPrOx modified with pyrene (blue), boron-dipyrromethene (green) and porphyrin (red). The right picture show the solution with a temperature gradient from bottom to top. Reprinted with permission from ref. 105. Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA.



2.2 Polypeptoids

Polypeptoids, *i.e.*, poly(*N*-alkyl glycine)s,⁸ in aqueous solution can exhibit lower critical solution (LCST) behavior, which they share with other tertiary amides like poly(2-oxazoline)s (see previous section) and also poly(meth)acrylamides.^{2,3}

Peptoid homopolymers with methyl (C₁, sarcosine) and ethyl (C₂) side chains are readily soluble in water while all other polypeptoids with longer alkyl side chains (C₃ and longer) were found to be insoluble.¹⁰⁸ Afterwards, it has been demonstrated that amorphous samples of polypeptoids with C₃ side chains, *i.e.*, *n*-propyl, allyl, and *i*-propyl (Fig. 7), can be dissolved in water at 20–40 g L⁻¹ and show LCST behavior; poly(*N*-propargylglycine), however, remains insoluble in water.^{109,110} The cloud point temperatures (T_{cp}) were found to increase in the order *n*-propyl (15–25 °C) < allyl (27–54 °C) < *i*-propyl (47–58 °C), depending on the chain length and polymer concentration (classical Flory-Huggins type 1 behavior). The phase transitions were reversible only for shorter time scales of a few hours. Long-term annealing of dilute aqueous solutions of poly(*N*-*n*-propylglycine) and poly(*N*-allylglycine) resulted in the formation of crystalline precipitates (melting at 188–198 °C and 157–165 °C, respectively) with complex morphologies (*cf.* crystallization of PETox or PiPrOx in hot water, see above).¹⁰⁹

It is worth to mention that thermoresponsive polypeptoid homopolymer fiber mats could be prepared by electrospinning of blends of semicrystalline poly(*N*-*n*-propylglycine) and high molar mass poly(ethylene oxide) (PEO).¹¹¹ Annealing of the electrospun fibers at about 100 °C and subsequent washing with water selectively removed the amorphous PEO fraction to give stable crystalline poly(*N*-*n*-propylglycine) fibers.

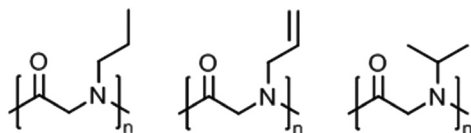


Fig. 7 Thermoresponsive polypeptoid homopolymers.

Thermo-induced aggregation and crystallization (see above) was observed for poly(*N*-*n*-propylglycine)-polysarcosine diblock copolypeptoids in water (double hydrophilic at $T < T_{cp}$ and amphiphilic at $T > T_{cp}$).¹¹² Interestingly, the morphology of initially spherical aggregates at $T > T_{cp}$ was not retained during crystallization of the hydrophobic poly(*N*-*n*-propylglycine) core, resulting in the formation of larger complex assemblies (100–500 nm in size) with flower-like, ellipsoidal, or irregular shapes (Fig. 8). Evidently, the crystallization of the hydrophobic core is not applicable for the stabilization of aggregates against dilution, as for instance desirable in drug delivery applications. Also, the incorporation of hydrophobic molecules or drugs into the crystallized compartment might be difficult.

The T_{cp} values could be adjusted for statistical copolymers with hydrophilic units, usually sarcosine or *N*-ethylglycine, and hydrophobic units, usually butyl or higher alkyl substituted glycines, at various ratios. Examples include poly[sarcosine-*ran*-(*N*-butylglycine)] with tunable T_{cp} values in the range of 27–71 °C (at 0.3 wt% in water; sarcosine content increasing from 42 to 73 mol%)^{113,114} and poly[(*N*-ethylglycine)-*stat*-(*N*-butylglycine)] 20–60 °C (at 0.1 wt% in water).¹¹⁵ For the latter case, a distinct impact of the architecture, linear *vs.* cyclic, on T_{cp} could be recognized. The phase transition of the cyclic copolypeptoids was shifted to lower temperature, by five degrees or less, as compared to the linear analogue with the same composition, which was explained in terms of lower entropic loss. Also, the T_{cp} was found to decrease upon the addition of sodium salts, the degree of depression being in line with the Hofmeister series, *i.e.*, sulphate > chloride > iodide. Such a salting-in/out effect was also observed for poly[sarcosine-*ran*-(*N*-butylglycine)].¹¹⁴

Interestingly, when comparing linear norbornyl-poly[(*N*-ethylglycine)-*ran*-(*N*-butylglycine)] and polynorbornene-*graft*-poly[(*N*-ethylglycine)-*ran*-(*N*-butylglycine)] bottlebrushes (prepared by ring-opening metathesis polymerization, ROMP), the polymer architecture seemed to have no impact on the T_{cp} .¹¹⁶ However, the phase behavior was strongly dependent on the thermal history of the samples and the presence of inorganic salts.

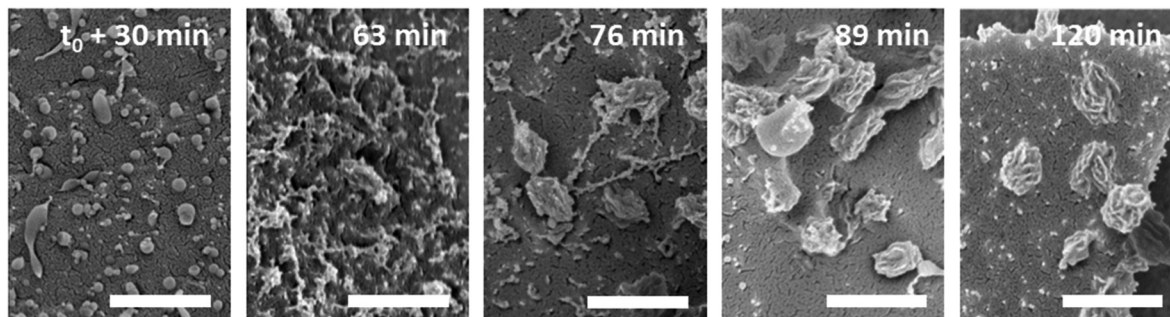


Fig. 8 Time-dependant evolution of aggregate structures, as visualized by cryogenic scanning electron microscopy (scale bar = 500 nm), in 1 wt% aqueous solutions of poly(*N*-*n*-propylglycine)₇₀-block-polysarcosine₂₃ at 48 °C ($T > T_{cp}$). Reprinted (modified) with permission from ref. 112. Copyright 2016 American Chemical Society.



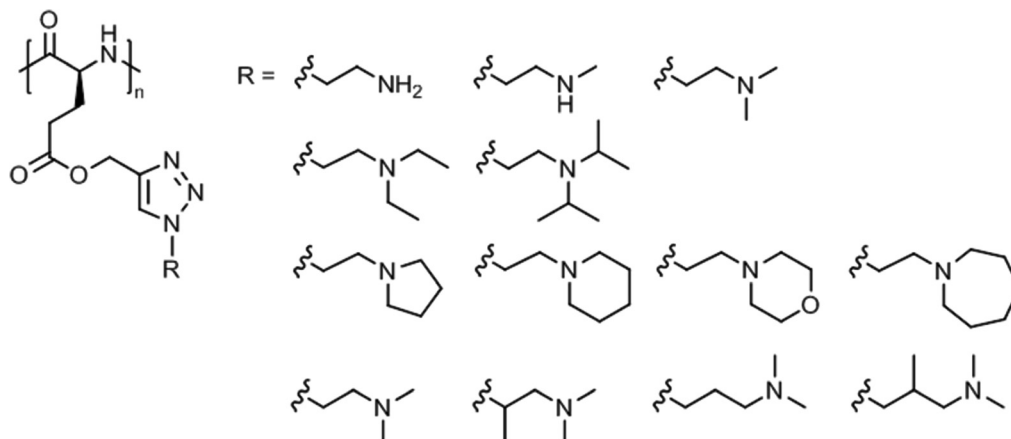


Fig. 11 Thermo- and pH-responsive poly(L-glutamate)s with amine side chains.

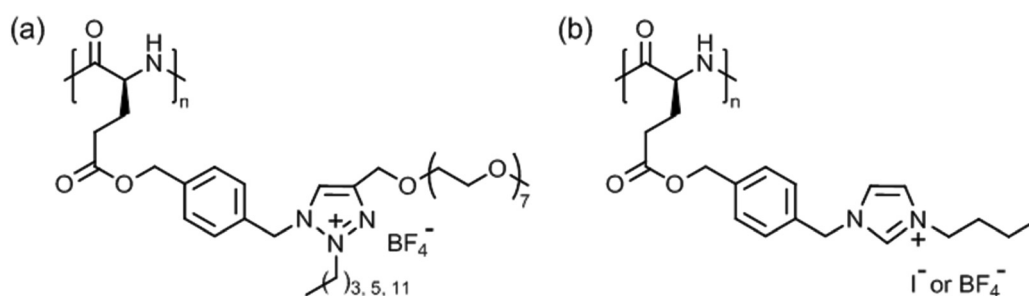


Fig. 12 Thermoresponsive poly(γ -benzyl-L-glutamate)s with (a) alkyl/oligoethylene glycol triazolium and (b) *n*-butyl imidazolium side chains.

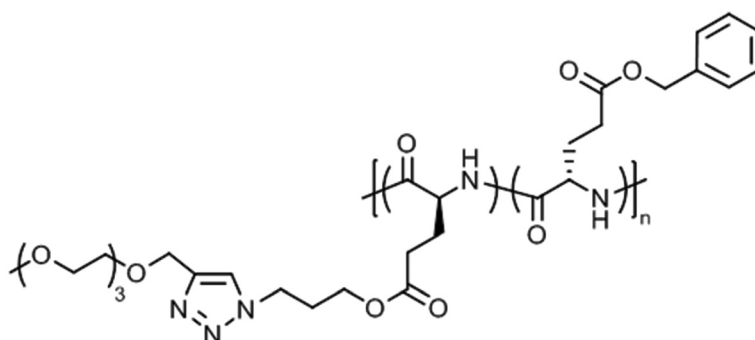


Fig. 13 Thermoresponsive copoly(L-glutamate) with benzyl and triethylene glycol side chains.

exhibited LCST behavior in deionized water and the T_{cp} could be varied in the range of 40–75 °C, depending on the alkyl/oligoethylene glycol substitution (alkyl = butyl, hexyl, dodecyl) and polymer concentration (0.1–0.6 wt%).¹²⁵ The T_{cp} 's were also affected considerably by the presence of salt (NaBF₄), *i.e.*, $\Delta T = -5$ °C to -25 °C, due to salting out effect. The most pronounced effect, however, was found for the permanently charged polypeptide with butyl/oligoethylene glycol side chains at 0.6 wt% NaBF₄.

The second polypeptide with *n*-butyl imidazolium side chains, however, showed UCST behavior in deionized water.¹²⁶

Depending on the counter ion, I⁻ or BF₄⁻, the transition or clearing temperature was 35 °C or 69 °C, respectively, at 0.1 wt%; no phase transition was observed for polypeptides with alkyl = methyl/Cl⁻, I⁻, BF₄⁻ and *n*-butyl/Cl⁻. The transition temperature was unaffected by the polymer chain length but was significantly affected by salts, and it increased in the presence of NaI and NaBF₄ and decreased in the presence of NaCl (*cf.* Hofmeister series). This effect was ascribed to electrostatic interactions and anionic exchange reactions.

Water-soluble random copoly(L-glutamate)s with benzyl and triethylene glycol pendants (Fig. 13) were found to exhibit



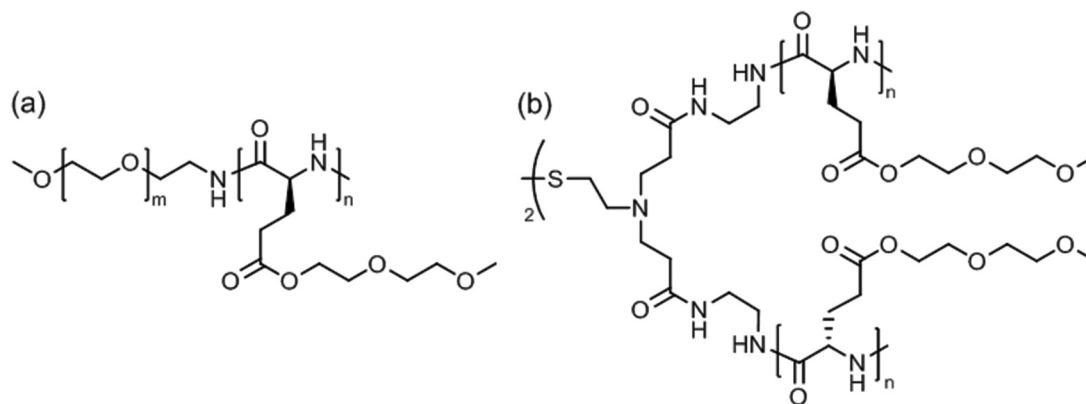


Fig. 14 Thermoresponsive poly[γ -(methoxy diethylene glycol)-L-glutamate]-based (a) block copolymer and (b) 4-arm star polymer.

thermoresponsive properties.¹²⁹ Depending on the composition, *i.e.*, ratio of hydrophobic benzyl groups *vs.* hydrophilic triethylene glycol groups, the T_{cp} could be tuned between 22 °C (57% hydrophilic units) and 53 °C (90% hydrophilic units) (at 0.2 wt% in water). Furthermore, the helicity of copolyptide chains increased from 65% to 90% with increasing triethylene glycol content.

Linear poly(ethylene glycol)₄₅-*block*-poly[γ -(methoxy diethylene glycol)-L-glutamate]₄₃ (Fig. 14a) was soluble in water (or 100 mM NaCl solution) at room temperature but formed wormlike micelles at a temperature above $T_{cp} = 53$ °C.¹³⁰ Aggregation occurred due to the temperature-induced dehydration of the polypeptide block without affecting its α -helical conformation. Extension of the thermal annealing time (12 hours at 80 °C) drove the secondary structure transformation of the polypeptide block from α -helix to β -sheet, which accounted for a transition from wormlike micelles into nanoribbons measuring about 70 nm in width and several micrometers in length.

Star-shaped poly[γ -(methoxy diethylene glycol)-L-glutamate] with a disulfide-containing core (apparent molar mass, $M_n = 15.5$ or 33.8 kDa) (Fig. 14b) exhibited dual thermo- and redox-responsiveness.¹³¹ Addition of dithiothreitol to the aggregates in water reduced the disulfide bonds, cutting the 4-arm star polypeptide into 2-arm star (linear) fragments, which however

caused a reduction of the size of aggregates from about 330 nm to 180 nm. The aggregate size gradually decreases upon heating (20–50 °C) due to the collapse of the polypeptide side chains; the process could be reversed by cooling. Interestingly, 3–4 wt% aggregate solutions formed a hydrogel at room temperature, which could be dissolved upon heating to above $T_{cp} \sim 40$ °C.

The graft copolymer (or molecular bottlebrush) poly(L-glutamate)-*graft*-poly[2-(2-methoxyethoxy)ethyl methacrylate] (molar mass, $M_n = 221$ kDa) (Fig. 15a) exhibited thermoresponsive LCST behavior in aqueous solution.¹³² The phase transition was rather broad in pure water ($T_{cp} \sim 27$ °C) but sharp in saline solution ($T_{cp} = 22$ –23 °C, 0.1–0.9 wt% NaCl). It was stated, based on circular dichroism spectroscopic measurements, that the helicity of polypeptide chains (DP ~ 45) was almost 100% at 25 °C and also at 60 °C. Aggregates (assumed to be spheres with helical polypeptide core and thermoresponsive polymethacrylate shell) were formed in water, measuring 150 nm in diameter at 25 °C and 60 nm at 60 °C.

Also the “hairy-rod” polypeptides consisting of a poly(L-glutamate)₄₀ backbone and poly[(methoxy diethylene glycol methacrylate)-*ran*-(methoxy triethylene glycol methacrylate)] side chains (grafting ratio $\sim 90\%$; molar mass, $M_n = 195$ –227 kDa) (Fig. 15b) displayed thermoresponsive properties.¹³³ The T_{cp} values, measured at 2 wt% in physiological

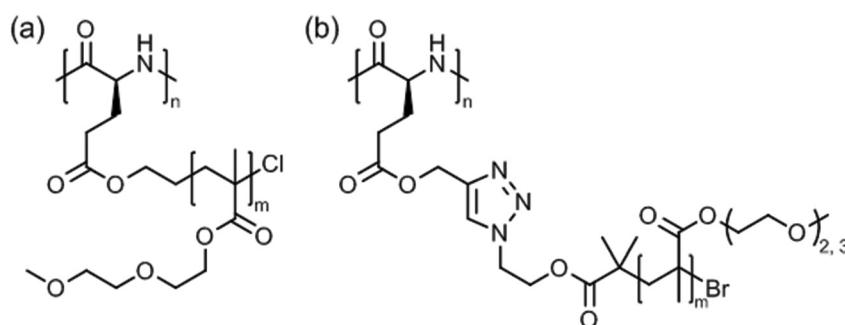


Fig. 15 Thermoresponsive “hairy-rod” graft copolymers with poly(L-glutamate) backbone and poly[methoxy oligo(ethylene glycol) methacrylate] side chains, prepared by (a) grafting from and (b) grafting onto.



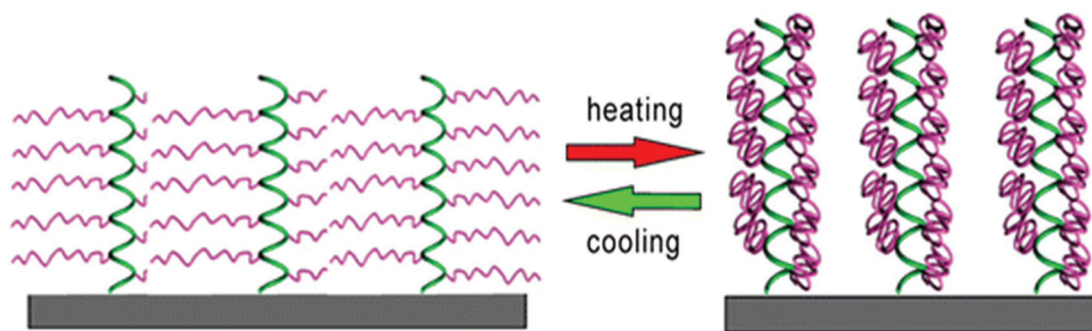


Fig. 16 Thermo-induced hydration/dehydration of polypeptide brushes; green = helical poly(L-glutamate) backbone, purple = thermoresponsive oligoethylene glycol side chains. Reprinted with permission from ref. 134. Copyright 2015 American Chemical Society.

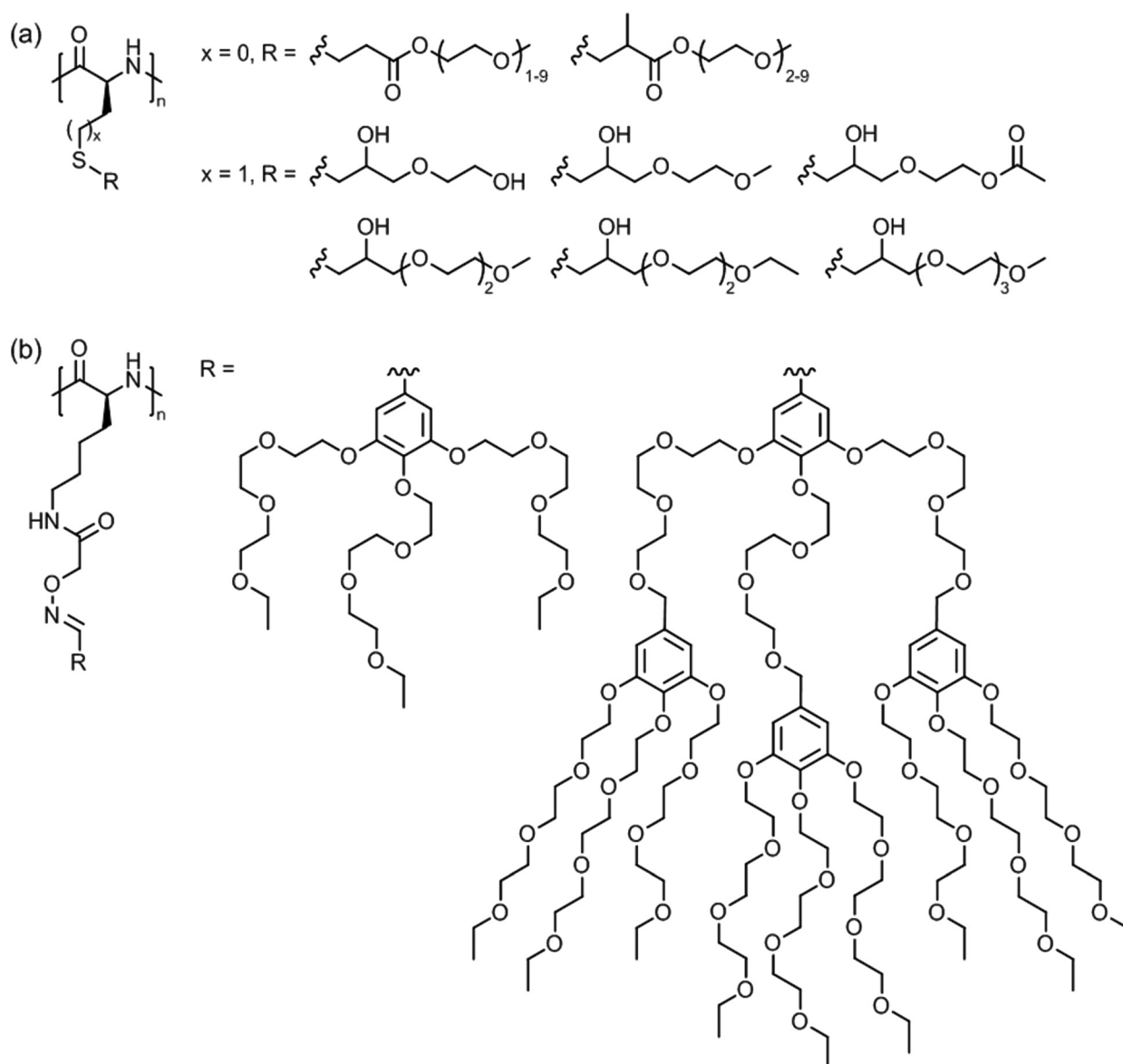


Fig. 17 Thermoresponsive polymers based on side chain modified (a) poly(L-cysteine) ($x = 0$) and poly(L-homocysteine) ($x = 1$) and (b) poly(L-lysine).



saline solution (0.9 wt% NaCl), were found to increase from 20 °C to 41 °C with increasing hydrophilicity of the side chains, *i.e.*, increasing amount of methoxy triethylene glycol methacrylate. In the same line, the hydrodynamic size of the aggregates formed in water increased from 170 nm to 310 nm. All polypeptide copolymers adopted 100% α -helical conformation, except the most hydrophilic one bearing poly(methoxy triethylene glycol methacrylate) side chains, 72%.

Klok *et al.* synthesized surface-tethered helical poly [γ -(oligoethylene glycol)-L-glutamate] brushes.¹³⁴ The polypeptide chains did not undergo any changes in the secondary structure between 10 °C and 70 °C, but revealed a significant dehydration upon heating from 10 °C to 40 °C. Interestingly, the film thickness remained unchanged due to the shape-persistent nature of the polypeptide brushes (Fig. 16).

2.3.2 Other polypeptide-based polymers. Poly(L-cysteine) modified with monomethoxy oligoethylene glycol (meth)acrylate (Fig. 17a, $x = 0$) were found to exhibit thermoresponsive behavior when the number of ethylene glycol units was between 3 and 5; the T_{cp} values were in the range of 50–70 °C at 0.2 wt% in water.¹³⁵ Deming *et al.* achieved a more predictable and wider tuning of T_{cp} , *i.e.*, $T_{cp} = 30$ –80 °C, with oligoethylene glycol-modified poly(L-homocysteine)s (Fig. 17a, $x = 1$).¹³⁶ The T_{cp} values were also found to be sensitive to the presence of Hofmeister salts ($\Delta T = \pm 20$ °C). Oxidation of the thioether linker to sulfoxide or sulfone led to an increase of the hydrophilicity of the polypeptide and thus increase of the T_{cp} to above the boiling point of water.

Poly(L-lysine)s bearing triethylene glycol dendrons of generation 1 and 2 (Fig. 17b) exhibited LCST behavior in pH 7 buffered aqueous solutions.¹³⁷ At 0.1 wt%, the cloud point temperatures were in the range of 30–37 °C depending on the polypeptide chain length and dendron generation.

3. Summary

Poly(2-oxazoline)s, polypeptoids, and polypeptides are interesting materials especially for use in biomedical applications, which not least is due to their good (bio-) compatibility and degradability. Recent efforts were focussed to implement external stimuli-responsiveness, for instance to temperature, pH, *etc.*, to these polymers for the generation of advanced smart materials.

Thermoresponsive poly(2-oxazoline)s are known for almost three decades while thermoresponsive polypeptoids and polypeptides have just emerged during the last five years (however, thermoresponsive elastin-like polypeptides and pH-responsive polypeptides are known for much longer). Accordingly, the research in thermoresponsive materials based on poly(2-oxazoline)s is far more established and yet more applications have been developed, for instance as biomedical devices, sensors, or molecular logic gates, as compared to polypeptoids and polypeptides. Applications of thermoresponsive polypeptoids and polypeptides are still scarce, which with the rapid research developments should change in the very near future.

Key parameter for the control of the thermoresponsive properties of a polymer, no matter if it is a poly(2-oxazoline), polypeptoid, polypeptide, or any other kind of material, is the hydrophilic–hydrophobic balance. This balance can be tuned by the proper choice of side chains or by the copolymerization of hydrophilic and hydrophobic monomers. Also the blending of homopolymers might be a suitable approach to tune the thermoresponsive behavior.

Yet a plethora of thermoresponsive polyamides have been prepared based of this concept of hydrophilic–hydrophobic balance (or by trial and error), though the self-assembly behavior, structure formation, and applications need to be further explored.

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