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Thionation of Amide-Based Polymers and Their Solution Behavior

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ACADEMIC DISSERTATION

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“Limits, like fears, are often just an illusion.”

Michael Jordan

Abstract

Thermoresponsive polymers exhibiting lower critical solution temperature (LCST) behavior in aqueous media are governed by an interplay between polymer hydration, hydrogen bonding, hydrophobic interactions, and chain dynamics. While tuning thermoresponsive behavior is commonly achieved through modification of polymer hydrophobicity via side-chain engineering or copolymerization, direct perturbation of the hydrogen-bonding characteristics of amide-containing thermoresponsive polymers remains comparatively underexplored. In this thesis, partial thionation of amide functionalities into thioamides is introduced as a versatile strategy for systematically tuning polymer–water interactions and aqueous phase behavior.

This cumulative dissertation is based on two publications and one preprint focusing on sulfur-containing amide-based polymers and their thermoresponsive behavior. The first publication demonstrates, for the first time, the partial thionation of poly(2-ethyl-2-oxazoline) (PEtOx) using Lawesson's reagent and establishes thionation as a post-polymerization tool for tuning the cloud point temperature and thermomechanical properties of poly(2-oxazoline)s. In the second study, the influence of thionation on structurally diverse thermoresponsive polymers was systematically investigated, with particular emphasis on the structurally isomeric systems poly(N-isopropylacrylamide) (PNIPAM), poly(2-*iso*-propyl-2-oxazoline) (P*i*PrOx), poly(2-ethyl-2-oxazine) (PEtOzi), and poly(N-vinylpyrrolidone) (PVP). Comparison of these polymers enabled the development of structure–property relationships connecting sulfur incorporation, hydrogen bonding, backbone and side chain structure, chain packing, and phase transition cooperativity. The third study expands the accessible chemical space of highly hydrophilic poly(2-oxazoline) and poly(2-oxazine) systems through the synthesis of novel ether-functionalized monomers, namely 2-methoxymethyl-2-oxazoline (MeOMeOx) and 2-methoxymethyl-2-oxazine (MeOMeOzi), then investigates the effects of both thioether incorporation and thionation on hydration stability and salt-induced thermoresponsive behavior.

Across all investigated systems, sulfur incorporation reduced polymer hydration stability and systematically shifted aqueous phase behavior toward lower cloud point temperatures or lower salt concentrations required for phase separation. However, the resulting solution behavior strongly depended on polymer structure

and phase transition mechanism rather than producing a universal shift in thermoresponsive behavior. In particular, the studies revealed that side-chain hydrophobicity primarily governs the magnitude of LCST shifts, whereas backbone structure, amide type, and chain flexibility determine the qualitative nature of phase separation and aggregation pathways.

The results further demonstrate that thionation represents a conceptually distinct approach for tuning thermoresponsive polymers because it simultaneously perturbs hydrogen bonding, polarity, and conformational mobility while largely preserving the overall polymer structure. Moreover, sulfur incorporation was shown to reveal "hidden" thermoresponsive behavior in highly hydrophilic polymer systems. Overall, this thesis establishes new structure–property relationships for sulfur-containing amide-based polymers and expands the molecular design principles available for responsive polymer materials in aqueous media.

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Dedicated to my family, especially to grandma.

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List of original publications

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I. **A. Hacioglu**, V. Baddam, A. Kerr, J. Kehrein, A. Bunker, R. Luxenhofer, "Thionation of Poly(2-ethyl-2-oxazoline) and Its Effect on Solubility and Cloud Point" Macromolecules **2024**, 57, 21, 10368–10378. https://doi.org/10.1021/acs.macromol.4c01341

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The publications are referred to in the text by their roman numerals.

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AH supported conceptualization, performed most of the experimental work, interpreted the analytical results and wrote the manuscript. Solution behavior work was supported by VB, and synthesis work was supported by AK. JK conducted molecular modelling and analyzed calculations, wrote the relevant molecular modelling part in the manuscript. AB supervised computational work, and RL conceptualized and supervised the experimental work. All authors critically reviewed the manuscript.

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AH conceptualized and performed most of the experimental work, interpreted the analytical results and wrote the manuscript. IE performed synthesis, solution behavior work, and analysis. DP conducted the computational work, wrote the molecular modelling relevant part in the manuscript. Analysis of the solution behavior work, and conceptualization was supported by VB, and synthesis work supported by AK. JK, and AB supervised computational work, SH conducted temperature-dependent NMR measurement and analysis, VA supervised the solution behavior work, RL supervised the experimental work. All authors critically reviewed the manuscript.

Publication III
AH and SNM conceptualized the work, interpreted the analytical results and wrote the manuscript. The experimental work was performed by AH, SNM and DS in equal weight. PVR supported the solution behavior related experimental work and analysis, SPH supported kinetic studies and characterization, VA supervised and contributed to solution behavior work, RL supervised the experimental work. All authors critically reviewed the manuscript.

List of Abbreviations

CROP	Cationic Ring-Opening Polymerization
DLS	Dynamic Light Scattering
DP	Degree of Polymerization
DSC	Differential Scanning Calorimetry
Đ	Dispersity
LCST	Lower Critical Solution Temperature
LR	Lawesson's Reagent
M_n	Number-average Molar Mass
µDSC	Micro Differential Scanning Calorimetry
PBuOx	Poly(2-butyl-2-oxazoline)
PC2MestOx	Poly(2-methoxycarbonyl ethyl-2-oxazoline)
PC3MestOx	Poly(2-methoxycarbonyl propyl-2-oxazoline)
PDEAOx	Poly(2-diethylamino-2-oxazoline)
PDI	Polydispersity Index
PEMAOx	Poly(2-dimethylamino-2-oxazoline)
PEtOEtOx	Poly(2-ethoxyethyl-2-oxazoline)
PEtOx	Poly(2-ethyl-2-oxazoline)
PEtOzi	Poly(2-ethyl-2-oxazine)
P*i*PrOx	Poly(2-isopropyl-2-oxazoline)
PMeOMeOx	Poly(2-methoxymethyl-2-oxazoline)
PMeOMeOzi	Poly(2-methoxymethyl-2-oxazine)
PMeOx	Poly(2-methyl-2-oxazoline)
PNAGA	Poly(N-acryloyl glycinamide)
PNIPAM	Poly(N-isopropylacrylamide)
P*n*PrOx	Poly(2-*n*-propyl-2-oxazoline)
POx	Poly(2-oxazoline)
POzi	Poly(2-oxazine)

PVP	Poly(N-vinyl pyrrolidone)
PVCL	Poly(N-vinyl caprolactam)
SEC	Size Exclusion Chromatography
TD	Thionation Degree
T_{cp}	Cloud Point Temperature
T_g	Glass Transition Temperature
UCST	Upper Critical Solution Temperature
UV–Vis	Ultraviolet–Visible Spectroscopy
Z_{avg}	Z-average Hydrodynamic Diameter

1 Introduction

Stimuli-responsive polymers capable of changing their physical properties in response to external stimuli have attracted interest over the recent decades due to their potential relevance in materials science, biotechnology, medicine, and soft matter physics.[1–3] Among the various stimuli investigated, temperature remains particularly attractive because it can be applied externally, results in a simple physical and, in most cases, reversible transition.[4,5] Thermoresponsive polymer behavior in aqueous solutions is mainly affected by polymer–water interactions, polymer–polymer association, chain flexibility, and entropic contributions coming from hydration and solvent structuring.[6] In particular, hydrogen bonding plays a central role in determining hydration stability and phase behavior. Consequently, structural modifications can profoundly alter thermodynamic interactions and lead to substantial changes in cloud point temperatures, aggregation pathways, and phase transition mechanisms. Therefore, understanding how molecular structure of a polymer controls these interactions is very important in the rational design of responsive polymer systems.

Among thermoresponsive materials, amide-containing polymers have a particularly important position because the amide functionality combines strong polarity with the ability to participate in both polymer–water and polymer–polymer hydrogen bonding interactions.[6,7] Depending on the precise structure of the repeating unit, amide-based polymers can display lower critical solution temperature (LCST),[8] or upper critical solution temperature (UCST) behavior in aqueous media.[9] Classical examples include poly(N-isopropylacrylamide) (PNIPAM), which exhibits highly cooperative LCST behavior dominated by dehydration and hydrogen-bond-mediated association, as well as poly(2-oxazoline)s (POx) and poly(2-oxazine)s (POzi), whose thermoresponsive behavior can be tuned systematically through backbone structure, side-chain identity, molar mass, and copolymer composition.[10–18] Particularly attractive in this context are POx and POzi systems, not only because they have tertiary amides partially on their backbone, but also because these polymer family can combine synthetic versatility, broad structural tunability, and favorable biocompatibility.[19–25] Depending on their side-chain structure, POx and POzi range from fully water-soluble systems to polymers exhibiting pronounced LCST behavior over nearly the entire temperature range of liquid water.

Despite the extensive literature on amide-containing thermoresponsive polymers, comparatively little is known about the corresponding thioamide-containing analogues. Replacement of the amide carbonyl oxygen atom by sulfur can potentially alter the physicochemical properties of the amide functionality. Thioamides possess reduced electronegativity, lower polarity, weaker hydrogen-bond accepting capability toward water, increased polarizability, and substantially larger rotational barriers around the C–N bond due to enhanced double-bond character.[26,27] Consequently, conversion of amides into thioamides is expected to strongly perturb polymer hydration, intermolecular association, chain dynamics, and ultimately thermoresponsive behavior in aqueous media.

While thioamides have long been studied in organic chemistry, peptide chemistry, and medicinal chemistry, thioamide-containing polymers in aqueous media remain comparatively underexplored. In particular, systematic studies investigating how thionation influences polymer hydration, solution behavior, and thermoresponsive phase transitions are still scarce. This is quite noteworthy because thionation provides a unique post-polymerization modification strategy that directly alters backbone polarity and hydrogen-bonding capability. Most common approach for tuning thermoresponsive behavior instead relies primarily on adjusting the overall hydrophilic/hydrophobic balance through copolymerization, side-chain engineering, or changes in polymer architecture. By comparison, direct modification of the hydrogen-bonding characteristics of thermoresponsive polymers has received remarkably little attention, despite the central role of hydrogen bonding in governing hydration and phase separation of amide-based systems. In this context, thionation represents a particularly intriguing molecular modification because it simultaneously perturbs hydrogen bonding, polarity, polarizability, and conformational rigidity while largely preserving the overall polymer structure.

2 State of the Art

2.1 Overview of Solution Behavior Theory

Polymer chains in solutions adopt conformations that are governed by a balance of inter-, and intramolecular interactions, together with chain flexibility.[28–30] Within the framework of Flory–Huggins theory, this behavior is described by the polymer–solvent interaction parameter (χ), which reflects solvent quality for a given polymer.[31,32] In good solvents ($\chi < 0.5$), favorable polymer–solvent interactions dominate, resulting in expanded coil conformations due to excluded volume effects. In contrast, in poor solvents ($\chi > 0.5$), segment–segment attractions become dominant, leading to chain collapse into compact globular conformations.[30,33]

The concept of solvent quality can be described using solubility parameters, which provide a molecular perspective on polymer–solvent compatibility. The earliest approach was introduced by Hildebrand, who related solubility to the cohesive energy density of a molecule through the Hildebrand solubility parameter (δ), defined as the square root of the cohesive energy per unit volume (Eq. 1).[34] Cohesive energy means the required energy to break a solvent into its gas state (Eq. 2). In this framework, compounds with similar δ values are expected to be miscible, whereas large differences in cohesive energy density lead to unfavorable mixing. While this approach is reasonably successful for nonpolar small molecule systems dominated primarily by dispersive interactions, it becomes insufficient for strongly polar or hydrogen-bonding systems such as aqueous polymer solutions.

$$\delta^2 = \frac{E_{cohesion}}{V_{mol}} \qquad \text{Eq. 1}$$

$$E_{cohesion} = \Delta H_{vaporization} - RT \qquad \text{Eq. 2}$$

To address these limitations, Hansen extended the Hildebrand concept by separating the cohesive energy into three distinct contributions arising from dispersive (δ_D), polar (δ_P), and hydrogen-bonding (δ_H) interactions.[35,36] The total cohesive energy density can be simply expressed as the sum of these individual interaction components (Eq. 3). Hansen solubility parameter has become particularly useful for polymers because it provides a more chemically intuitive

description of how specific intermolecular interactions govern solubility and phase behavior. Over time, numerous studies have demonstrated that the Hansen approach provides a conceptually and thermodynamically meaningful framework with more nuanced predictive capability for polymer systems.[37,38] More recent developments have furthermore focused on improving its applicability toward increasingly complex and previously unknown systems by incorporating additional thermodynamic considerations and refining the treatment of specific intermolecular interactions, particularly hydrogen bonding.[39]

$$\delta^2_{\text{Hansen}} = \delta^2_D + \delta^2_P + \delta^2_H \qquad \text{Eq. 3}$$

The conformation and aqueous solubility of polymer chains are strongly influenced by the chemical identity of their repeating units. Polar or hydrogen-bonding functionalities enhance polymer hydration and stabilize solvated coil conformations, whereas hydrophobic moieties promote intrachain association and reduce solubility.[6,32,40] In aqueous systems, this balance is particularly pronounced for amphiphilic polymers, where hydrophilic segments interact favorably with water while hydrophobic segments minimize contact with the surrounding solvent. As a result, polymer behavior in water is governed by a complex interplay of non-covalent interactions, including hydrogen bonding, van der Waals forces, ionic interactions, and hydrophobic effects, together with entropic contributions arising from chain conformational freedom and solvent structuring.[6]

Changes in external parameters can perturb this balance and induce significant conformation or phase transitions.[41] Among these parameters, temperature plays a central role, because it directly influences both enthalpic interactions and entropic contributions.[4,42,43] Temperature changes alter the relative strength of polymer–solvent and polymer–polymer interactions, leading to changes in coil dimensions and, in thermoresponsive systems, ultimately to coil-to-globule transitions. In solution, thermoresponsive polymers commonly display either lower critical solution temperature (LCST),[42] or upper critical solution temperature (UCST) behavior (Figure 1).[9,44]

Polymers exhibiting LCST behavior are soluble at relatively low temperatures due to favorable interactions with water, typically dominated by hydrogen bonding between polymer segments and surrounding water molecules. Upon heating above the LCST, these interactions weaken, while hydrophobic associations and intermolecular polymer–polymer interactions become increasingly favorable.[45] This results in the expulsion of water from the polymer hydration shell, collapse of the polymer chains, and eventual phase separation.

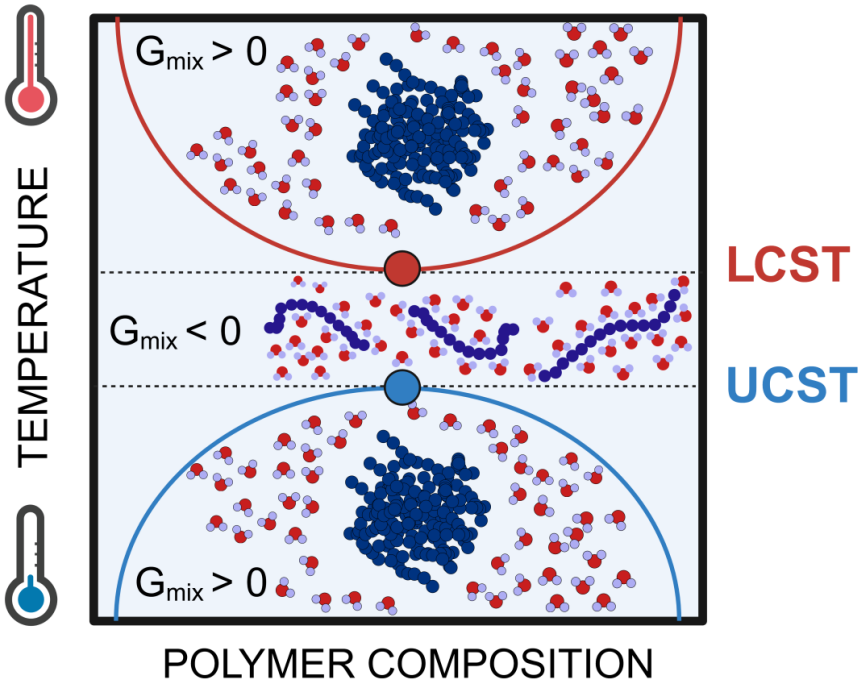

Figure 1 Schematic representation of lower critical solution temperature (LCST) and upper critical solution temperature (UCST) phase behavior in aqueous polymer solutions. Below the LCST, favorable polymer–water interactions stabilize solvated polymer coil conformations, and the Gibbs free energy of mixing remains negative ($\Delta G_{mix} < 0$). Upon heating above the LCST, dehydration and enhanced polymer–polymer interactions drive coil collapse and phase separation ($\Delta G_{mix} > 0$). In contrast, UCST systems exhibit phase separation at low temperatures due to dominant interpolymer interactions, whereas heating disrupts these associations and restores polymer solubility.

LCST transition can be understood thermodynamically using the Gibbs free energy of mixing: [29,30,46]

$$\Delta G_{mix} = \Delta H - T\Delta S \qquad \text{Eq. 4}$$

At lower temperatures, favorable enthalpic contributions arising primarily from polymer–water hydrogen bonding stabilizes the dissolved state ($\Delta G_{mix} < 0$). Upon heating, these interactions are progressively weakened, while the entropy gain associated with the release of structured water molecules surrounding the polymer chains becomes increasingly significant. As a result, the unfavorable entropy of mixing begins to outweigh the exothermic enthalpic contributions, and the $T\Delta S$ term dominates, rendering ΔG_{mix} positive and driving phase separation. Within the framework of Flory–Huggins theory this behavior is reflected in the temperature dependence of the polymer–solvent interaction parameter χ, which typically increases with temperature in LCST systems.[32] The resulting loss of

thermodynamic stability of the homogeneous solution leads to phase separation at elevated temperatures. This entropy-driven dehydration process is closely associated with the hydrophobic effect, which promotes coil collapse and subsequent aggregation of polymer chains in aqueous solution. [6,47]

In contrast to LCST systems, UCST behavior is characterized by phase separation at lower temperatures. It is primarily driven by favorable enthalpic interactions between polymer segments, such as hydrogen bonding, ionic interactions, or dipole–dipole associations.[9] These strong and specific intermolecular interactions promote polymer association, resulting in a negative enthalpy of mixing ($\Delta H_{mix} < 0$) together with a significant loss of configurational entropy due to formation of relatively ordered polymer-rich domains. As the temperature increases, thermal energy disrupts these intermolecular interactions, reducing their strength. Consequently, the entropic contribution becomes dominant, rendering ΔG_{mix} negative and leading to dissolution of the polymer chains. Within the framework of the Flory–Huggins theory, this behavior corresponds to a decrease in χ with increasing temperature, resulting in stabilization of the mixed state at elevated temperatures. Thus, UCST behavior is characterized by enthalpy-driven phase separation at low temperatures and entropy-driven mixing upon heating.[9]

2.2 Amide-Based Polymers in Water

Understanding the behavior of amide functional groups is fundamentally important for describing polymer solution behavior in aqueous media. Amides are arguably (one of) the most essential functional groups in chemistry and biology, most prominently constituting in peptide bonds that build up the backbone of proteins and polypeptides.[48,49] Due to their pronounced polarity, partial double bond character, and their ability to participate in hydrogen bonding both as hydrogen-bond donors and acceptors, amides strongly influence molecular organization, hydration, and intermolecular association in water.[50,51] Depending on their structure and local environment, amide groups can engage in polymer–water interactions as well as inter- and intramolecular amide–amide hydrogen bonding. For this reason, amide-containing polymers are frequently regarded as simplified synthetic model systems for understanding hydration-driven phenomena in macromolecules, including conformational transitions, aggregation, and phase separation in aqueous solution.[50,51] At the same time, their synthetic accessibility and structural versatility have established amide-based polymers as one of the most extensively investigated classes of thermoresponsive materials.[43] In aqueous media, the interplay between polymer hydration, hydrophobic interactions, and amide-mediated association governs the overall solution behavior, and determines whether a polymer remains molecularly dissolved or undergoes phase separation.

Depending on the precise structure of the repeating unit, amide-based polymers can exhibit either lower critical solution temperature (LCST) or upper critical solution temperature (UCST) behavior in water (Figure 2). In LCST-type systems, increasing temperature destabilizes polymer hydration, resulting in dehydration, chain collapse, and phase separation upon heating.[6,42] In contrast, UCST behavior originates predominantly from interpolymer interactions, mostly involving hydrogen bonding between amide functionalities, leading to polymer association and phase separation upon cooling.[9,44] Consequently, variations in amide structure, side-chain hydrophobicity, backbone flexibility, or hydrogen-bonding capability can alter the thermodynamic balance between polymer–water and polymer–polymer interactions, thereby strongly influences aqueous solution behavior.

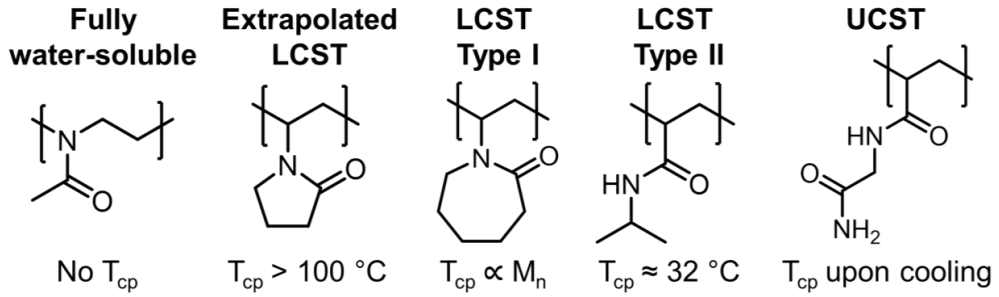

Figure 2 Representative examples of aqueous solution behavior observed for different classes of amide-containing polymers. Poly(2-methyl-2-oxazoline) (PMeOx) represents a fully water-soluble polymer without LCST behavior. Poly(N-vinyl pyrrolidone) (PVP) illustrates thermoresponsive polymers with extrapolated LCST values above the boiling point of water. Poly(N-vinyl caprolactam) (PVCL) exhibits classical LCST-Type I behavior with molar mass-dependent cloud points, whereas poly(N-isopropylacrylamide) (PNIPAM) displays cooperative LCST-Type II behavior dominated by inter- and intramolecular hydrogen bonding. Poly(N-acryloyl glycinamide) (PNAGA) is shown as a representative UCST-type polymer exhibiting phase separation upon cooling.

Differences in amide type (secondary, tertiary, or cyclic), backbone architecture, and side-chain composition can significantly influence hydration strength, solubility, and the resulting cloud point temperatures (T_{cp}).[6,43] This structural sensitivity becomes particularly evident when considering the prototypical behavior of poly(N-isopropylacrylamide) (PNIPAM), which remains the most extensively studied thermoresponsive polymer with secondary amide repeating units. PNIPAM exhibits an LCST in water at approximately 32 °C, completely independent from its M_n. At its T_{cp}, the solvent quality deteriorates, as reflected by a decrease in the second virial coefficient (χ increases), leading to a coil-to-globule transition of the polymer chains.[52] In dilute solution, individual collapsed chains form stable

globules, whereas at higher concentrations, these can further associate into mesoglobular structures.[53,54]

PNIPAM phase transition is closely linked to a restructuring of its hydration environment. Below the LCST, PNIPAM is stabilized by a structured hydration shell, particularly around the hydrophobic isopropyl groups, often described as a "water cage".[55,56] Upon heating, the disruption of this hydration shell plays a central role in driving the transition. However, the process is not a complete dehydration; even above the cloud point, a significant fraction of amide groups remains hydrogen bonded.[57] Instead, the transition involves a redistribution of hydrogen bonding, where polymer–water interactions are partially replaced by intra- and intermolecular polymer–polymer interactions.[58] Importantly, this transformation occurs in a cooperative manner. Rather than a gradual, segment-by-segment dehydration, PNIPAM chains collapse through the formation of cooperative domains that undergo dehydration collectively (Figure 3).[59,60] This cooperative mechanism accounts for the sharp LCST transitions and distinguishes PNIPAM from less associative systems. It also highlights that its phase behavior is governed not simply by the presence of hydrogen bonding, but by how these interactions are spatially organized and coupled along the polymer chain.[54,58,61] In that regard, thermoresponsive behavior of PNIPAM is defined as Type II in literature (cooperative, association-dominated, M_n-independent).[54,61]

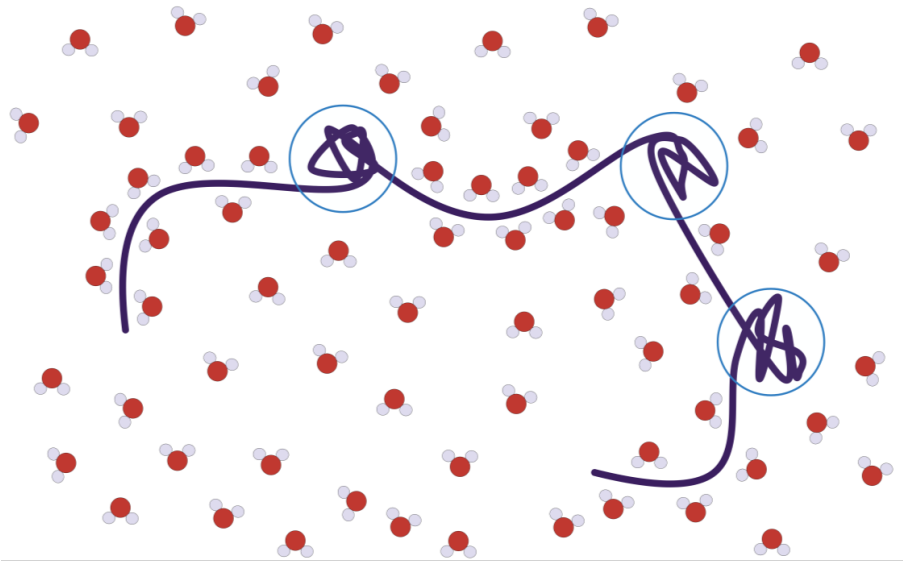

Figure 3 Schematic illustration of the cooperative phase transition behavior of poly(N-isopropylacrylamide) (PNIPAM) in aqueous solution. Below the LCST, polymer chains are hydrated through extensive polymer–water hydrogen bonding. Upon heating, dehydration of the polymer induces cooperative intrachain collapse and formation of locally compact domains, which subsequently promote intermolecular association and macroscopic phase separation, re-illustrated from the reference.[59]

In contrast, polymers lacking hydrogen bond donor functionality exhibit less cooperative thermoresponsive behavior. For example, poly(N-vinylcaprolactam) (PVCL), which contains cyclic tertiary amide repeat units, displays LCST-type phase separation but with broader transitions and less hysteresis compared to PNIPAM.[54,62,63] This behavior is primarily caused by the absence of an H-bond donor (N–H groups) on the sidechain which results in no interchain hydrogen bonding, leading to a more gradual change in solvation and a reduced tendency for cooperative aggregation. Reduced cooperativity also results in the molar mass dependency of cloud points. In literature, polymers with this type of behavior are defined as Type I (non-cooperative, Flory–Huggins-like, M_n-dependent).

A structurally related but substantially more hydrophilic system is poly(N-vinyl pyrrolidone) (PVP), which contains a five-membered cyclic tertiary amide side chain.[64] Compared to PVCL, the pyrrolidone repeat units contain fewer methylene groups, shifting the hydrophilic–hydrophobic balance strongly toward hydration.[65] As a consequence, PVP remains fully water-soluble under ambient conditions and does not exhibit observable LCST-type phase separation in water. Nevertheless, from a thermodynamic perspective, highly hydrophilic non-ionic polymers may still possess an intrinsic LCST located above the boiling point of water.[66,67] This has been demonstrated for PVP either via increased pressure or adding salts from the Hofmeister series.[66,68]

Such intrinsically thermoresponsive polymers illustrate that the LCST behavior strongly depends on the solvent quality. Solvent quality can be altered either by increasing pressure or by introducing salts from the Hofmeister series. Specifically, kosmotropic salts stabilize the hydrogen-bonding network of water and thereby decrease the efficiency of hydration for dissolved solutes.[69–72] For neutral LCST-type polymers, this results in classical salting-out behavior: Water structuring and increased ionic strength reduce the availability of water molecules for hydrating polar amide groups, weaken polymer–water interactions, and consequently promote polymer–polymer association.[57,73] As a result, the cloud point temperature typically decreases with increasing salt concentration. Conversely, chaotropic salts destabilize hydrogen-bonding network of water, typically results in a salting-in effect with increase of the cloud points. [69,70,73]

Thermoresponsive behavior is not limited to vinyl-based polymers, but is also observed in other tertiary amide-containing systems such as polypeptoids.[74,75] Similar to many non-ionic thermoresponsive polymers, the aqueous solution behavior of polypeptoids is highly sensitive to side-chain hydrophobicity. Whereas short alkyl-substituted polypeptoids such as polysarcosine and poly(N-ethyl glycine) remain readily water-soluble, increasing the side-chain length progressively reduces hydration stability and can induce LCST-type phase behavior.[75] In particular, propyl-substituted polypeptoids exhibit cloud point

temperatures strongly dependent on polymer concentration and molar mass, characteristic of Flory–Huggins Type I thermoresponsive behavior.[75]

Despite these attractive solution properties, broader exploration of thermoresponsive polypeptoids remains comparatively limited by synthetic challenges.[76] Polypeptoid synthesis commonly relies on N-carboxyanhydride monomers which requires comparatively demanding synthetic procedures.[77,78] In addition, precise sequence control and access to structurally diverse monomers remain more challenging than for many living chain-growth polymerization systems.[76] Within this broader context, poly(2-oxazoline)s (POx) and poly(2-oxazine)s (POzi) occupy a unique position among amide-based polymers. Their tertiary amide functionality is partially incorporated into the polymer backbone, not capable of hydrogen-bond donation while retaining hydrogen-bond accepting interactions. As a result, their solution behavior is dominated primarily by polymer–water interactions with comparatively reduced interchain association, leading to thermoresponsive transitions that are generally less cooperative and more tunable than those observed in secondary amide systems. Combined with the straightforward synthesis of structurally diverse monomers and the living nature of cationic ring-opening polymerization (CROP), these properties make POx and POzi particularly attractive model systems for systematically investigating how modifications of the amide functionality influence polymer phase behavior in aqueous media.

2.3 Poly(2-oxazoline) Family

2.3.1 Chemistry and Synthesis

Poly(2-oxazoline)s (POx) and poly(2-oxazine)s (POzi) are predominantly synthesized via living cationic ring-opening polymerization (CROP) of their corresponding cyclic imino ether monomers.[79–82] Since the initial development of this polymerization strategy, a broad range of monomers bearing diverse substituents at the 2-position has been reported.[83–85] While a limited number of monomers are commercially available, the majority require prior synthesis. Several synthetic routes have been established for the preparation of 2-oxazoline monomers (Figure 4). Among the most commonly employed methods is the Witte–Seeliger synthesis, which involves the reaction of monoethanolamine with nitriles or, alternatively, with non-activated carboxylic acids.[86] Another widely used approach is the Wenker method, which proceeds via a two-step sequence involving the formation and subsequent cyclization of β-haloamides derived from carboxylic acids.[87]

For the synthesis of 2-oxazine monomers, analogous strategies have been developed (Figure 4). These include a modified Witte–Seeliger reaction employing

3-amino-1-propanol and nitriles,[82,88] as well as cyclodehydration reactions of N-(γ-hydroxypropyl) amides,[89] which can be performed either in the presence or absence of acid catalysts. An alternative route involves the reaction of aldehydes with 1,3-azido alcohols.[82,90] These synthetic methodologies enable access to a wide structural variety of monomers with different side chains, which is essential for tailoring polymer properties.

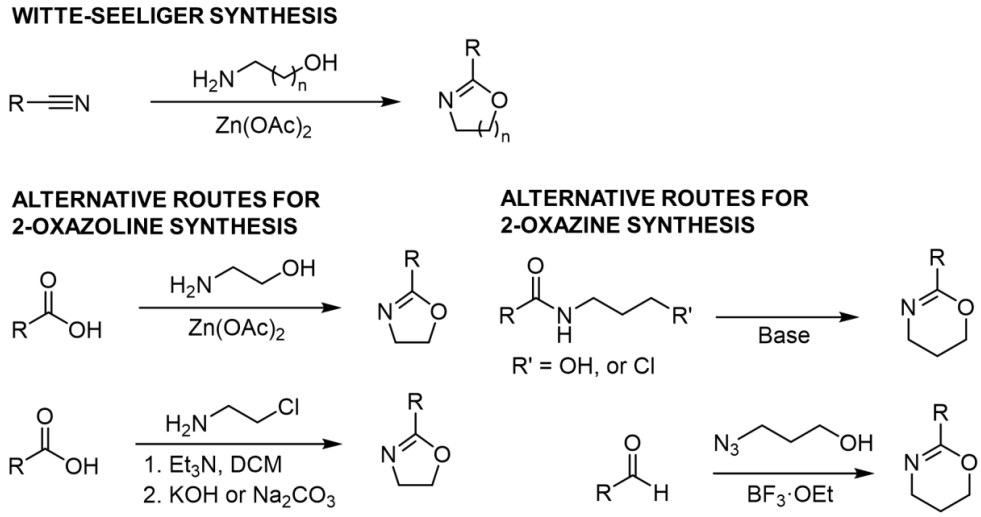

Figure 4 Synthetic routes toward 2-oxazoline and 2-oxazine monomers. The classical Witte–Seeliger synthesis involves cyclization of nitriles with amino alcohols in the presence of catalysts such as zinc acetate. Alternative synthetic strategies for 2-oxazolines include condensation of carboxylic acids with 2-chloroethylamine or aminoethanol derivatives, whereas 2-oxazines can additionally be accessed through cyclization of N-(3-hydroxypropyl)- or N-(3-chloropropyl)-amides or via reactions of aldehydes with 3-azidopropanol. Structural variation of the substituent R enables systematic tuning of polymer properties after polymerization.

The CROP mechanism of 2-oxazolines and 2-oxazines proceeds via three fundamental steps: initiation, propagation, and termination (Figure 5). [91,92] In the initiation step, the lone pair of the monomer nitrogen attacks an electrophilic initiator, typically an alkylating agent, resulting in the formation of a cationic iminium species. Common initiators include haloalkanes, alkyl tosylates, and alkyl triflates, with the latter being particularly advantageous due to their high reactivity, which ensures rapid and quantitative initiation.[92] Fast initiation relative to propagation is critical for achieving controlled polymerization behavior, products with low molar mass distributions.

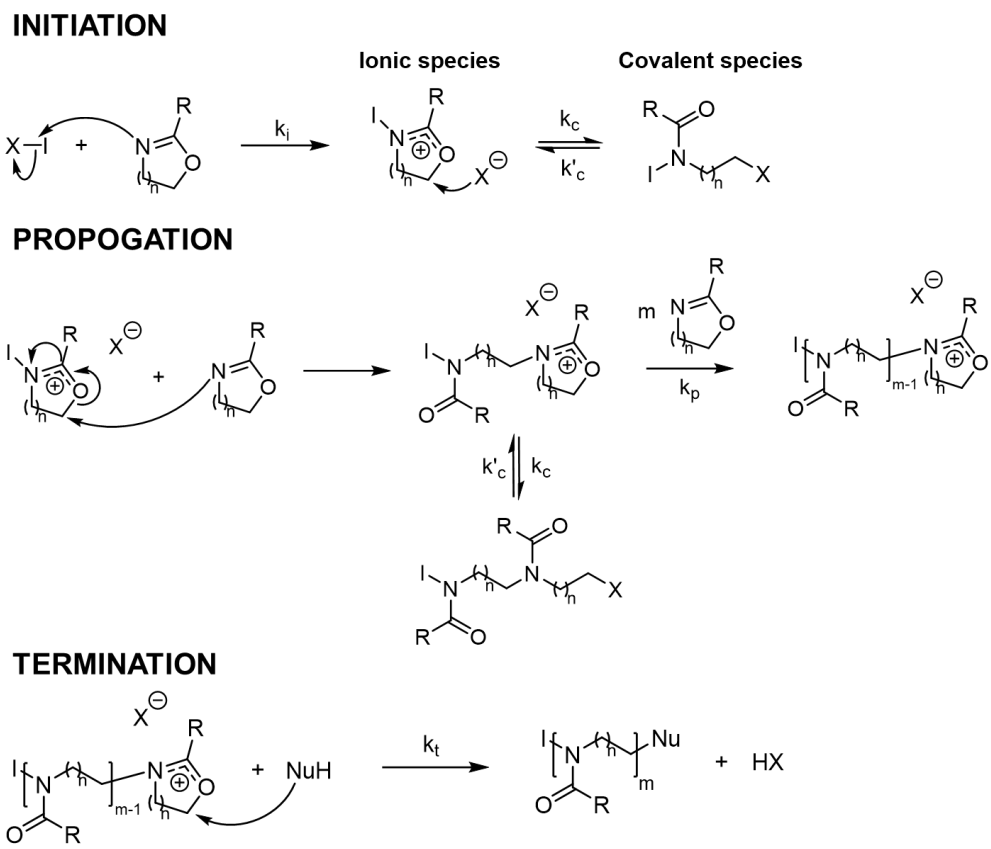

Figure 5 Mechanism of living cationic ring-opening polymerization (CROP) of 2-oxazoline and 2-oxazine monomers. Polymerization proceeds through initiation by an alkylating agent, generating active oxazolinium or oxazinium species. During propagation, reversible equilibria between ionic and covalent species may occur, while successive monomer addition leads to chain growth via ring-opening. Termination is achieved through nucleophilic attack, enabling introduction of defined end groups.

Following initiation, chain growth occurs through successive nucleophilic attacks of monomer molecules at the electrophilic oxazolinium (or oxazinium) chain end, accompanied by ring opening and formation of amide linkages along the polymer backbone. Ideally, the propagating chain ends remain active throughout the reaction without undergoing termination or chain transfer, allowing precise control over molar mass and resulting in polymers with narrow dispersity.[91,92] However, side reactions such as chain transfer and coupling (primarily via β-elimination) have been reported especially at higher degrees of polymerization (Figure 6).[91,93–95] These processes can cause branching, broaden molecular weight distributions, and limit achievable chain lengths with high definition. To avoid or reduce the probability of this, excellent purification of monomers, initiators, and solvents is essential to maintain controlled polymerization conditions.

Termination of the living polymer chains is typically achieved through the addition of nucleophilic reagents, which react with the electrophilic chain end. Common terminating agents include nitrogen-, oxygen-, and sulfur-based nucleophiles, such as amines, carboxylates, and thiols.[91] This step not only stops chain growth but also enables the introduction of functional groups at the ω-chain-end of the polymer. In some cases, particularly when weak nucleophiles such as water are used,[96] alternative termination pathways may occur on the second position, leading to structural variations at the chain end (Figure 6).[91,92]

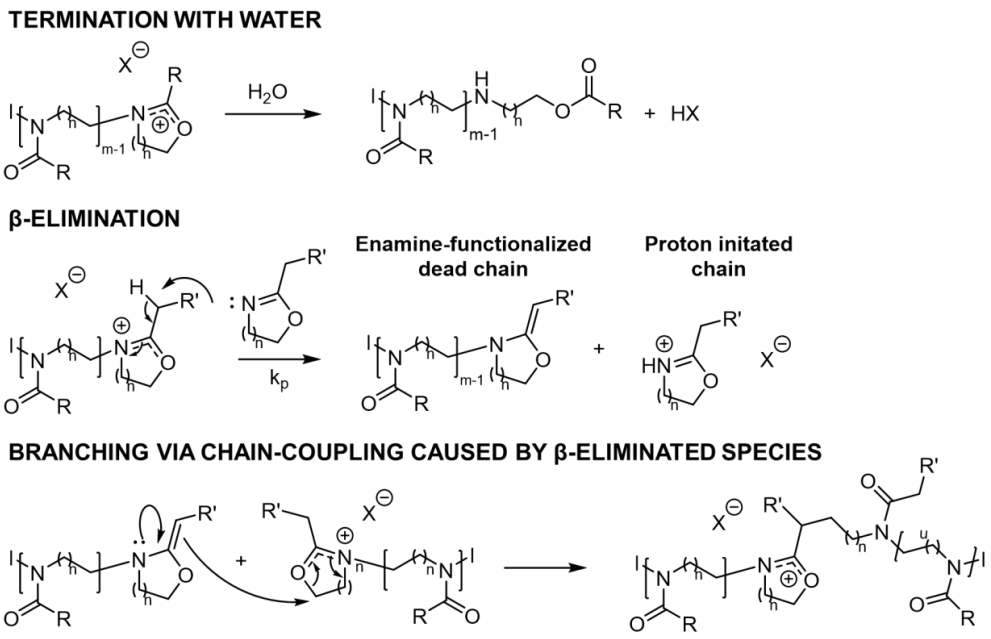

Figure 6 Representative termination and side-reaction pathways in cationic ring-opening polymerization (CROP) of 2-oxazolines and 2-oxazines. Besides intentional nucleophilic termination, active oxazolinium or oxazinium chain ends may react with water, resulting in formation of ester end groups. Competing β-elimination reactions generate enamine-functionalized dead chains together with proton-initiated species capable of reinitiating polymerization. The resulting unsaturated chain ends may additionally undergo chain-coupling reactions, leading to branching and broadening of molar mass distributions.

2.3.2 Solution Behavior of POx/POzi

The aqueous solution behavior of poly(2-oxazoline)s (POx) and poly(2-oxazine)s (POzi) is highly sensitive to side-chain hydrophobicity and backbone flexibility. Among the most important structural parameters governing hydration and thermoresponsive behavior is the length and structure of the alkyl substituent at the 2-position. Increasing side-chain length systematically decreases polymer hydrophilicity and lowers the cloud point temperature (T_{cp}), eventually shifting the

polymers from fully water-soluble systems toward LCST-type thermoresponsive behavior and finally complete water insolubility (Figure 7).

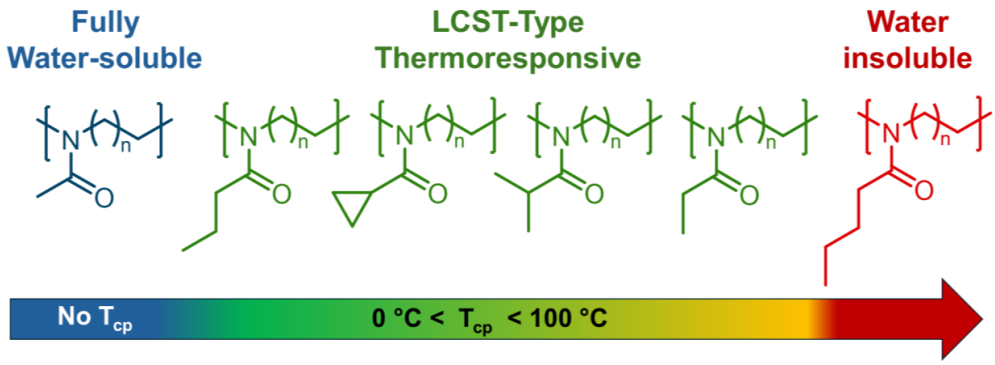

Figure 7 Influence of side-chain structure on the aqueous solution behavior of poly(2-oxazoline)s (POx) and poly(2-oxazine)s (POzi). Increasing side-chain hydrophobicity progressively shifts these polymers from fully water-soluble behavior toward LCST-type thermoresponsiveness and ultimately water insolubility. Polymers bearing short alkyl substituents, such as poly(2-methyl-2-oxazoline) (PMeOx) or poly(2-methyl-2-oxazine) (PMeOzi), remain highly water-soluble, whereas systems containing ethyl-, propyl-, or cyclopropyl-substituted repeat units exhibit LCST-type phase transitions within the experimentally accessible aqueous temperature range. Further increasing side-chain hydrophobicity leads to water-insoluble polymers such as poly(2-butyl-2-oxazoline) (PBuOx) and related POzi analogues.

Poly(2-methyl-2-oxazoline) (PMeOx) with only one methyl group on its side chain is completely water soluble and is generally considered one of the most hydrophilic POx homopolymers. However, more recent studies explored alternative POx homopolymers with heteroalkyl side chains and demonstrated their higher hydrophilicity.[97,98] Regarding those polymers, a more in-depth discussion will follow in Chapter 4. Increasing the side-chain length of PMeOx by only one methylene group changes the solution behavior drastically. Poly(2-ethyl-2-oxazoline) (PEtOx) shows LCST-type thermoresponsive behavior depending on molar mass and concentration.[99] Further increasing hydrophobicity through propyl or butyl substituents lowers the T_{cp} progressively,[100] such that poly(2-*n*-propyl-2-oxazoline) (P*n*PrOx),[101] poly(2-*iso*-propyl-2-oxazoline) (P*i*PrOx),[102] and poly(2-*cyclo*-propyl-2-oxazoline) (P*c*PrOx)[103] phase separate close to (or below) physiological temperatures, whereas poly(2-butyl-2-oxazoline) becomes mostly water-insoluble.[100,104] A comparable trend is observed for POzi systems, although the additional methylene group in the polymer backbone generally increases chain flexibility and hydrophobicity relative to the corresponding POx analogues.[104,105]

Among the thermoresponsive POx homopolymers, PEtOx represents one of the most extensively studied systems. Early investigations on high molar mass PEtOx

reported T_{cp} values approaching 70 °C in water.[99] Later studies demonstrated that aqueous PEtOx solutions display classical LCST-Type I behavior consistent with Flory–Huggins-type phase transition, characterized by gradual dehydration and continuous coil collapse upon heating.[106] The T_{cp} of PEtOx strongly depends on molar mass, concentration, and polymer architecture. In particular, decreasing molar mass increases T_{cp}, and linear PEtOx samples below approximately 10 kDa generally no longer exhibit observable LCST behavior under standard conditions.[107] Nevertheless, thermoresponsive behavior can still emerge in architectures providing locally increased polymer density, such as block copolymers,[108] polymer brushes,[109] or star-shaped systems.[110] Star-shaped PEtOx architectures, for example, typically exhibit lower T_{cp} values compared to linear analogues of similar molar mass due to the increased local segment concentration and altered chain packing.[110]

Another important thermoresponsive member of the POx family is poly(2-*iso*-propyl-2-oxazoline) (P*i*PrOx), which exhibits LCST-Type I behavior with a pronounced molar mass dependence of T_{cp}.[111–114] In contrast to PEtOx, however, P*i*PrOx additionally displays a strong tendency toward crystallization both in bulk and in aqueous solution above its T_{cp}.[114,115] Upon heating through the LCST transition, P*i*PrOx chains may reorganize into ordered domains, resulting in partial crystallization, pronounced thermal hysteresis, and kinetically hindered rehydration.[111–114] In this regard, the solution behavior of P*i*PrOx may also be considered partially cooperative. However, unlike its structural isomer PNIPAM, where cooperative collapse is strongly driven by intra- and intermolecular H-bonding interactions involving the secondary amide groups, aggregation in P*i*PrOx originates predominantly from hydrophobic association and packing of the -isopropyl side chains. Evidence for this cooperative character can also be observed in microcalorimetric measurements.[113] In contrast to more classical non-cooperative LCST-Type I polymers such as PEtOx or PVCL,[62] which typically display comparatively broad and weak calorimetric transitions, P*i*PrOx exhibits relatively sharp endothermic transitions during dehydration depending on its molar mass.[113,116,117] Such sharp calorimetric features indicate a more cooperative phase transition process involving collective dehydration and aggregation of polymer segments rather than gradual demixing.[118]

Besides PNIPAM, PPrOx possesses another structural isomer, namely poly(2-ethyl-2-oxazine) (PEtOzi), which also exhibits LCST-Type I thermoresponsive behavior. Although PEtOzi bears the identical ethyl side chain as poly(2-ethyl-2-oxazoline) (PEtOx), its T_{cp} is substantially lower due to the additional methylene group within the polymer backbone.[105,119] This extra backbone methylene increases chain flexibility, lowers the glass transition temperature, and generally enhances the overall hydrophobicity of POzi relative to the corresponding POx homologue. Interestingly, despite its increased backbone hydrophobicity, PEtOzi

often exhibits higher T_{cp} values than the structurally related propyl-substituted POx systems P*i*PrOx and P*n*PrOx at comparable molar masses.[101,105] This observation demonstrates that thermoresponsive behavior in POx/POzi systems cannot be rationalized solely on the basis of overall hydrophobicity or simple carbon counting. Instead, backbone flexibility, segmental mobility, chain packing, and the nature of intermolecular association additionally play important roles in determining hydration and phase separation behavior.

Beyond alkyl-substituted POx and POzi, incorporation of heteroatom-containing side chains provides an additional and highly versatile strategy for tuning hydration and thermoresponsive behavior. In these systems, not only hydrophobicity, but also side-chain polarity, hydrogen-bonding capability, and ionizability contribute to the overall aqueous solution behavior. Consequently, comparative structural changes can strongly influence thermoresponsiveness (Figure 8).

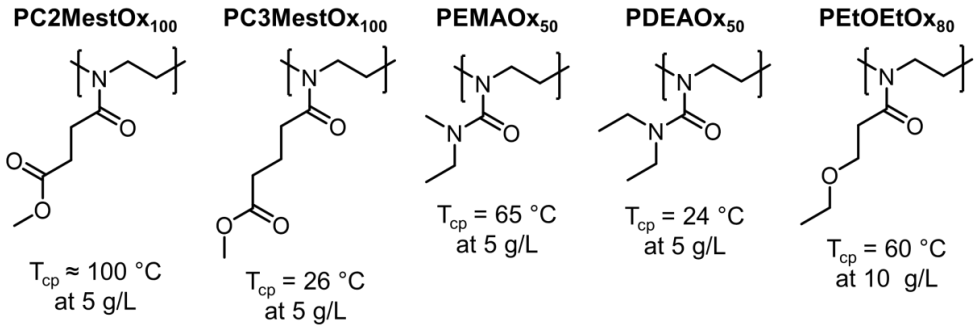

Figure 8 Examples of thermoresponsive poly(2-oxazoline)s containing heteroatom-functionalized side chains. Incorporation of ester-, tertiary amine-, or ether-containing substituents enables fine tuning of polymer hydration and LCST-type behavior over a broad temperature range.

One early example comprises POx bearing methyl ester-containing side chains.[100,120,121] Such polymers are particularly interesting because the ester functionality not only modifies hydration and thermoresponsive behavior, but also provides a reactive group for further post-polymerization modification.[122] Bouten et al. demonstrated that homopolymers containing methyl ester-functionalized repeat units exhibit tunable LCST behavior with T_{cp} values ranging from 24 °C to 100 °C depending on sidechain.[120] Furthermore, post-polymerization modification of these ester functionalities enabled access to dual pH- and thermoresponsive POx systems.[123]

Another important class comprises POx containing tertiary amine functionalities within the side chain. In these polymers, solution behavior becomes strongly dependent on both temperature and pH due to protonation and deprotonation of the amino groups.[124] Sedlacek et al. introduced poly(2-

dialkylamino-2-oxazoline)s as a family of dual thermo- and pH-responsive polymers exhibiting tunable cloud point temperatures over a broad range.[124] Depending on the amino substituent, the resulting polymers ranged from completely hydrophilic to thermoresponsive, and eventually hydrophobic systems. Thermoresponsive systems displayed LCST-type behavior with T_{cp} values ranging from near room temperature up to 65 °C.[124]

Ether-functionalized POx systems further highlight the remarkable sensitivity of POx hydration toward side-chain polarity.[97,98,121] In contrast to simple alkyl substituents, ether-containing side chains introduce PEG-like hydration characteristics with exceptional hydrophilicity while certain substituents still allow thermoresponsive behavior.[97] Illustrative example is poly(2-ethoxyethyl-2-oxazoline) (PEtOEtOx), which exhibits LCST-type behavior despite the more polar side chain. Such systems demonstrate that highly hydrated POx can nevertheless show thermoresponsive character when polymer–water interactions become sufficiently sensitive toward temperature-induced dehydration.

One important route for inducing thermoresponsive behavior in highly hydrophilic POx systems could involve the addition of kosmotropic salts. In general, the aqueous phase behavior of any amide-based polymer is highly sensitive not only to polymer structure, but also to solvent quality and external additives.[6] Addition of kosmotropic salts lowers the T_{cp} through salting-out effects by destabilizing polymer hydration and H-bonding, whereas chaotropic ions may conversely stabilize hydrated polymer chains and increase water solubility.[70–72,100,125] Such salt effects have been extensively investigated for alkyl-substituted POx and POzi systems, where systematic relationships between ion type, polymer hydrophobicity, and LCST behavior have been established.[70] Interestingly, despite the considerable amount of literature concerning POx solution thermodynamics and Hofmeister-series effects, comparable investigations on POx systems bearing heteroatom-containing side chains, including amino-, ester-, or ether-functionalized derivatives, remain largely absent. Consequently, how these highly hydrophilic and polarity-sensitive side chains influence salt-induced dehydration and thermoresponsive behavior is still poorly understood.

2.4 Thioamides and Thionation

Thioamides are sulfur analogues of amides in which the carbonyl oxygen is replaced by a sulfur atom. Although this substitution appears minimal from a structural perspective, it leads to pronounced changes in the electronic structure and physicochemical properties of the amide moiety. In contrast to amides, the smaller electronegativity difference between carbon and sulfur reduces polar character of the C=S bond and alters the relative contribution of resonance structures.[126,127] As a result, greater charge transfer from the nitrogen atom toward the thiocarbonyl

group is observed, leading to an increased contribution of iminium-like resonance structures and a higher degree of C=N double bond character.[26] This electronic redistribution manifests in a higher rotational barrier around the C–N bond in thioamides compared to their oxygen analogues, which renders the thioamide linkage more conformationally rigid.[26,27,126,128]

Beyond conformational effects, thioamide substitution significantly modifies non-covalent interactions. The increased size and polarizability of sulfur result in a more diffuse electron density, which weakens its ability to act as a hydrogen bond acceptor.[27,129] Conversely, the N–H bond in primary and secondary thioamides is more acidic, leading to enhanced hydrogen bond donor strength.[130] This asymmetric modulation of hydrogen bonding (stronger donation but weaker acceptance) would have important consequences for solvation and intermolecular association. As it was introduced in the previous chapters, solution behavior of amide-based macromolecules is largely dependent on hydrogen bonding of the carbonyl group in aqueous media, where this shift can substantially alter polymer–water interactions.

In addition to these structural and interaction-related effects, thioamides display distinct redox and coordination properties. The presence of sulfur lowers the oxidation potential relative to amides and introduces a strong affinity toward soft metal ions such as Cu(I), Ag(I), and Hg(II), enabling thioamides to act as effective ligands in coordination chemistry.[131,132] These features, have been exploited in applications ranging from photophysical probes to metal-binding materials. In biological systems, thioamides are relatively rare but occur in special thiopeptides, often of bacterial origin, where they contribute to antimicrobial activity and metal binding.[131] Synthetic incorporation of thioamides into peptides and proteins has further enabled their use as fluorescence quenchers,[129,132] photoswitches,[133–136] and modulators of protein folding and pharmacokinetic properties,[137–139] highlighting their utility as impactful amide replacements. They are also more reactive compared to amides, which can expand the synthetic accessibility to alternative structures.[140]

2.4.1 Synthesis, Thionation Reagents

From a synthetic standpoint, thioamides can be accessed through a variety of well-established strategies, which broadly fall into direct thionation of amides with thionation reagents, or the Willgerodt-Kindler reaction.[141–143] However, Willgerodt-Kindler is considered challenging for synthesizing complex thioamide containing molecules due to low chemoselectivity.[144] Classical thionation reagents include phosphorus pentasulfide (Berzelius reagent),[145,146] and Lawesson's reagent,[147–149] which enable efficient oxygen-to-sulfur substitution (Figure 9). These reagents are widely used due to their operational simplicity and compatibility

with a range of functional groups. Other classical phosphorus pentasulfide-based thionation reagents include Davy's reagent,[150] Japanese (Heimgartner's) reagent,[151,152] Belleau's reagent,[153] Woollins' thionation reagent,[154] and Curphey's reagent[155] which were primarily developed to improve solubility, handling, selectivity, or purification compared to phosphorus pentasulfide itself. Alternative structures include the Woollins' reagent, the selenium analogue of Lawesson's reagent, has also attracted considerable attention for oxygen-to-selenium exchange reactions.[156] More recently, other sulfurization systems with improved operational simplicity have been introduced. Among these, Bergman's reagent, an ionic pyridinium complex formed from pyridine and phosphorus pentasulfide, stands out because of its higher stability, milder reactivity, and simplified workup procedures.[157] Comparative studies showed that thionation reactions performed with Bergman's reagent often does not need extensive chromatographic purification, which is commonly required for Lawesson's reagent-derived byproducts.[158] Additional compounds, namely 7-phenyl-2,4,6,8,9-pentathia-1,3,5-triphosphaadamantane-1,3,5-trisulfide, have furthermore been developed as an air-stable and H_2S-free thionation reagent.[159]

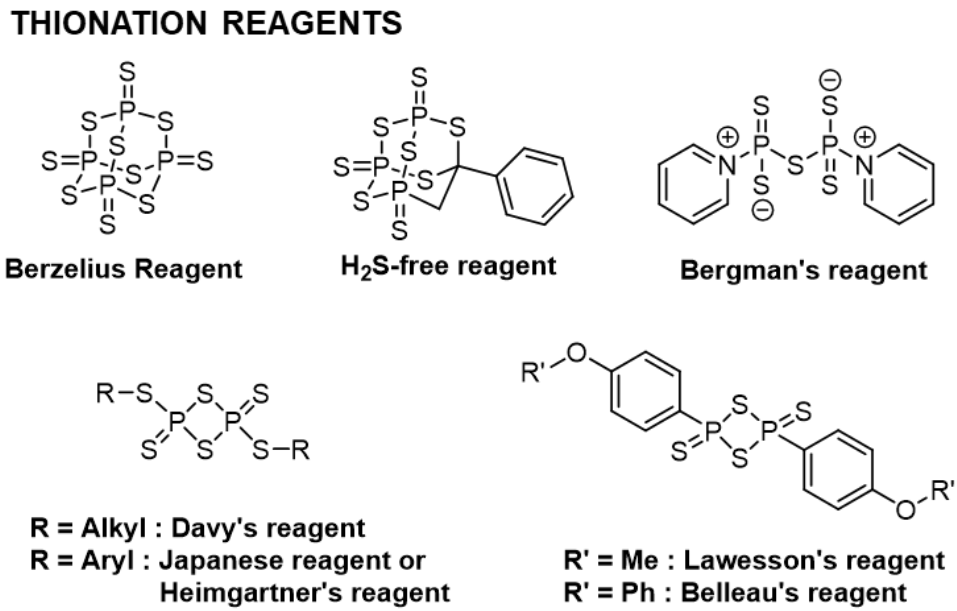

Figure 9 Thionation reagents commonly used for oxygen-to-sulfur conversion of carbonyl compounds. Classical reagents include phosphorus pentasulfide (Berzelius reagent) and its modified derivatives such as Davy's reagent, Japanese (Heimgartner's) reagent, Bellau's reagent, and Lawesson's reagent. Structural modifications primarily improve reagent solubility, handling, selectivity, and purification.

Despite the diversity of sulfurization reagents, Lawesson's reagent (LR) remains by far the most widely employed thionation reagent for synthetic applications.[144] Its broad popularity originates from its commercial availability, efficiency and its selective conversion ability. Consequently, LR has found extensive use in small-molecule synthesis, peptide modification, and increasingly in polymer modification reactions. Mechanistically, LR exists in equilibrium with a reactive dithiophosphine ylide species generated through dissociation of the four-membered phosphorus–sulfur ring.[141,144,148,160] This reactive intermediate subsequently gets attacked by the carbonyl oxygen of the amide, forming a transient four-membered cyclic intermediate. Subsequent cleavage of the P–S and C–O bonds ultimately results in oxygen-to-sulfur exchange and formation of the corresponding thioamide together with phosphorus-containing byproducts (Figure 10).[161]

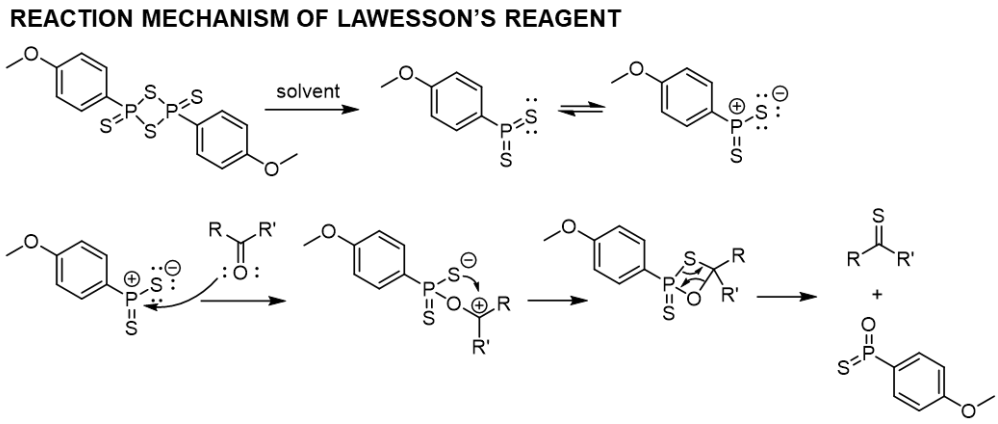

Figure 10 Thionation reaction mechanism of Lawesson's reagent. Upon heating, Lawesson's reagent undergoes dissociation to form reactive dithiophosphine ylide intermediates. Subsequent nucleophilic attack of the carbonyl oxygen on the electrophilic phosphorus center leads to formation of a four-membered cyclic intermediate. Rearrangement and cleavage of the P–S and C–O bonds ultimately yield the corresponding thiocarbonyl compound together with phosphorus-containing byproducts.

2.4.2 Examples of Thionated Polymers

Despite the widespread use of Lawesson's reagent and related sulfurization reagents in small-molecule synthesis, thionation reactions have historically remained comparatively uncommon in polymer chemistry. One likely reason is the difficulty associated with purification and removal of phosphorus-containing byproducts, particularly for polymers where chromatographic purification is impractical. Furthermore, thionation often substantially alters polymer solubility, or in certain cases may cause side reactions, which can complicate both purification and characterization of modified polymers.

Nevertheless, several examples of thionated polymer systems have been reported in the literature. Many studies focused primarily on conjugated materials designed for electronic or optical applications. For example, diketopyrrolopyrrole-containing conjugated polymers have been thionated using Lawesson's reagent to yield dithioketopyrrolopyrrole-based polymers with modified optical absorption and enhanced charge-transport properties.[162–164] Similarly, Hifumi et al. reported thionation of poly(arylene ether phosphine oxide)s to obtain poly(arylene ether phosphine sulfide)s exhibiting increased glass transition temperatures due to the altered backbone structure and increased rigidity; and higher refractive indices introduced by sulfur incorporation.[165]

Polyamide-based systems have also attracted attention because thioamide functionalities possess enhanced affinity toward soft metal ions. Deletre et al. investigated the modification of several commercial polyamide materials, including nylon derivatives, poly(ether-block-amide)s using Lawesson's reagent.[166] However, details of characterization, and thionation degrees were not reported, most likely because the resulting partially thionated materials suffered from poor solubility and limited processability. A more recent study on an alternative post-polymerization modification strategy of high molar mass polyethylene-ketones demonstrated bulk effects of H-bonding differences between amides and thioamides.[167] Alternative studies on thionated cyclic oligoamides and polyamides further demonstrated enhanced metal-binding capabilities and potential utility in water purification applications.[168–172]

Besides direct post-polymerization thionation, alternative synthetic approaches toward thioamide-containing polymers have also been explored. In particular, multicomponent polycondensation reactions involving elemental sulfur have become an important route toward sulfur-rich polythioamides. [143,144,173] In these systems, sulfur is incorporated directly during polymerisation. Such strategies have been extensively investigated in materials chemistry because sulfur-containing polymers often exhibit strong metal coordination, altered electronic structure, and improved affinity toward heavy metal ions. [174–177]

In contrast to these predominantly hydrophobic polymer systems, reports on thionated water-soluble polymers remained very limited for many years. Early studies described thionated copolymers of poly(N-vinylpyrrolidone) (PVP),[178,179] and poly(N-vinylcaprolactam) (PVCL),[180] although characterization of the resulting materials and their solution behavior was rather limited. More relevant insights into the physicochemical consequences of thioamide incorporation have emerged from peptide and protein chemistry, where thioamide substitutions have been used to improve conformational stability,[181] bioavailability,[139] and pharmacokinetic behavior.[182] More recently, single thioamide insertions on lipopolymer linkers decreases the pK_a of ionizable polymer–lipid nanoparticles, resulting in significantly enhanced mRNA transfection efficiency.[183]

Specifically for POx-based systems, direct access to thioamide-based polymers through CROP of cyclic imino thioether monomers is currently not feasible. The corresponding thiazoline monomer (specifically 2-methyl-2-thiazoline) has been shown to be essentially non-polymerizable under typical CROP conditions, which has so far prevented direct synthesis of fully or partially thionated POx through CROP.[184] Consequently, post-polymerization thionation presently represents the most practical strategy for accessing thioamide-containing POx materials. In this context, studies that were published during the timeframe of this thesis have begun exploring partial thionation of amide-based polymers and how it influences polymer properties and water interactions in aqueous media,[184–186] indicating the growing interest in thioamide-containing thermoresponsive polymers.

3 Objectives of the Thesis

Amide-containing polymers represent one of the most important classes of water-soluble and thermoresponsive macromolecules. Small structural variations in the repeating unit can influence their chain collapse, aggregation pathways, and phase separation behavior in water. While these relationships have been extensively studied for conventional amide-based polymers, considerably less is known about the corresponding thioamide-containing analogues, despite their fundamentally altered polarity, hydrogen-bonding capability, and conformational rigidity of thioamides compared to amides.

The central hypothesis of this thesis is that partial thionation of amide-containing polymers fundamentally perturbs polymer–water interactions by reducing overall polarity, weakening hydrogen bonding with water, and increasing conformational rigidity through the enhanced double-bond character of thioamides. Consequently, thionation is expected to systematically decrease hydration stability and alter thermoresponsive behavior in aqueous media. However, the extent and mechanistic consequences of these effects should be strongly dependent on polymer structure. In particular, thionation of polymer repeating units that are partially on the backbone is expected to influence hydration and aggregation behavior much more strongly than increasing hydrophobicity only.

Based on this hypothesis, the primary aim of this thesis is to investigate thionation as a post-polymerization modification strategy for systematically tuning polymer–water interactions and thermoresponsive behavior in amide-based polymers (Figure 11). A central objective is to determine whether thionation represents a generally applicable approach for modifying thermoresponsive polymers or whether its effects strongly depend on polymer architecture and molecular interactions. To address this question, structurally diverse polymer systems were investigated, including structurally isomeric polymers possessing identical repeat unit compositions ($C_6H_{11}NO$), but different solution behavior. This comparative platform enables systematic evaluation of how backbone structure, chain flexibility, hydrogen bonding, and aggregation mechanisms govern both thionation efficiency and the resulting changes in solution behavior.

Another important objective is to identify the structural limits governing accessible LCST-type behavior in highly hydrophilic polymer systems. In this context, it was specifically examined under which conditions thionation induces

thermoresponsiveness, suppresses hydration entirely, or fundamentally alters aggregation pathways. To disentangle the influence of sulfur incorporation in different chemical environments, novel ether-functionalized 2-oxazoline and 2-oxazine monomers were synthesized and polymerized, thereby expanding the accessible chemical space of POx and POzi systems. Comparison between thioether-containing copolymers and directly thionated polymers enabled differentiation between effects arising primarily from increased side-chain hydrophobicity and those originating from direct conversion of amides into thioamides (Figure 11).

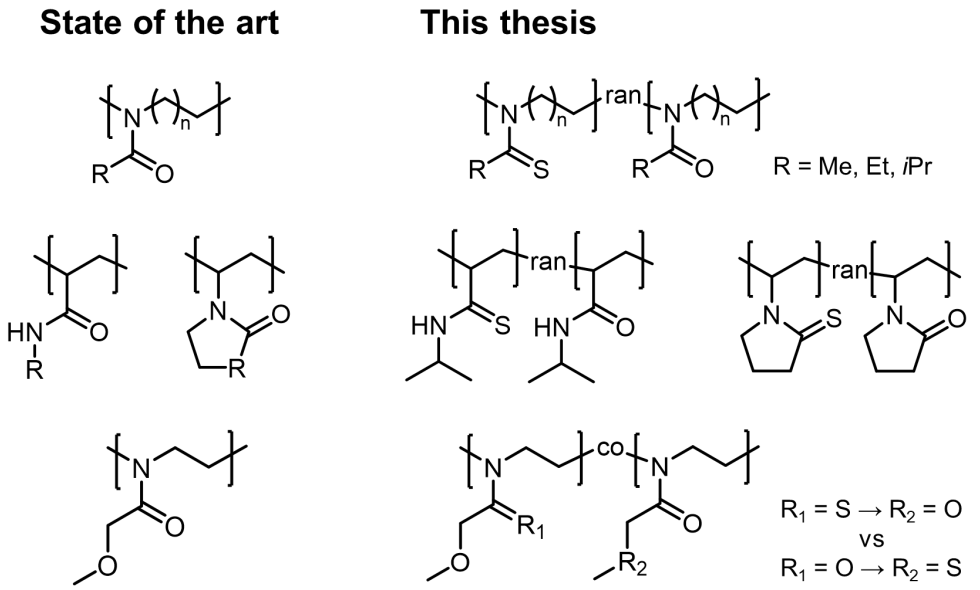

Figure 11 Overview of the polymer systems investigated in this thesis. Previous strategies for tuning aqueous solution behavior and thermoresponsive properties of amide-containing polymers have predominantly relied on side-chain engineering, copolymerization, or modification of overall hydrophobicity. This thesis explores partial thionation as a fundamentally different molecular approach for directly perturbing the polarity, hydrogen-bonding capability, and conformational properties of amide functionalities.

4 Results & Discussion

4.1 Experimental Notes

Detailed descriptions of the synthetic procedures, polymerization conditions, analytical methods, and characterization techniques discussed throughout the following chapters can be found in the corresponding publications, preprints, and their respective Supporting Information. These materials are available through the publishers' websites or via ChemRxiv. To avoid unnecessary repetition, only the most relevant experimental details and discussion directly related to the scope of this thesis are presented herein. Additionally, the key characteristics of the homopolymers investigated throughout this work are summarized below (Table 1).

Table 1 Key characterization data for the homopolymers used or synthesized.

Polymer	DP_{target}	$M_{n,\ target}$ (kDa)	DP_{NMR}	$M_{n,\ NMR}$ (kDa)	$M_{n,\ SEC}$ (kDa)*	Đ	Yield (g / %)	T_g (°C)
P*i*PrOx	103	11.8	186	21.2	25.2	1.11	5.2 / 74 %	65
PEtOzi	98	11.2	352	40.0	28.1	1.12	0.9 / 26 %	21
$PMeOx_{50}$	51	4.4	55	4.8	6.9	1.16	8.2 / 76 %	66
$PMeOx_{550}$	550	47.0	575	49.1	37.5	1.31	6.4 / 70 %	73
PNIPAM	100	11.3	123	14.1	15.3	1.06	6.2 / 77 %	128
$PMeOMeOx_{25}$	25	3.2	28	3.5	7.1	1.17	0.5 / 79 %	17
$PMeOMeOx_{50}$	50	6.0	71	8.6	12.9	1.28	0.6 / 62 %	31
$PMeOMeOx_{80}$	80	9.7	82	9.8	18.8	1.22	1.2 / 67 %	31
$PMeOMeOzi_{80}$	80	10.8	81	10.8	21.1	1.24	0.8 / 44 %	5
grad-S25**	100	12.1	86	10.4	19.1	1.29	1.4 / 70 %	45
grad-S50**	100	12.5	100	12.5	17.5	1.36	1.5 / 75 %	41
grad-S75**	100	12.9	99	12.7	17.0	1.47	1.6 / 80 %	40
block-S50**	135	16.7	91	11.3	19.2	1.40	1.6 / 81 %	42
PEtOx***	n.a.	n.a.	n.a.	n.a.	13.1	3.88	n.a.	55
PVP***	n.a.	n.a.	n.a.	n.a.	5.5	1.67	n.a.	157

*Calibration made with PMMA standards.

** Copolymers of P(MeOMeOx-MeSMeOx), S indicating approximate S/N percentage.

*** PEtOx is Aquazol50 from Kremer Pigmente; PVP is Kollidon17 from BASF.

4.2 Synthetic Part [I, II, III]

This section describes the synthesis and characterization of novel ether-functionalized 2-oxazoline and 2-oxazine monomers and their polymerization via cationic ring-opening polymerization (CROP); the preparation of sulfur-containing copolymers, and post-polymerization thionation reactions using Lawesson's reagent (LR). The synthetic work was designed to systematically investigate how sulfur incorporation influences the properties and aqueous solution behavior of structurally diverse amide-based polymers. Particular emphasis was placed on structurally isomeric polymers possessing the identical repeat unit composition ($C_6H_{11}NO$), namely poly(N-isopropylacrylamide) (PNIPAM), poly(2-*iso*-propyl-2-oxazoline) (P*i*PrOx), and poly(2-ethyl-2-oxazine) (PEtOzi), in order to elucidate how differences in amide type, backbone structure, chain flexibility, hydrogen bonding, and phase separation mechanism govern thionation induced changes in thermoresponsive behavior. In addition, tertiary amide-based polymers with varying side-chain polarity and hydrophilicity, including poly(2-ethyl-2-oxazoline) (PEtOx), poly(2-methyl-2-oxazoline) (PMeOx), poly(N-vinylpyrrolidone) (PVP), and poly(2-methoxymethyl-2-oxazoline) (PMeOMeOx), were investigated to establish broader structure–property relationships related to thionation effects. Ether-functionalized POx derivatives enabled direct comparison between thioether-containing copolymers and thioamide-containing polymers, allowing differentiation between effects arising primarily from increased hydrophobicity due to sulfur incorporation and those originating from direct conversion of the amide functionality into a thioamide. Through this combined molecular design strategy, the influence of sulfur incorporation on hydration, aggregation, thermoresponsive behavior, and thermomechanical properties could be systematically investigated across a broad range of amide-based polymer systems.

4.2.1 Synthesis and Polymerization of Novel Monomers [III]

Ether-functionalized poly(2-oxazoline)s (POx) and poly(2-oxazine)s (POzi) represent an attractive class of highly hydrophilic polymers, as the incorporation of oligoether-like side chains can provide hydration characteristics reminiscent of poly(ethylene glycol) (PEG). Despite this potential, access to such polymers has remained limited until our study, not because of incompatibility with cationic ring-opening polymerization (CROP),[85] but rather due to challenges associated with monomer synthesis and stability. Earlier studies on ether-substituted 2-oxazolines, particularly 2-methoxyethyl-2-oxazoline (MeOEtOx), reported difficulties during monomer synthesis via the Witte–Seeliger route due to β-elimination of methanol, which prevented efficient monomer isolation (Figure 12).[97] As a consequence, poly(2-methoxymethyl-2-oxazoline) (PMeOMeOx) was previously considered

inaccessible through direct CROP of the corresponding monomer and instead synthesized through multistep post-polymerization modification routes involving poly(2-ethyl-2-oxazoline) (PEtOx) hydrolysis to polyethylenimine followed by reacylation.[97,98] Although effective, these strategies suffer from very poor atom economy (13.5%),[187] limited architectural versatility, and reliance on potentially toxic intermediates.

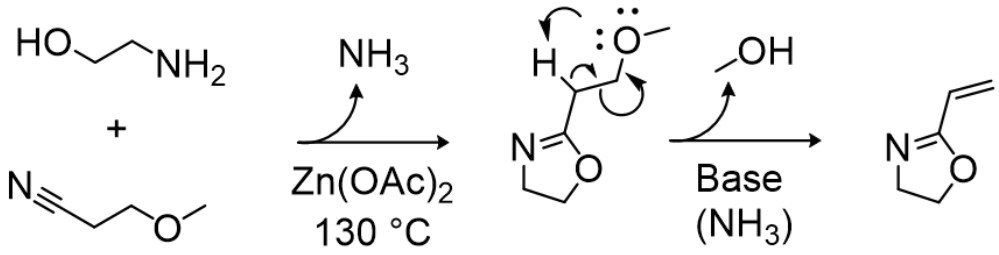

Figure 12 Schematic representation of the unsuccessful synthesis of 2-methoxyethyl-2-oxazoline (MeOEtOx) reported by Sedlacek et al.[97]

Beyond homopolymers, copolymerization offers an additional strategy to investigate and tune thermoresponsive behavior in POx-based systems. By combining hydrophilic and more hydrophobic repeat units within a single macromolecule, copolymerization enables systematic modulation of polymer–water interactions, hydration stability, and phase separation behavior.[188,189] In this context, incorporation of 2-methylthiomethyl-2-oxazoline (MeSMeOx) is particularly interesting, as sulfur-containing substituents can alter side-chain polarity, increase hydrophobicity, and significantly influence intermolecular interactions in aqueous solution.[190,191] Comparison of such thioether-containing copolymers with directly thionated analogues furthermore provides a unique opportunity to differentiate between effects arising from sulfur incorporation in the side chain and those resulting from direct modification of amide functionality into a thioamide.

Motivated by these considerations, methoxymethyl-functionalized 2-oxazoline and 2-oxazine monomers were synthesized and subsequently polymerized via CROP, with particular focus on their polymerization behavior and accessibility through direct monomer routes. This strategy provides access to well-defined polymers bearing highly hydrophilic ether-functionalized side chains that are difficult to obtain through conventional synthetic approaches. Building on this platform, copolymerization with the thioether-containing monomer MeSMeOx enabled systematic investigation of sulfur incorporation through side-chain functionalization.

Both 2-methoxymethyl-2-oxazoline (MeOMeOx) and 2-methoxymethyl-2-oxazine (MeOMeOzi) were successfully synthesized via the Witte–Seeliger route

using methoxyacetonitrile and the corresponding alkanolamines (Figure 13). Successful monomer synthesis was confirmed by spectroscopic methods.III The isolated yields amounted to 55% for MeOMeOx and 48% for MeOMeOzi, comparable to previously reported values obtained through alternative synthetic procedures.[191–193] Notably, the yield for MeOMeOx is comparable to the reported by Huang et al.[194] using an alternative 3-step route based on methoxyacetic acid and monoethanolamine (yield = 52 %). Importantly, the successful synthesis of MeOMeOx via the direct Witte–Seeliger approach contrasts with earlier reports describing instability of ether-functionalized 2-oxazolines under similar conditions.[97] This difference likely originates from the shorter methoxymethyl substituent in MeOMeOx, which lacks the structural requirements for the β-elimination pathway observed for longer methoxyethyl-containing analogues.

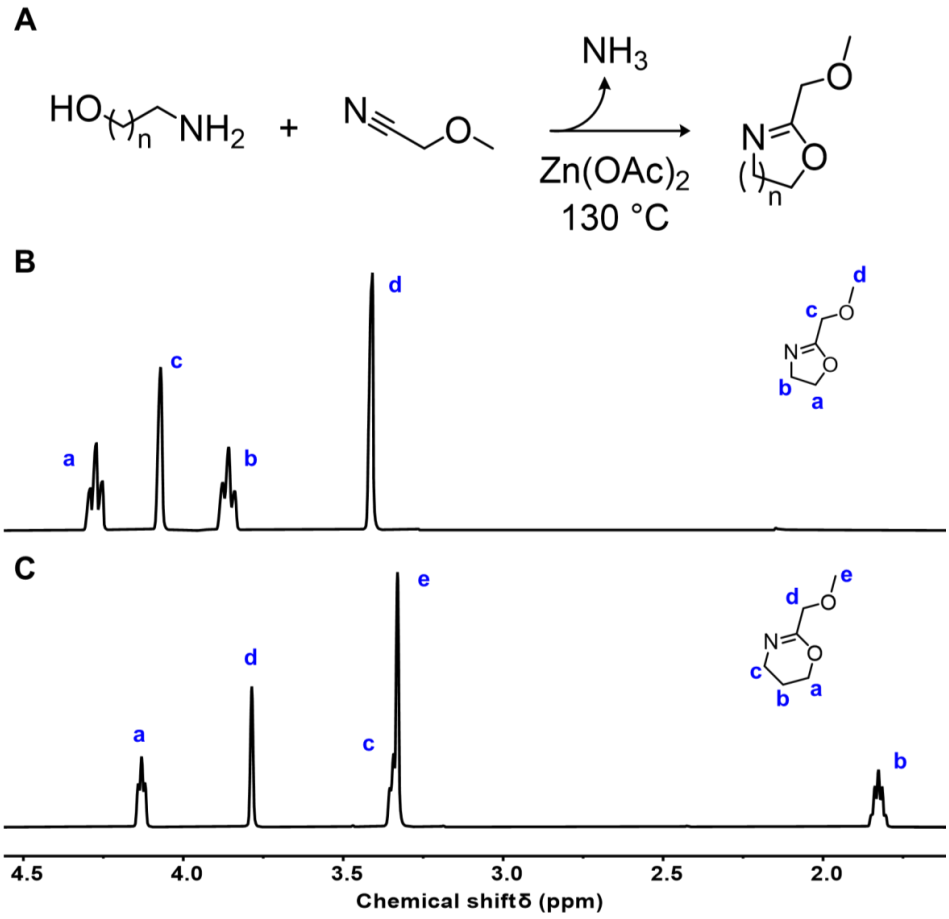

Figure 13 (A) Generalized reaction scheme for synthesis of methoxymethyl functionalized cyclic imino ether monomers via Witte-Seeliger route. (B) shows ^{1}H NMR spectra of 2-methoxymethyl-2-oxazoline, and (C) shows 2-methoxymethyl-2-oxazine with peak assignments.

Following the monomer synthesis, we set out to demonstrate control over the degree of polymerization of PMeOMeOx homopolymers at 3 different degrees of polymerization (DP = 25; 50; 80) and a PMeOMeOzi$_{80}$ via CROP. With a similar approach, we copolymerized MeOMeOx with MeSMeOx at different comonomer ratios (75:25 (grad-S25); 50:50 (grad-S50); 25:75 (grad-S75)) to yield P(MeOMeOx-*grad*-MeSMeOx) copolymers. For testing sequential monomer addition, a block copolymer of PMeOMeOx$_{60}$-*b*-PMeSMeOx$_{75}$ (block-S50) was synthesized. And kinetic data collected for homopolymers of DP = 80 were directly compared to PMeOx and PMeOzi under the identical conditions.

Monomer conversion was quantitative (>99%) for all polymerizations, and product spectra are consistent with the expected structures and agree well with literature data for PMeOMeOx.[97,98] Notably, SEC indicated essentially monomodal molar mass distributions of the polymers. For homopolymers (Figure 14), elution shifted to lower retention times with increasing molecular weight, as expected.

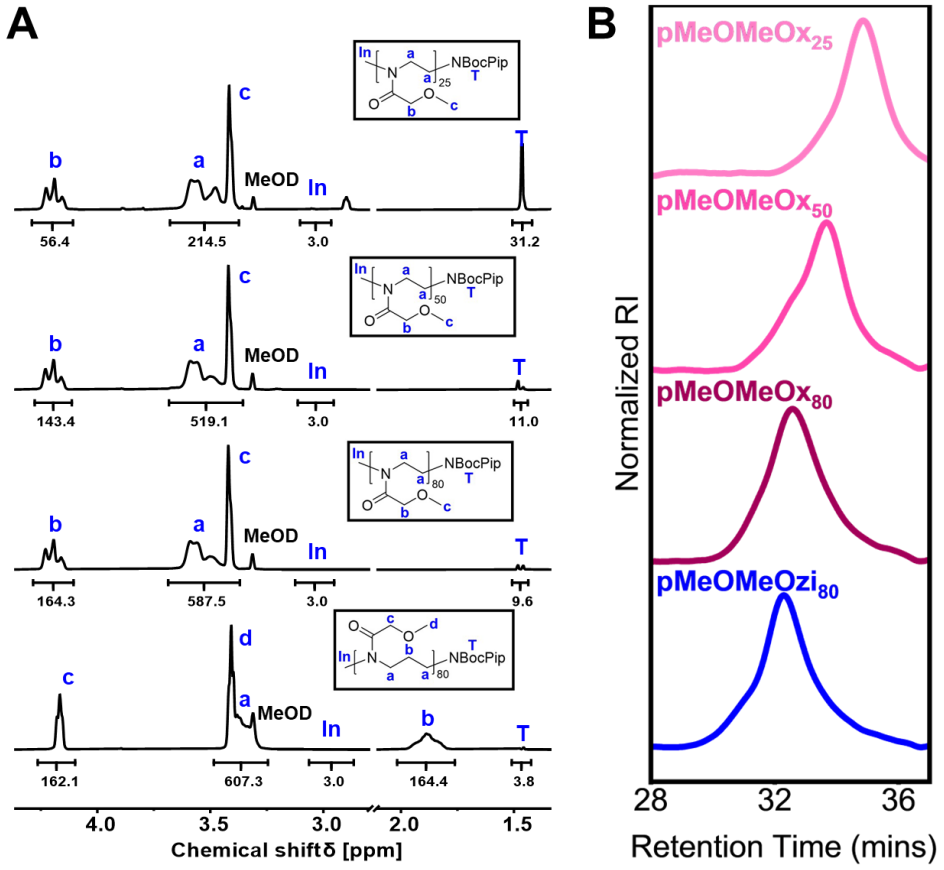

Figure 14 (A) Chemical structures of the synthesized polymers and corresponding integrated ^{1}H NMR spectra measured in MeOD. (B) SEC elugrams with normalized refractive index intensities in DMF with LiBr (1 g L^{-1}) as eluent.

Kinetic plots show linear M_n increase with monomer conversion, consistent with a controlled CROP. SEC analysis revealed narrow Đ for PMeOx (Đ < 1.2), and moderately broader distributions for PMeOMeOx, and PMeOMeOzi (Đ < 1.3), indicating the influence of side-chain structure on polymerization behavior. The presence of the ether substituent is expected to increase the acidity of the α-protons, thereby increases tendency towards chain transfer via β-elimination.[88] Semi-logarithmic plots of monomer consumption obtained by ^{1}H NMR (Figure 15) displayed controlled/linear behavior for MeOMeOx, MeOx, and MeOMeOzi, consistent with pseudo-first-order kinetics and a constant concentration of propagating species throughout the polymerization. The corresponding propagation rate constants were determined to be $k_{p,MeOMeOx} = 4.8 \times 10^{-3}$ L mol^{-1} s^{-1}, $k_{p,MeOMeOzi} = 8.7 \times 10^{-3}$ L mol^{-1} s^{-1}, and $k_{p,MeOx} = 1.6 \times 10^{-3}$ L mol^{-1} s^{-1}.

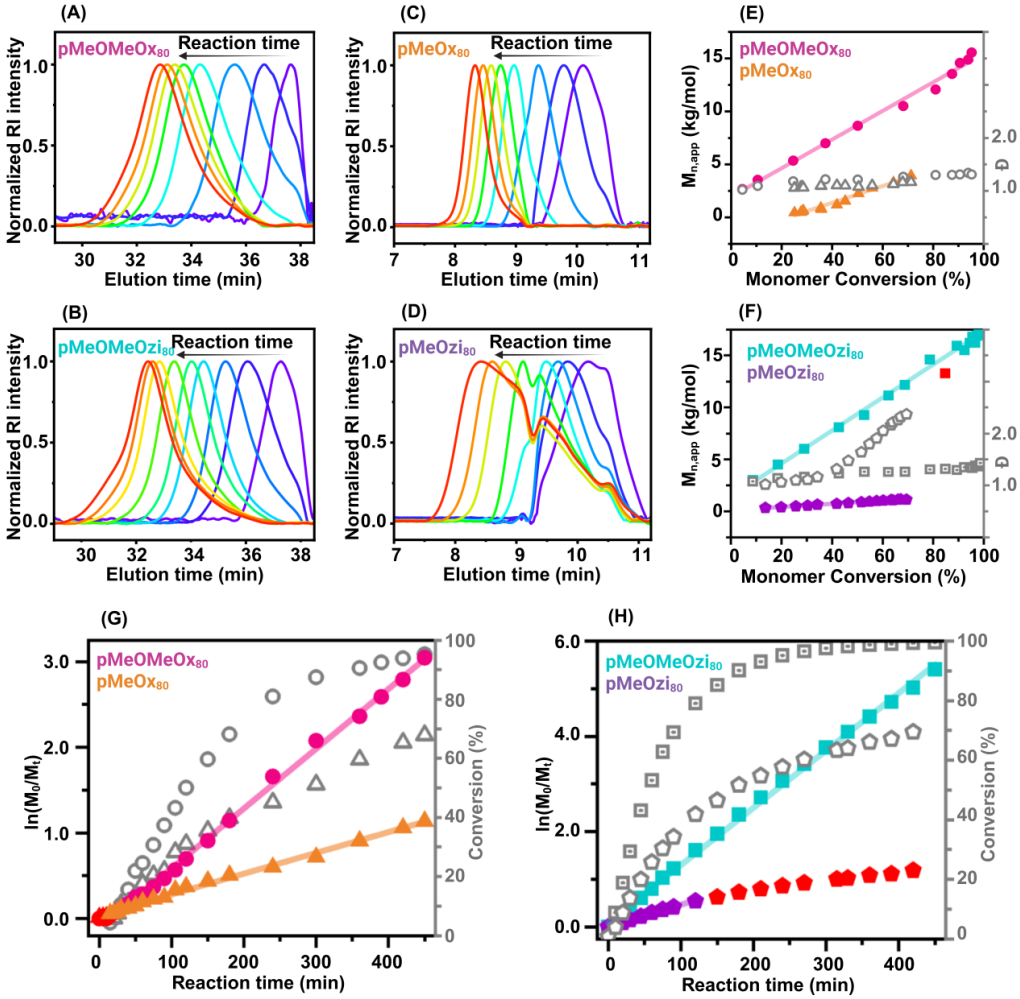

Figure 15 Kinetic study of MeOMeOx and MeOx homopolymerization in ACN at 80 °C, and MeOMeOzi and MeOzi homopolymerization in PhCN at 110 °C (target DP= 80). (A-D) SEC elugrams of polymerization reaction controls at different reaction times for (A) PMeOMeOx: 15 (purple), 30, 60, 120, 180, 240, 300, 450 min (red), (B) PMeOMeOzi: 10 (purple), 20, 30, 45, 60,90, 120, 240, 450 min (red), (C) PMeOx: 50 (purple), 75, 120, 180, 240, 300, 360, 450 min (red), (E) PMeOzi: 45 (purple), 60, 75, 90, 120, 180, 240, 420 (red) min. (E-F) Evolution of number average molecular weight (M_n) and dispersity ($Đ$) as a function of monomer conversion for (E) MeOMeOx and MeOx, and (F) MeOMeOzi and MeOzi, determined by SEC. (G-H) Time-dependent monomer conversion and the corresponding $\ln[M_o]/[M_t]$–time plot for (G) MeOMeOx and MeOx, and (H) MeOMeOzi and MeOzi, as determined by ^{1}H NMR analysis. Linear fits yielded slopes of 1.2×10^{-4} and 0.4×10^{-4} min^{-1} for MeOMeOx and MeOx, respectively, and 2.0×10^{-4} and 0.8×10^{-4} min^{-1} for MeOMeOzi and MeOzi, respectively. Only data up to a reaction time of 75 min was regarded in the determination of the slope via linear regression.

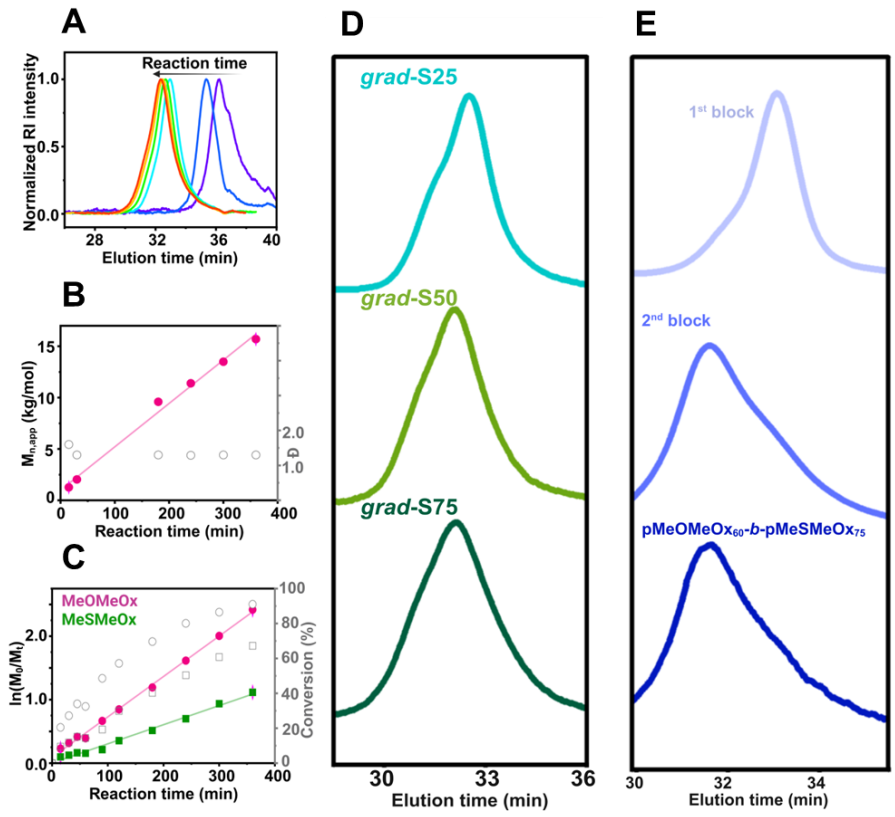

Figure 16 Kinetic study of MeOMeOx : MeSMeOx (50 : 50) copolymerization in ACN at 80 °C. (A) SEC elugrams of polymerization reaction controls taken after 15 (purple), 30, 180, 240, 300, and 360 min (red). (B) Evolution of M_n and $Đ$ as obtained by SEC upon increasing monomer conversion. (C) Time-dependent MeOMeOx and MeSMeOx conversion and the corresponding ln[M_o]/[M_t]–time plot of MeOMeOx/MeSMeOx copolymerization as determined by GC analysis. (D) SEC elugrams of gradient copolymers. (E) SEC traces of block-S50 synthesis, showing the elugrams during synthesis before the second block was added (top), before the terminating agent was added (middle), and the product (bottom).

Table 2 Slope, $[I]_0$ and calculated propagation rate constants k_p for polymerizations.

Polymer	Slope (10^{-4} s^{-1})	$[I]_0$ (10^{-1} mol L^{-1})	k_p (10^{-3} L mol^{-1} s^{-1})	Solvent	T (°C)
PMeOMeOx$_{80}$	1.2	0.24	4.8	ACN	80
PMeOx$_{80}$	0.4	0.25	1.6	ACN	80
PMeOMeOzi$_{80}$	2.0	0.23	8.7	PhCN	110
PMeOzi$_{80}$	0.8	0.25	3.1*	PhCN	110
Monomer 1	**Monomer 2**	k_{p1} (10^{-3} L mol^{-1} s^{-1})	k_{p2} (10^{-3} L mol^{-1} s^{-1})	r_1 (k_1/k_2)	r_2 (k_2/k_1)
MeOMeOx	**MeSMeOx**	5.6	2.6	2.15	0.46

*Only data up to a reaction time of 75 min was regarded

Notably, the propagation rate constants of MeOMeOx and MeOMeOzi are approximately 3-fold and 2.8-fold higher than those of their non-methoxymethyl analogues MeOx and MeOzi, respectively (Table 2), demonstrating that incorporation of the methoxymethyl side chain consistently accelerates propagation in both POx and POzi systems. To the best of our knowledge, these monomers represent the fastest propagating alkyl-substituted 2-oxazoline and 2-oxazine monomers reported to date.[91,195]

Gradient copolymers displayed displayed broader distribution ($Đ \approx 1.29–1.47$), with a high molar mass shoulder shifting to lower elution times as the MeOMeOx fraction increased. We further studied the kinetics for copolymerization of MeOMeOx and MeSMeOx to yield a grad-S50 (Figure 16). In line with homopolymerization, SEC analysis showed a linear increase in M_n values with the reaction time and monomer conversion. The SEC elugrams remained monomodal throughout the reaction. From kinetic measurements, we observed significantly faster consumption of MeOMeOx than MeSMeOx ($k_{p,MeOMeOx} = 5.6\times10^{-3}$ L mol^{-1} s^{-1}, and $k_{p,MeSMeOx} = 2.6\times10^{-3}$ L mol^{-1} s^{-1}) (Table 2). Taken together, the copolymerization of MeOMeOx and MeSMeOx proceeds in a controlled living manner and supports the formation of gradient architecture. Lastly, Figure 16E shows the decrease in the elution time by the addition of the second block in the PMeOMeOx$_{60}$-*b*-PMeSMeOx$_{75}$, which proves the livingness of the MeOMeOx chain during CROP.

4.2.2 Synthesis of Thionated Copolymers [I, II, III]

Thionation reactions were carried out using Lawesson's reagent (LR) (Figure 17, Table 3). In a typical reaction, the polymer and desired amount of LR were introduced into a double-neck round-bottom flask under an argon atmosphere. The reactions were conducted in dichloromethane (DCM) under reflux conditions at polymer concentrations of approximately 0.8–1 g/L and allowed to proceed overnight unless otherwise stated. After completion, the reaction mixtures were transferred into dialysis membranes (MWCO 1 kDa) and purified by dialysis against acetone followed by water with multiple solvent exchanges over 4–7 days in order to remove residual reagent, low-molar-mass byproducts, and impurities. The purified polymers were subsequently isolated by freeze-drying.

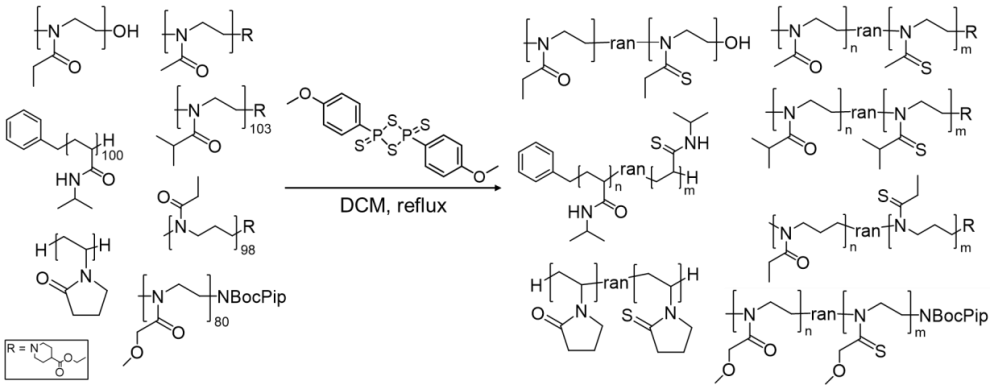

Figure 17 Thionation reaction schemes.

Table 3 Reaction conditions and characterization results of thionated products.

Sample ID	Molar ratio (LR:RU)	Target TD	TD_{NMR}	S/N ratio (EA)	Yield (g/%)	M_n (kDa) / Đ (SEC)	T_g (°C)
PEtOx-S3	37.5:500	15 %	3 %	2.6 %	0.70 / 60 %	19.6 / 2.81	57
PEtOx-S8	50:500	20 %	8 %	8.3 %	4.41 / 88 %	25.1 / 2.09	59
PEtOx-S12	50:500	20 %	12 %	10.4 %	2.93 / 93 %	13.8 / 3.53	61
PEtOx-S16	75:500	30 %	16 %	16.8 %	1.00 / 99 %	14.5 / 3.41	60
PEtOx-S20	75:500	30 %	20 %	21.1 %	1.10 / 95 %	13.1 / 3.46	63
PEtOx-S42	125:500	50 %	42 %	41.9 %	0.79 / 79 %	13.1 / 2.84	72
PNIPAM-S11	17:100	34 %	11 %	13.1 %	0.54 / 98 %	14.9 / 1.06	132
PNIPAM-S17	25:100	50 %	17 %	18.3 %	0.21 / 37 %	16.0 / 1.06	136
P*i*PrOx-S2	5:100	10 %	1.2 %	1.4 %	0.14 / 28 %	21.0 / 1.17	62
P*i*PrOx-S10	17:100	34 %	10 %	10.7 %	0.33 / 82 %	22.1 / 1.14	61
PEtOzi-S9	5:100	10 %	9 %	12.6 %	0.29 / 84 %	26.3 / 1.14	25
Thio-PVP	25:100	50 %	25 %	34.6 %	0.37 / 67 %	5.1 / 1.82	172
$PMeOx_{50}$-S10	2.5:50	10 %	10 %	13.7 %	1.44 / 82 %	11.4 / 1.10	79
$PMeOx_{50}$-S30	8:50	33 %	30 %	30.2 %	1.42 / 65 %	12.6 / 1.10	89
$PMeOx_{550}$-S5	25:550	10 %	5 %	4.7 %	1.21 / 88 %	34.5 / 1.35	78
$PMeOx_{550}$-S20	52:550	20 %	20 %	18.8 %	1.28 / 97 %	38.7 / 1.34	87
PMeOMeOx-S24	10:80	25 %	24 %	32.5 %	0.55 / 91 %	12.6 / 1.27	45
PMeOMeOx-S43	20:80	50 %	43 %	59.6 %	0.56 / 93 %	14.9 / 1.25	54

Under the investigated conditions, thionation with LR generally proceeded non-stoichiometrically, and the experimentally obtained degrees of thionation (TD) were frequently lower than those expected from quantitative modification (Table 3). This behavior was particularly evident for polymers such as PEtOx, PNIPAM,

P*i*PrOx, and PVP, where low LR loadings produced little or no detectable thionation even after prolonged reaction times. In the case of PEtOx, reactions targeting TDs between 15 and 50% yielded products containing only 3–42% sulfur incorporation, while extension of the reaction time increased conversion only moderately. Similarly, for PNIPAM and PVP, initial reactions targeting approximately 10% TD resulted in negligible or undetectable modification, requiring substantial increases in LR loading before measurable thionation could be achieved. P*i*PrOx behaved comparably, where a reaction targeting 10% TD yielded only trace sulfur incorporation, while significantly higher reagent loadings were required to obtain meaningful modification levels. These observations demonstrate that precise control over targeting low TD values remains challenging.

Besides polymer structure, the reaction medium itself played a decisive role in determining thionation efficiency. LR-mediated thionation reactions are classically performed in toluene,[148] where the reagent exhibits optimum reactivity; however, most water-soluble amide-containing polymers investigated here are insoluble in this solvent. Acetonitrile, although capable of dissolving both LR and the polymers, resulted in undesired side reactions and has previously been reported to promote crosslinking during polymer thionation.[184,196] Chloroform has likewise been associated with relatively poor thionation efficiencies in related systems.[185] In contrast, DCM provided consistently improved results while avoiding detectable crosslinking or side reactions under the investigated conditions. The improved performance of DCM likely arises from its slightly higher polarity relative to chloroform, which enhances polymer solvation and facilitates access of LR to the amide functionalities while remaining compatible with the sulfur-transfer mechanism of the reagent. The importance of solvent effects is further supported by reports showing somewhat improved thionation efficiencies for PVP when reactions are conducted in toluene.[185]

The pronounced dependence of thionation efficiency on polymer structure strongly suggests that steric accessibility and backbone dynamics govern the sulfur-transfer process. Formation of the reactive four-membered intermediate between LR and the carbonyl group requires sufficient approachability of the amide functionality, and steric congestion around the carbonyl carbon can significantly reduce reactivity. Similar effects have been reported in the literature for other carbonyl-containing polymers.[197] Notably, polylactic acid has been shown to be unreactive toward LR even under harsh conditions, including prolonged reaction times, elevated temperatures, and excess reagent, which has been attributed to steric shielding of the ester carbonyl groups combined with unfavorable electronic effects destabilizing reactive intermediates. In contrast, structurally less hindered polymers such as poly(ε-caprolactone) undergo efficient thionation.[197] These results indicate that comparable steric and conformational effects also govern thionation reactions in amide-containing polymers.

In this context, the thionation reaction of PMeOx proved particularly informative. In contrast to the relatively hindered polymers discussed above, thionation of PMeOx proceeded quantitatively for most of the attempts (Table 3). The comparatively higher efficiency observed for PMeOx can plausibly be attributed to the reduced steric hindrance surrounding the amide groups, which facilitates approach of the transient LR intermediates toward the amide carbonyl groups. Importantly, only reactions targeting very low TDs deviated significantly from quantitative behavior ($PMeOx_{550}$-S5), again suggesting that approach of the LR intermediates become less favorable for lower modification degrees.

An even more pronounced effect was observed for the more flexible systems. PEtOzi showed near quantitative conversion under identical conditions, while PMeOMeOx similarly yielded TDs of 24% and 43% when targeting 25% and 50% modification, respectively. The enhanced reactivity of these polymers is consistent with their increased backbone flexibility relative to other poly(2-oxazoline)s, which likely improves accessibility of the amide groups. These observations collectively suggest that backbone flexibility plays a central role in determining thionation efficiency. More flexible polymer chains can more readily adopt conformations that expose the amide carbonyl to the reagent, whereas rigid or sterically congested structures hinder efficient thionation with LR.

Size exclusion chromatograms reflect altered solution properties in general (Figure 18). For most of the thionated samples, slight shifts toward lower average molar masses were observed relative to the parent polymers. In the absence of significant broadening or formation of low-molar-mass fractions, these shifts are unlikely to arise primarily from degradation reactions. Instead, they are more reasonably attributed to reduced hydrodynamic volume caused by partial collapse of the polymer coils due to poorer solvent compatibility of the thionated repeat units.

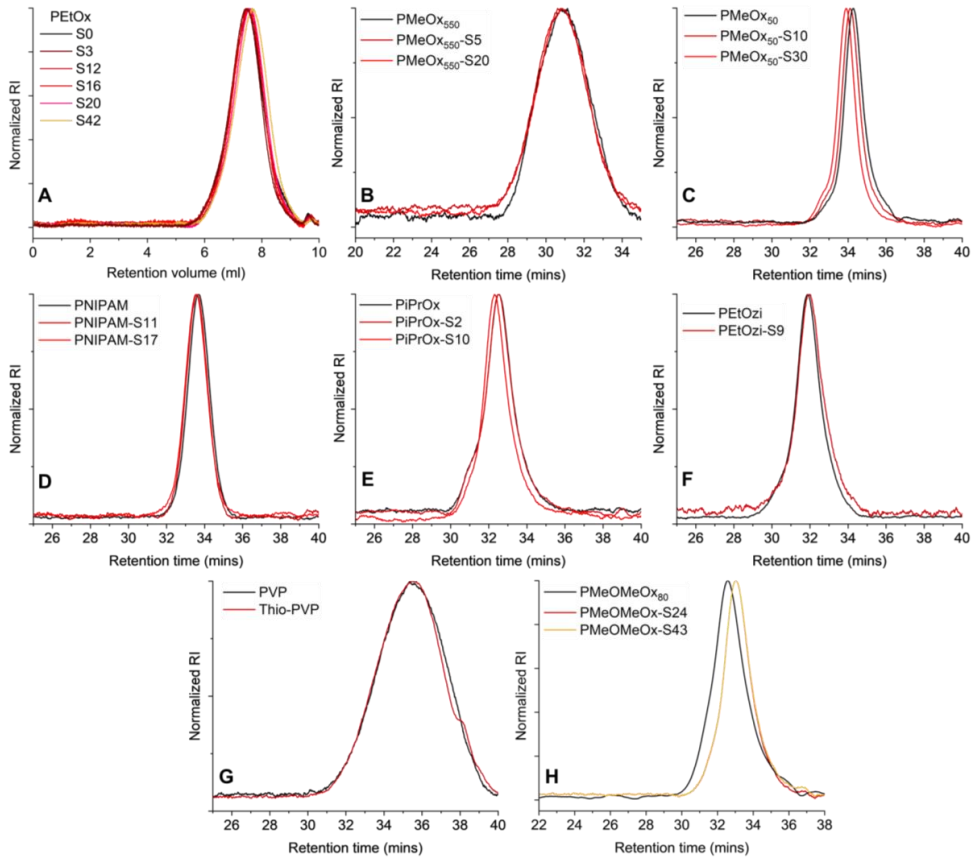

Figure 18 SEC elugrams with normalized refractive index intensities (A) in HFIP with CF_3COOK (3 g L^{-1}), (B-H) in DMF with LiBr (1 g L^{-1}) as eluent.

4.2.3 Thionation Effects on Thermomechanical Properties [I, II, III]

The introduction of thioamide groups had pronounced consequences for the thermal properties of the investigated polymers. Thermogravimetric analysis of thionated PEtOx derivatives revealed systematically decreased decomposition onset temperatures with increasing degree of thionation (TD), consistent with the generally lower thermal stability of thioamides relative to amides reported in the literature.[198] In contrast, differential scanning calorimetry (DSC) demonstrated that thionation generally increased the glass transition temperature (T_g), indicating reduced segmental mobility upon sulfur incorporation.

For most polymer systems investigated, T_g exhibited an approximately linear increase with increasing TD (Figure 19, Table 4). Although the limited number of independent replicates does not allow quantitative correlation analysis, the observed trends consistently indicate that increasing thioamide incorporation progressively restricts polymer chain mobility. Importantly, substantial differences

in the slopes of these trends were observed between polymer systems, suggesting that the sensitivity of chain dynamics toward thioamide incorporation strongly depends on polymer architecture. Among the investigated polymers, PMeOx displayed the steepest increase in T_g, with approximately 0.7 °C per mol% TD for PMeOx samples, while PVP (m = 0.60) and PMeOMeOx$_{80}$ (m = 0.54) also showed pronounced responses (Table 4). In contrast, PEtOx and PEtOzi exhibited more moderate increases of approximately 0.4 °C per mol% TD. Extrapolation of these trends suggests that fully thionated analogues would possess remarkably high glass transition temperatures, approaching ≈ 140 °C for PMeOx, ≈ 95 °C for PEtOx, and potentially exceeding 200 °C for PVP. While these extrapolated values should be interpreted cautiously, they nevertheless emphasize the strong influence of thioamide incorporation on polymer dynamics.

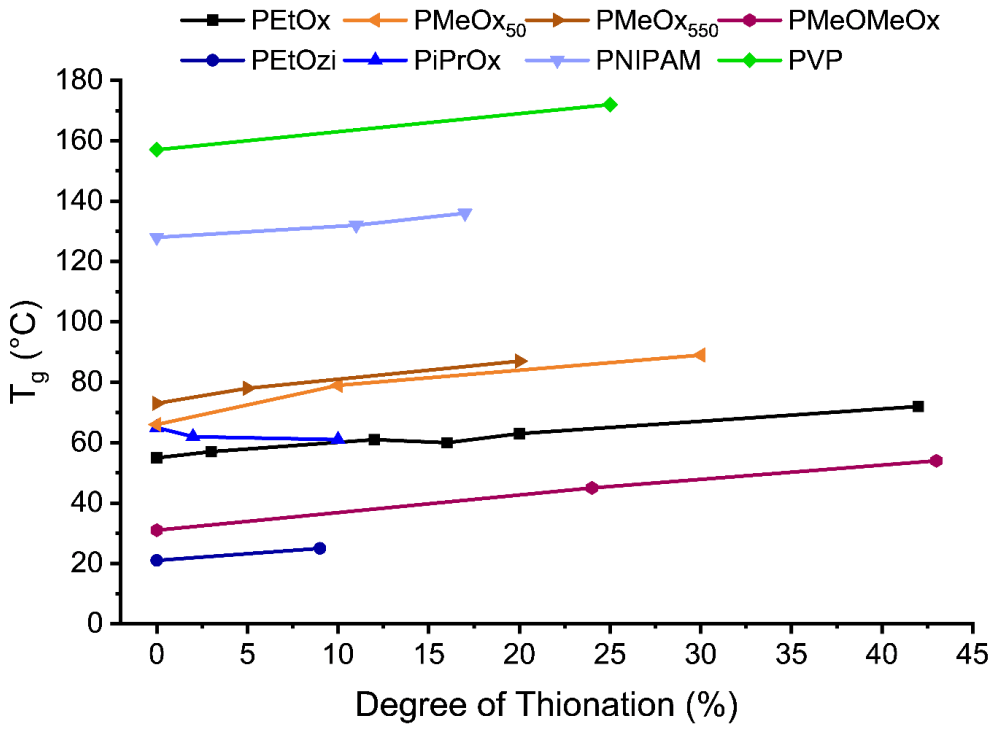

Figure 19 Glass transition temperature (T_g) dependence on the degree of thionation.

Table 4 Linear regression of glass transition temperature (T_g) dependent degree of thionation (TD) data.

Polymer	Slope	Intercept	R^2	Approximated T_g at max TD
PEtOx	0.40	55	0.98	95
PEtOzi	0.44	21	1	65
P*i*PrOx	-0.32	64	0.66	n.a.
PNIPAM	0.45	128	0.97	173
$PMeOx_{50}$	0.73	68	0.93	141
$PMeOx_{550}$	0.68	74	0.98	142
PVP	0.60	157	1	217
$PMeOMeOx_{80}$	0.54	31	0.99	85

The increase in T_g upon thionation is primarily attributed to the altered electronic structure of the amide linkage rather than simply the presence of the larger sulfur atom. Replacement of oxygen with sulfur increases the contribution of iminium-like resonance structures and enhances the double-bond character of the C–N bond, resulting in a substantially higher rotational barrier for thioamides compared to conventional amides.[128,199] Since segmental mobility in these polymers strongly depends on rotational freedom around backbone substituents, restriction of amide bond rotation directly decreases chain flexibility and increases T_g. This interpretation is supported by infrared spectroscopy data on PEtOx thionation, where progressive suppression of the amide C–N stretching vibration and emergence of new bands assigned to thioamide C–N stretching modes indicated increased double-bond character upon sulfur incorporation.[I]

Importantly, comparison with sulfur-containing side-chain analogues demonstrates that the observed thermal effects originate predominantly from thioamide formation rather than from sulfur incorporation itself. Gradient copolymers of PMeOMeOx and the corresponding thioether-containing monomer PMeSMeOx exhibit broadened T_g characteristic of gradient copolymers, but no systematic dependence of T_g on sulfur content has been observed.[III] In contrast, direct thionation of PMeOMeOx resulted in a clear and systematic increase in T_g from 31 °C for the non-thionated polymer to 45 °C and 54 °C for partially thionated derivatives.[III] This distinction strongly suggests that the increase in T_g is not primarily caused by steric effects associated with the larger sulfur atom, but rather by the increased rigidity of the thioamide linkage itself. The substantially higher rotational barrier of the thioamide C–N bond therefore appears to be the dominant factor governing the observed reduction in segmental mobility.

Interestingly, P*i*PrOx derivatives deviated substantially from the general trend observed for the other polymers (Figure 19, Table 4). Although thionation disrupted crystallization behavior even at very low TDs, broadened glass transition regions

and reduced T_g values were observed for P*i*PrOx-S10.[II] The disappearance of crystallization at such low sulfur incorporation is particularly notable, as gradient copolymers of P*i*PrOx and PMeOx reportedly retain semicrystallinity up to considerably higher MeOx comonomer incorporation levels (above ~20%).[200] The suppression of crystallinity in the thionated materials is likely associated with a combination of increased rotational barriers and steric perturbations introduced by the thioamide functionality, which disrupt regular side-chain packing required for crystalline domain formation.

At the same time, the broadened T_g observed for P*i*PrOx-S10 resembles behavior commonly reported for gradient copolymers and may indicate heterogeneous local distribution of thioamide units along the polymer chain. Supporting this interpretation, the ^{1}H NMR spectra displayed multiple distinct backbone resonances at elevated chemical shifts, tentatively assigned to thionated repeat units surrounded by different numbers of neighboring thioamide groups.[II] Although these observations do not conclusively establish sequence distribution, they suggest that local compositional heterogeneity may influence cooperative segmental dynamics in this system. Such heterogeneity could disrupt the continuity of amide-rich domains and reduce cooperative packing efficiency, thereby lowering the observed T_g despite the intrinsically higher rotational barrier associated with thioamide formation.

4.3 Solution Behavior Studies [I, II, III]

This section describes the influence of thionation on the aqueous solution behavior of the investigated amide-based polymers and discusses how sulfur incorporation modifies hydration, phase separation, and aggregation processes. Partial thionation had a profound impact on polymer–water interactions across all investigated systems. In most cases, the thionated polymers remained hydrated and water-soluble at sufficiently low temperatures but underwent LCST-type phase separation upon heating. Compared to pristine polymers, the modified samples generally exhibited reduced hydration stability, systematically decreased cloud point temperatures (T_{cp}), and increased turbidity even below the phase transition temperature (Figure 20). At higher TD, several systems furthermore showed incomplete dissolution or sedimentation, indicating that sulfur incorporation substantially alters the balance between polymer–water and polymer–polymer interactions.

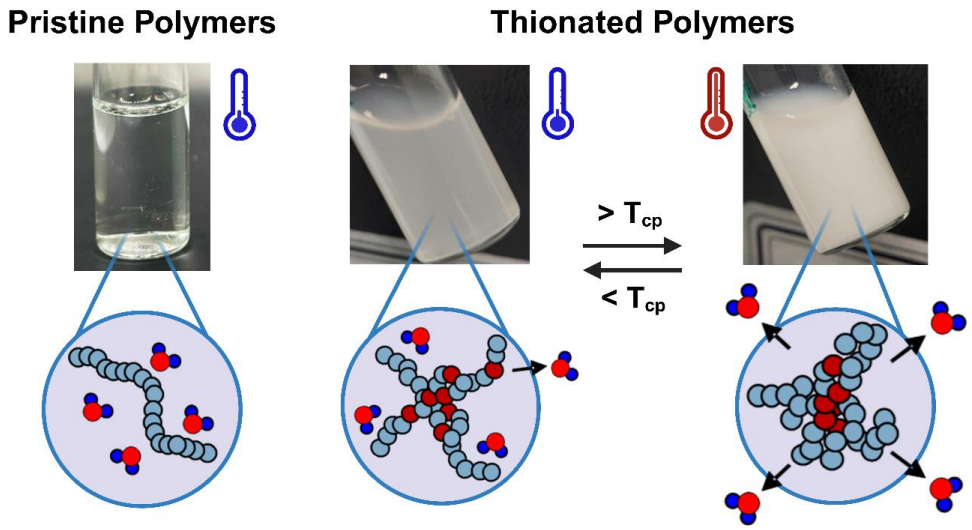

Figure 20 Schematic representation of the solution behavior for pristine and thionated polymers in water. Even minimal thionation (P*i*PrOx-S2 with 2% TD shown as example) increases hydrophobicity, restricts chain expansion, and forms turbid solutions of multimolecular aggregates in water. Upon heating, reduced hydrogen bonding further promotes agglomeration at lower temperatures.

Beyond the general reduction in hydration stability, the effects of thionation strongly depend on polymer structure, backbone flexibility, hydrogen-bonding characteristics, and side-chain composition. In particular, comparison of structurally isomeric polymers revealed pronounced differences in aggregation pathways, cooperativity of phase separation, and thermal hysteresis. Furthermore, comparison between thioether-containing copolymers and directly thionated polymers enabled direct comparison between effects arising primarily from increased side-chain hydrophobicity and those resulting from direct modification of the amide functionality into a thioamide.

4.3.1 Thionation Degree Effects on LCST-Type Polymers [I, II]

Despite the structural diversity of the investigated polymers, increasing TD systematically shifted the T_{cp} to lower values (Figure 21). For PEtOx, for example, T_{cp} decreased from approximately 65 °C for the pristine polymer to below room temperature above 15% thionation, with samples of TD above 20% approaching overall limit of water solubility. Similar reductions in hydration stability were observed for PNIPAM, P*i*PrOx, and PEtOzi. Overall, these observations demonstrate that partial conversion of amides into thioamides strongly destabilizes polymer hydration and pushes the T_{cp} to lower temperatures in aqueous solution.

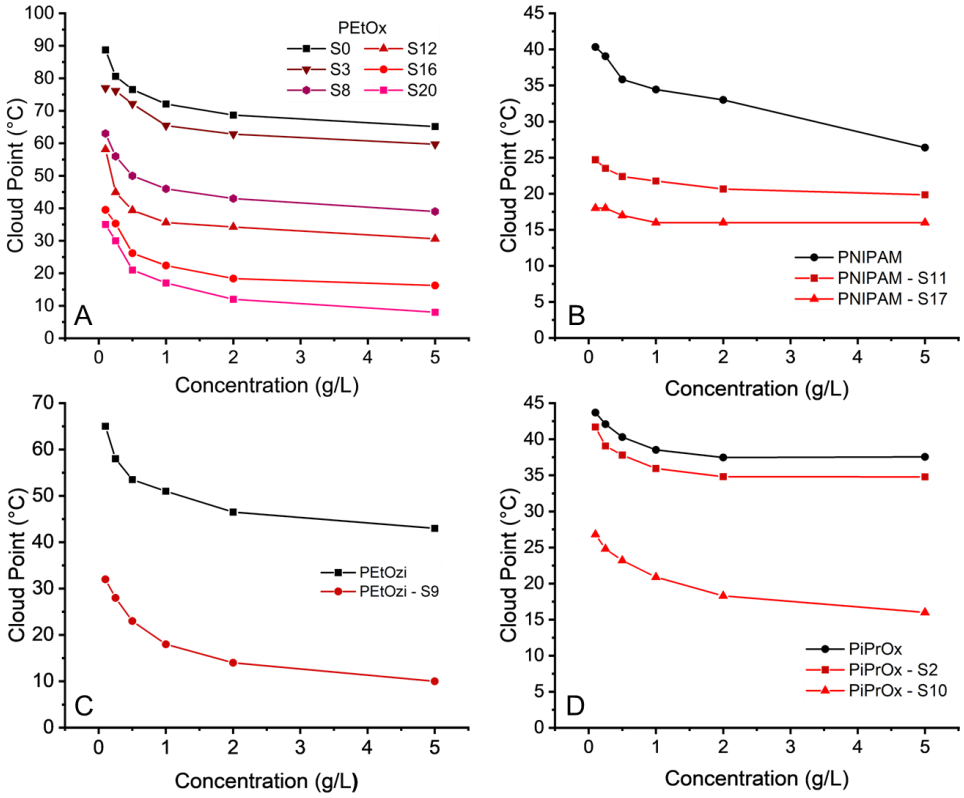

Figure 21 Phase diagrams of pristine and thionated LCST-type polymers.

Within the experimentally accessible composition range, the decrease in T_{cp} appeared linear for all systems, although the limited number of independent replicates and available data points does not permit absolute quantitative analysis. Nevertheless, comparison of the apparent slopes does suggest clear differences in the sensitivity of the investigated polymers toward thionation (Figure 22, Table 5). Among the investigated systems, PEtOzi exhibited the strongest response, with T_{cp} decreasing by −3.7 °C per mol% TD, followed closely by PEtOx (−3.0 °C per mol% TD). In contrast, P*i*PrOx and PNIPAM displayed substantially smaller apparent shifts of approximately −1.7 and −1.1 °C per mol% TD, respectively.

Importantly, very similar slopes observed for PEtOx and PEtOzi despite their different backbone structures. This suggests that side-chain identity plays a dominant role in determining the magnitude of T_{cp} change upon thionation. Since both polymers possess identical ethyl sidechains, thionation appears to perturb hydration primarily through altering the balance between hydrophobic side-chain interactions and backbone hydration. Temperature-dependent ^{1}H NMR measurements further supported the close similarity between the solution behavior of PEtOx- and PEtOzi-based systems during phase separation. [I,II] For both pristine

and thionated polymers, increasing temperature primarily resulted in pronounced broadening and intensity loss of the backbone-associated signals, whereas the side-chain methyl resonances remained comparatively visible even above the phase transition temperature.[I,II] Such behavior indicates that for PEtOx and PEtOzi the LCST transition is accompanied mainly by restricted mobility upon dehydration of the polymer backbone segments, while the ethyl sidechains retain a certain degree of local mobility within the collapsed aggregates. This observation further supports the conclusion that side-chain identity plays a dominant role in governing the thermoresponsive behavior and thionation-induced solution behavior change in these systems.[II] Furthermore, the persistence of detectable side-chain signals above T_{cp} suggests that the phase-separated structures remain partially hydrated and dynamically heterogeneous rather than forming completely rigid precipitates.

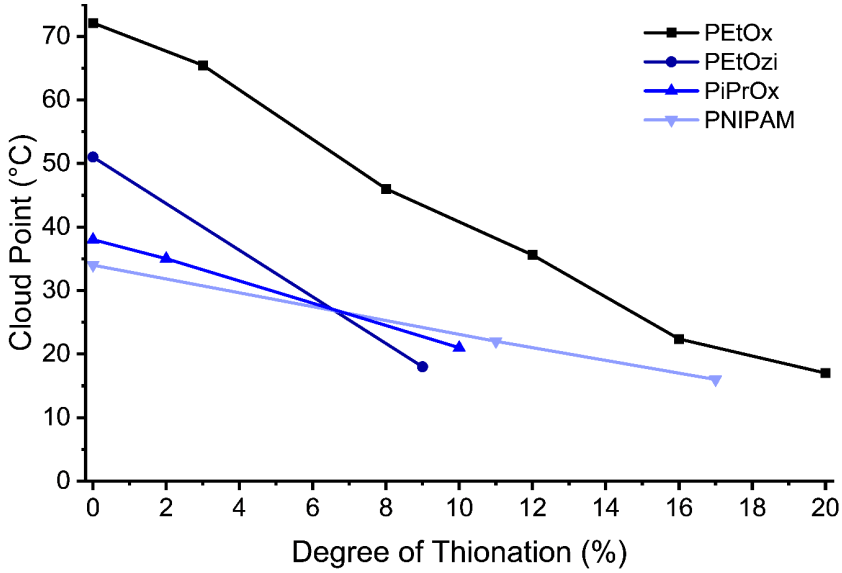

Figure 22 Cloud point (T_{cp}) dependence on the degree of thionation at 1 g/l polymer concentration.

Table 5 Linear regression of cloud point (T_{cp}) dependent degree of thionation (TD) data.

Polymer	Slope	Intercept	R^2	Approximated TD_{max}
PEtOx	-3.00	72	0.98	24
PEtOzi	-3.67	51	1	14
P*i*PrOx	-1.71	38	0.99	22
PNIPAM	-1.06	34	0.99	32

Importantly, PNIPAM and P*i*PrOx behave fundamentally different from the other investigated polymers regarding their molecular interactions and phase

separation mechanisms, which is also reflected in the temperature-dependent ^{1}H NMR measurements.[II] Whereas PEtOx and PEtOzi and their thionated counterparts retained comparatively visible side-chain resonances above the phase transition temperature together with gradual broadening and attenuation of the backbone-associated signals, PNIPAM and P*i*PrOx display substantially more abrupt signal intensity loss upon heating.[II] In particular, the spectra of pristine PNIPAM above T_{cp} showed nearly complete disappearance of polymer resonances, consistent with the highly cooperative collapse and strong restriction of segmental mobility characteristic of LCST Type II behavior. Despite having the Type I character, P*i*PrOx and its thionated derivative exhibits an intermediate behavior between these extremes, in agreement with its more complex phase separation mechanism involving both dehydration and ordering upon chain collapse. Accordingly, the comparatively smaller apparent slopes observed for P*i*PrOx (−1.7 °C per mol% TD) and especially PNIPAM (−1.1 °C per mol% TD) should not be interpreted simply as weaker sensitivity toward thionation. In contrast to the tertiary amide-based polymers investigated here, PNIPAM contains secondary amide repeat units capable of strong inter- and intramolecular hydrogen bonding interactions, which are primarily responsible for its cooperative phase transition behavior. Consequently, thionation not only reduces hydration stability, but also alters the cooperative dehydration and aggregation characteristic of PNIPAM. This distinction is also reflected in the temperature-dependent ^{1}H NMR spectra, where thionated PNIPAM samples retain very weak but still detectable polymer resonances above the phase transition temperature, similar to the behavior observed for pristine and thionated P*i*PrOx.[II] Therefore, direct comparison of the apparent regression slopes with those obtained for the other polymer systems should be interpreted cautiously. The distinct thermoresponsive behavior of thionated PNIPAM and P*i*PrOx, particularly in relation to the underlying structure–property relationships governing their phase transition behavior, is discussed in more detail in the following section.

4.3.2 Thionation Effects on Thermoresponsive Behavior [II]

Although partial thionation systematically reduced the T_{cp} of all investigated polymers, the effects on thermoresponsive behavior are substantially depending on the underlying phase separation mechanism and molecular interactions of the parent polymer. Particularly pronounced differences were observed for PNIPAM and P*i*PrOx, where thionation altered not only hydration stability, but also the cooperativity, aggregation pathway, and structural evolution of the phase-separated state. In contrast, PEtOzi displayed comparatively moderate changes, with thionation primarily increasing hydrophobicity while largely preserving the overall LCST-type transition mechanism.

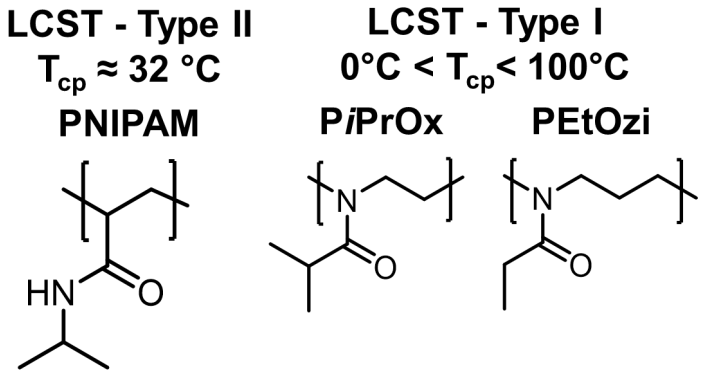

Figure 23 Structures of structurally isomeric thermoresponsive homopolymers with $C_6H_{11}NO$ constitutional repeat units.

For PNIPAM, thionation fundamentally altered the characteristic thermoresponsive behavior associated with its highly cooperative LCST-Type II transition. Besides decreasing T_{cp}, the pronounced thermal hysteresis observed for pristine PNIPAM was almost completely suppressed upon thionation (Figure 24 A). Since hysteresis in PNIPAM is commonly attributed to strong inter- and intramolecular hydrogen bonding interactions that retard rehydration of collapsed chains, its disappearance strongly suggests that thioamide incorporation weakens these interactions and facilitates more reversible dissolution upon cooling.

A second major difference was observed in the aggregation behavior. In contrast to pristine PNIPAM, where heating resulted in complete loss of transmittance at higher concentrations, thionated PNIPAM samples displayed intermediate transmittance plateaus even above T_{cp} (Figure 24A). This behavior indicates formation of stable mesoglobular aggregates rather than macroscopic precipitation. Dynamic light scattering (DLS) measurements strongly supported this interpretation (Figure 24C). At 0.1 g/L, pristine PNIPAM formed relatively large and polydisperse aggregates after phase separation (Z_{avg} ≈ 240–260 nm, PDI ≈ 0.30), whereas below T_{cp} essentially no reliable scattering signal was observed due to the highly solvated polymer coils. In contrast, thionated PNIPAM derivatives already exhibited detectable scattering below T_{cp}, suggesting partial hydrophobic pre-aggregation induced by sulfur incorporation. PNIPAM-S17 formed smaller aggregates (Z_{avg} ≈ 74 nm) than PNIPAM-S11 (Z_{avg} ≈ 134–168 nm) below the phase transition temperature, consistent with the higher residual turbidity observed for PNIPAM-S11. Upon heating, both polymers formed comparatively small and highly uniform aggregates, with PNIPAM-S11 showing Z_{avg} ≈ 130 nm (PDI ≈ 0.10) and PNIPAM-S17 forming even more compact species with Z_{avg} ≈ 80–90 nm (PDI ≈ 0.08). In all cases, the aggregate size distributions remained narrow and monomodal.

Microcalorimetric measurements further demonstrated that the sharp and cooperative dehydration process characteristic of pristine PNIPAM became substantially broadened after thionation (Figure 24B). This loss of cooperativity is consistent with the broadened turbidity transitions observed in optical measurements and indicates disruption of the highly coordinated dehydration sequence typical for PNIPAM. Interestingly, no systematic relationship between transition enthalpy (ΔH) and thionation degree was observed, suggesting that the altered thermal behavior primarily originates from modified aggregation pathways rather than major differences in the total amount of retained hydration water. Higher ΔH of thionated samples, however, could be originated from the increased acidity of secondary thioamide -NH- groups, resulted in slightly better hydration than the pristine PNIPAM despite the incorporated sulfur, and slightly higher amount of bound water.

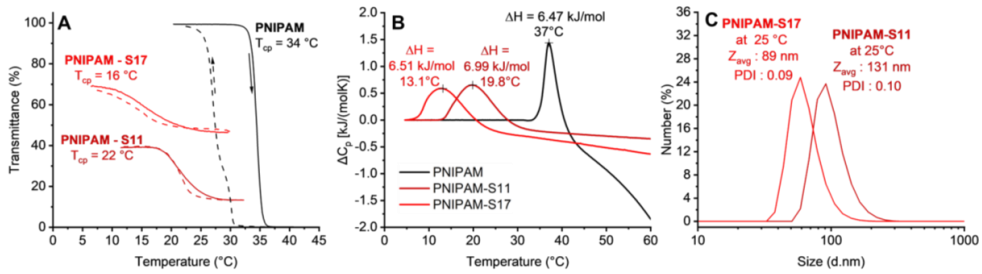

Figure 24 Solution behavior of PNIPAM and their thionated analogues in aqueous media. (A) Turbidimetry heating–cooling curves at 1 g/L showing LCST-type phase transitions. (B) μDSC thermograms highlighting changes in the transition temperature and enthalpy upon thionation. (C) DLS size distributions of thionated PNIPAM samples above T_{cp} at 0.1 g/L.

Mechanistically, the LCST transition of pristine PNIPAM involves a highly cooperative process comprising dehydration of the isopropyl sidechains, collapse of the polymer backbone, disruption of polymer–water hydrogen bonds, and simultaneous formation of inter- and intramolecular amide–amide interactions.[201,202] Thionation appears to disrupt this process in two complementary ways. First, weaker hydrogen bonding capability of thioamide moieties reduces cooperative interchain association. Second, the altered intermolecular interactions favor formation of smaller mesoglobules instead of extended secondary aggregates. Together, these effects reduce kinetic trapping of collapsed chains and facilitate faster rehydration upon cooling, thereby strongly suppressing thermal hysteresis.

Compared to PNIPAM, pristine P*i*PrOx displays distinctly different solution behavior character with LCST-Type I behavior. In addition to its molar mass-dependent T_{cp}, P*i*PrOx is known to form crystalline domains upon phase separation

in aqueous media. Turbidimetry measurements revealed that cooling curves of pristine P*i*PrOx plateaued below complete transmittance recovery at higher concentrations, indicating incomplete rehydration, attributed to partial crystallization of collapsed polymer domains (Figure 25A). Microcalorimetric measurements further supported this interpretation by showing bimodal exothermic features during repeated heating–cooling cycles, corresponding to stepwise hydration of amorphous and crystalline chain fractions.[II] Such behavior is consistent with earlier reports attributing crystallization of P*i*PrOx to its comparatively high backbone mobility, which enables organization of isopropyl sidechains into semi-crystalline domains even below the bulk T_g.[111,113,114]

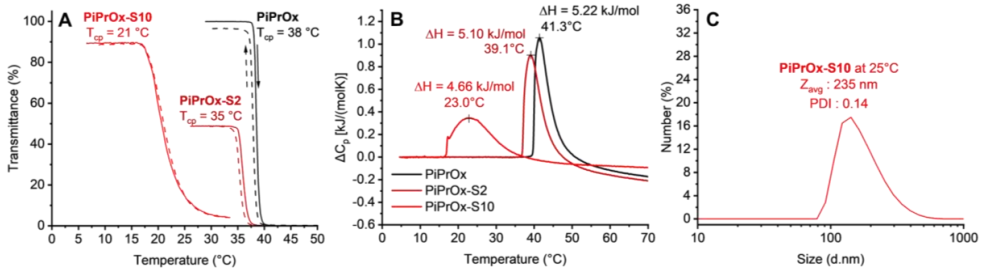

Figure 25 Solution behavior of P*i*PrOx and their thionated analogues in aqueous media. (A) Turbidimetry heating–cooling curves at 1 g/L showing LCST-type phase transitions. (B) µDSC thermograms highlighting changes in the transition temperature and enthalpy upon thionation. (C) DLS size distributions of P*i*PrOx-S10 above T_{cp} at 0.1 g/L.

Upon thionation, the aggregation and ordering behavior of P*i*PrOx changed substantially. Turbidimetry measurements of P*i*PrOx-S2 and P*i*PrOx-S10 no longer showed the incomplete transmittance recovery characteristic of the pristine polymer (Figure 25A), indicating suppression of rapid crystallization in water. Nevertheless, µDSC measurements suggest that structural ordering in aqueous solution was not completely eliminated. P*i*PrOx-S10 displayed pronounced thermal hysteresis during repeated heating–cooling cycles, while P*i*PrOx-S2 retained weak bimodal features in the cooling scans, suggesting the presence of slower and kinetically hindered crystallization processes (Figure 26 A-C).[II] This interpretation is further supported by long-term storage experiments, where P*i*PrOx-S10 solutions gradually formed macroscopic precipitates over approximately two weeks at 7 °C, demonstrating that ordered aggregation can still occur over sufficiently long timescales (Figure 26 D). Overall, thionation appears to suppress rapid crystallization primarily by restricting backbone mobility through increased rotational barriers of the thioamide bonds, while still preserving a residual tendency toward structural organization.

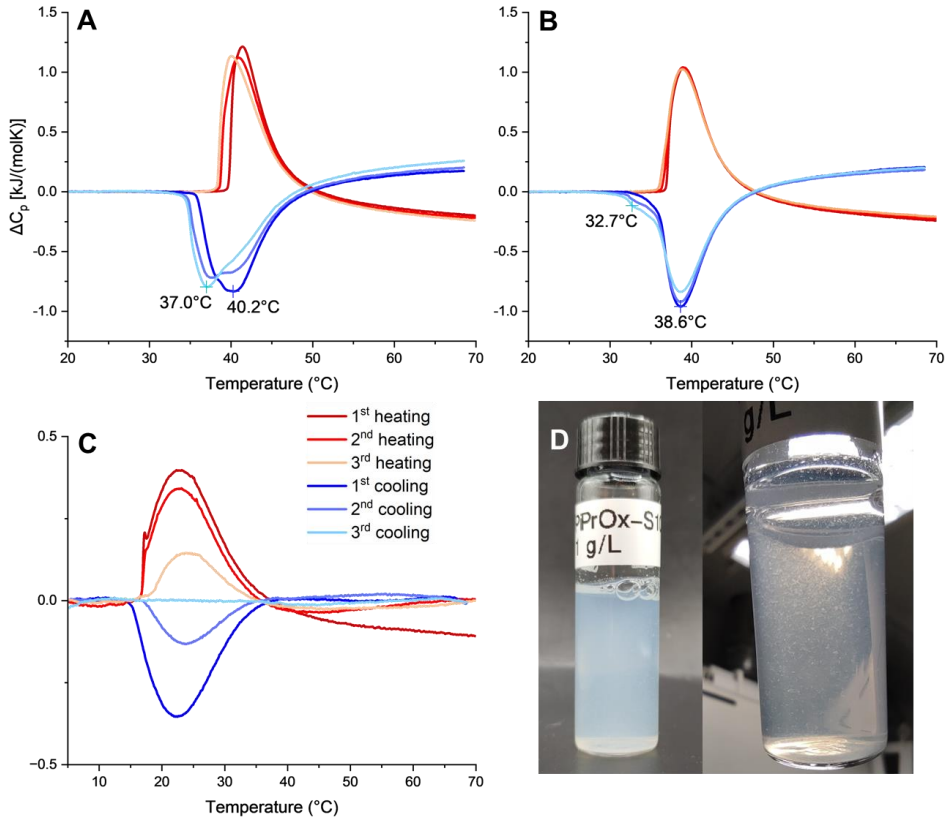

Figure 26 Microcalorimetry thermograms of (A) P*i*PrOx, (B) P*i*PrOx-S2, and (C) P*i*PrOx-S10 with heating and cooling curves at 1 °C/min heating/cooling rate. (D) Shows the macroscopic aggregates of P*i*PrOx-S10 after storage for 2 weeks at 7 °C.

In contrast to PNIPAM, ΔH of P*i*PrOx scaled with thionation degree (Figure 25B), indicating that sulfur incorporation progressively alters polymer-water H-bonding interactions during the dehydration process. DLS measurements additionally revealed that P*i*PrOx-S10 formed comparatively homogeneous aggregates upon heating, with predominantly monomodal size distributions (Z_{avg} ≈ 230–240 nm, PDI ≈ 0.14 at 0.1 g/L), whereas pristine P*i*PrOx produced larger and more polydisperse aggregates (Z_{avg} > 300 nm, PDI > 0.25). Thus, while thionation does not fundamentally change the LCST-Type I nature of P*i*PrOx, it significantly modifies the ordering and aggregation pathways associated with phase separation.

Compared to PNIPAM and P*i*PrOx, pristine PEtOzi displayed comparatively simple LCST-type solution behavior without pronounced hysteresis or ordering phenomena. Turbidimetry measurements revealed relatively sharp phase transitions with only minor hysteresis at higher concentrations (>1 g/L) (Figure 27A), while more diluted samples resulted in broader transitions that no longer reached complete loss of transmittance.[II] In contrast to the relatively uniform

aggregates formed by thionated PNIPAM and P*i*PrOx, DLS measurements revealed broader, multimodal, and overall larger aggregate distributions for both pristine and thionated PEtOzi (Figure 27C). Thionation increased aggregate size further, consistent with increased hydrophobicity, but did not fundamentally alter the overall thermoresponsive behavior or aggregation mechanism of the polymer similarly as in the PEtOx case.[I]

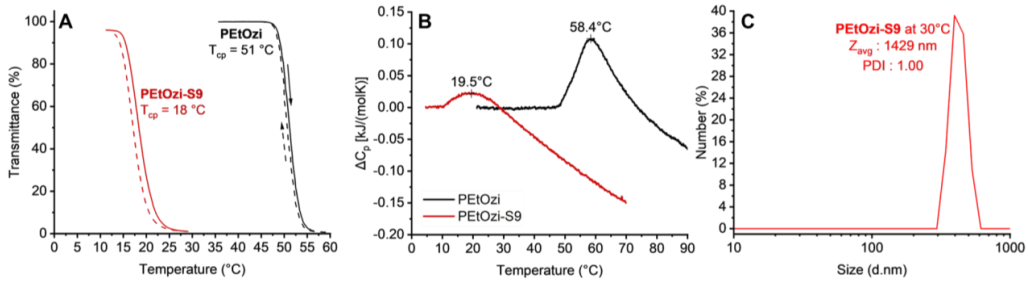

Figure 27 Solution behavior of PEtOzi and PEtOzi-S9 in aqueous media. (A) Turbidimetry heating–cooling curves at 1 g/L showing LCST-type phase transitions. (B) µDSC thermograms highlighting changes in the transition temperature upon thionation. (C) DLS size distributions of PEtOzi-S9 above T_{cp} at 0.1 g/L.

Taken together, the investigated LCST-type polymers demonstrate that thionation not only systematically reduces hydration stability but can also profoundly alter the underlying thermoresponsive mechanism depending on the molecular structure of the parent polymer. In systems such as PNIPAM and P*i*PrOx, thionation significantly modifies the cooperativity, aggregation pathway, and structural organization accompanying phase separation, whereas in PEtOx- and PEtOzi-based systems the primary effect is a combination of decreased H-bonding and gradual destabilization of hydration driven largely by side-chain hydrophobicity. Importantly, the results further suggest that the response toward sulfur incorporation strongly depends on the intrinsic hydrophilic–hydrophobic balance of the parent polymer. This aspect becomes even more evident for highly water-soluble polymers such as PVP, PMeOx, and ether-functionalized POx systems, where sulfur incorporation through either direct thionation or thioether-containing side chains can induce markedly different effects on hydration stability and thermoresponsive behavior. These structure–property relationships are discussed in the following section.

4.3.3 Thionation Effects on Water-soluble Polymers [II, III]

The results discussed in the previous sections demonstrate that thionation systematically destabilizes polymer hydration and shifts LCST-type phase transitions toward lower temperatures. However, the consequences of sulfur incorporation become particularly revealing for highly water-soluble polymers located close to or beyond the thermoresponsive boundary in aqueous solution. In these systems, thionation no longer merely modifies an existing LCST transition, but instead determines whether reversible thermoresponsive behavior can emerge at all. Particularly informative comparisons can therefore be made between highly hydrophilic polymers such as PMeOx, PVP, and the ether-functionalized PMeOMeOx/PMeOMeOzi systems, as these polymers differ strongly in backbone structure, side-chain polarity, and intrinsic hydration stability.

The effect of thionation on PMeOx was particularly pronounced similarly as for the thermoresponsive polymers. While pristine PMeOx is highly water-soluble and does not exhibit LCST-type behavior, partial thionation destabilizes its hydration. $PMeOx_{50}$-S30 became completely insoluble in water, whereas samples with lower thionation degree formed colloidally stable but non-thermoresponsive dispersions at 10 g/L (Figure 28). Thus, thionation itself is not enough for inducing LCST-type phase separation observed for the other amide-based systems. These observations emphasize the critical role of side-chain hydrophobicity for thermoresponsive behavior. With only a methyl substituent, PMeOx apparently lacks sufficient hydrophobic driving force for cooperative dehydration and coil collapse. Consequently, reduced hydration upon thionation leads directly toward insolubility rather than a reversible LCST transition.

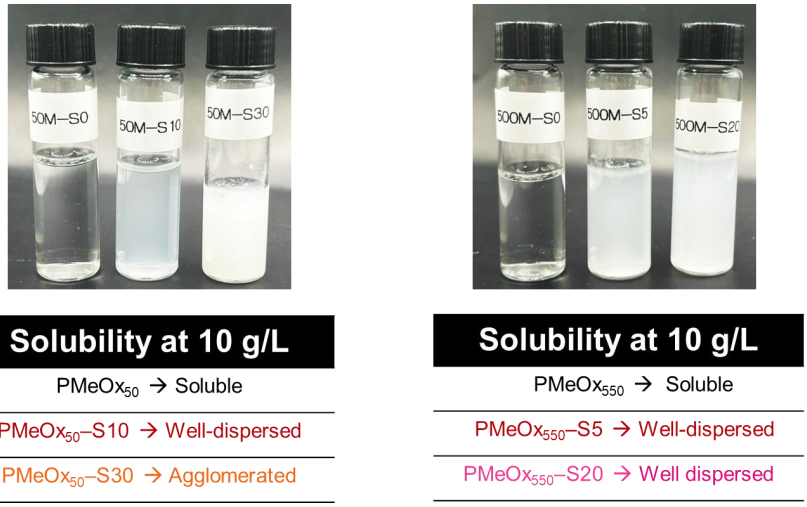

Figure 28 Dispersions of PMeOx samples and their thionated counterparts (at 10 g/L concentration and room temperature).

A similarly instructive but fundamentally different behavior was observed for PVP. Pristine PVP is fully water-soluble and, unlike its structural isomers PNIPAM, P*i*PrOx, or PEtOzi, does not exhibit LCST-type behavior below 100 °C, at ambient pressure. Remarkably, partial thionation (~25%) induced distinct LCST-type phase separation in aqueous solution (Figure 29), representing one of the first examples where thermoresponsive behavior was introduced into PVP through direct post-polymerization backbone modification. Previous approaches toward thermoresponsive pyrrolidone-based polymers relied primarily on copolymerization, side-chain alkylation, or structural modification of the repeating unit.[203–206] In contrast, the present results demonstrate that direct conversion of amides into thioamides alone can sufficiently perturb hydration to induce reversible phase separation. The resulting transitions were comparatively broad and strongly concentration dependent, extending over several (tens of) K, which likely originates from less cooperativity, relatively low M_n and high dispersity of the commercial PVP sample employed. Importantly, the emergence of LCST behavior in thionated PVP, together with the absence of reversible thermoresponsive behavior in thionated PMeOx, demonstrates that thionation itself does not universally generate LCST transitions. Instead, sulfur incorporation shifts the balance between hydration and hydrophobic association, while the underlying polymer structure determines whether this shift produces reversible phase separation or direct loss of solubility.

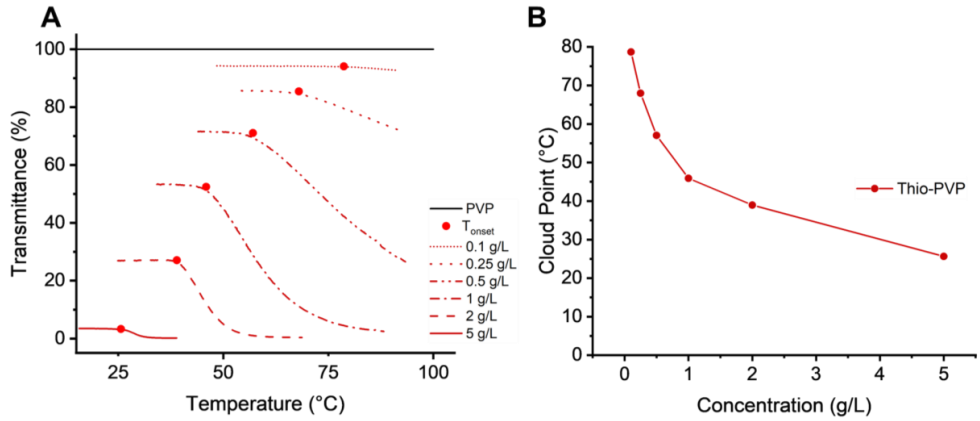

Figure 29 Solution behavior of Thio-PVP in aqueous media. (A) Turbidimetry heating curves at different concentrations showing broad LCST-type phase transitions. (B) Phase diagram of thionated PVP (TD = 25%).

To further investigate hydration stability across these highly hydrophilic systems, aqueous polymer solutions were studied in the presence of Na_2SO_4, a kosmotropic salt known to promote dehydration and LCST-type phase separation through salting-out effects.[68,70–72] Increasing salt concentration progressively

destabilizes polymer hydration by disrupting hydrogen bonding between water and polymer polar groups, thereby decreasing T_{cp}. Among the investigated homopolymers, PMeOMeOx displayed the highest resistance toward salt-induced phase separation (Figure 30). At 10 g/L, LCST-type transitions were observed only at relatively high Na_2SO_4 concentrations between 1.0 and 1.3 M, with T_{cp} decreasing from approximately 84 °C to 15 °C as salt concentration increased. Interestingly, pMeOx under identical conditions did not exhibit thermoresponsive behavior but instead underwent direct salting-out at 1.2 M Na_2SO_4, despite its well-known hydrophilicity. These observations support the earlier hypothesis by Sedlacek and co-workers suggesting that PMeOMeOx may possess even higher effective hydration stability than PMeOx.[97] While, PMeOMeOzi underwent phase separation already between 0.7 and 1.0 M Na_2SO_4, consistent with the generally higher hydrophobicity of POzi relative to POx. Comparison with PVP further highlights the exceptional hydration stability of PMeOMeOx and PMeOMeOzi. Together, these observations establish the qualitative trend for the water solubility of the investigated polymers:

$$\text{PMeOMeOx} > \text{PMeOx} > \text{PMeOMeOzi} > \text{PVP}$$

with respect to hydration stability in aqueous solution (Figure 30, Table 6).

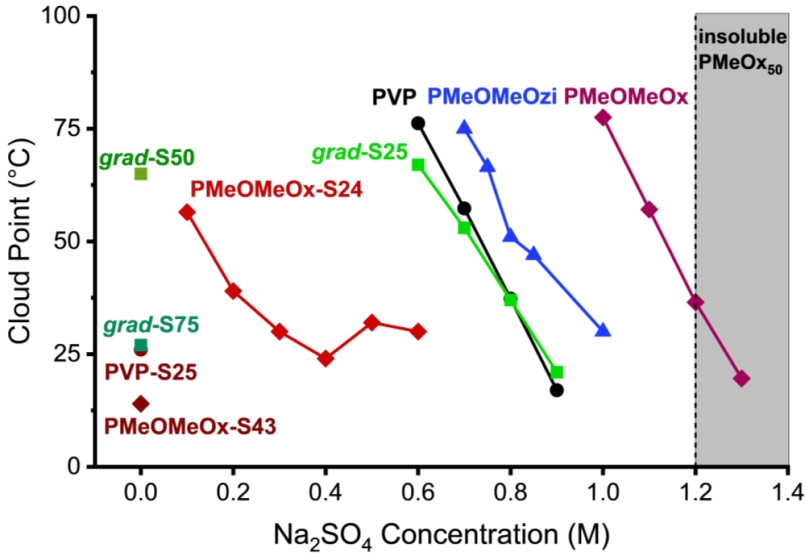

Figure 30 Salt concentration-dependent cloud point temperatures (T_{cp}) of highly hydrophilic POx/POzi-based polymers in aqueous Na_2SO_4 solutions. Increasing salt concentration lowers T_{cp} through kosmotropic salting-out effects. Comparison between pristine polymers, thioether-containing gradient copolymers, and partially thionated polymers highlights the fundamentally different influence of side-chain sulfur incorporation and direct thionation on polymer hydration and thermoresponsive behavior.

Table 6 Linear regression of salt concentration dependent cloud point (T_{cp}) data.

Polymer	Slope	Intercept	R^2	T_{cp} in pure water
PVP	-197	195	0.99	195
PMeOMeOx	-194	271	0.99	271
PMeOMeOzi	-148	175	0.94	175
grad-S25	-154	160	0.99	160

Introduction of sulfur-containing functionalities systematically shifted these systems toward lower T_{cp} values and lower the salt concentrations required for phase separation. Gradient copolymers containing thioether-functionalized repeat units displayed progressively reduced hydration stability with increasing sulfur content. Whereas grad-S50 remained water-soluble and exhibited a T_{cp} of approximately 65 °C in pure water, grad-S75 already formed dispersions at 10 g/L. Nevertheless, saturated solutions extracted from these dispersions ($c_{polymer} \approx 1.9$ g/L) still showed a thermoresponsive behavior with $T_{cp} = 27$ °C. While for grad-S25 a salt concentration above 0.6 M was needed for observing a T_{cp}. These observations indicate that incorporation of thioether-containing sidechains gradually increases polymer hydrophobicity.

As expected, direct thionation exerted substantially stronger effects on solution behavior. Partial thionation shifted phase transitions toward significantly lower salt concentrations and lower temperatures compared to the corresponding thioether-containing systems. For example, PMeOMeOx-S24 already displayed thermoresponsive behavior between 0.1 and 0.6 M Na_2SO_4, while highly thionated PMeOMeOx-S43 was no longer fully soluble in pure water at 10 g/L. Nevertheless, saturated solutions extracted from these dispersions ($c_{polymer} \approx 0.8$ g/L) still exhibited distinct LCST-type transitions with $T_{cp} = 14$ °C. Compared to the thioether-containing copolymers, partially thionated polymers also displayed substantially broader phase transitions and increased turbidity already below T_{cp}, indicating that thionation perturbs polymer hydration much stronger than side-chain sulfur incorporation alone.

Fitting the salt concentration-dependent cloud point temperatures further highlighted differences in hydration stability and dehydration behavior between the investigated polymers (Figure 30, Table 6). For PVP, PMeOMeOx, PMeOMeOzi, and grad-S25, T_{cp} decreased approximately linearly with increasing Na_2SO_4 concentration, consistent with classical salting-out behavior induced by kosmotropic salts. Interestingly, PVP and PMeOMeOx exhibited nearly identical slopes. However, extrapolation toward zero salt concentration revealed quite different intrinsic T_{cp} values of approximately 195 °C for PVP and 271 °C for PMeOMeOx, may be considered as an indicator for the exceptionally high hydration stability of the methoxymethyl-functionalized POx system. In contrast,

PMeOMeOzi displayed a smaller slope relative to PMeOMeOx. The reduced slope observed for PMeOMeOzi may suggest that the more flexible POzi backbone and increased intrinsic hydrophobicity already favor partial dehydration in pure water, thereby lowering the relative impact of additional salt-induced destabilization. A similarly reduced slope was observed for the thioether-containing grad-S25 copolymer, consistent with increased hydrophobicity decreasing the sensitivity toward kosmotropic salt-induced dehydration.

In contrast to these approximately linear systems, PMeOMeOx-S24 deviated substantially from linear behavior. PMeOMeOx-S24 exhibited a pronounced nonlinear decrease in T_{cp} with increasing salt concentration together with significantly broadened phase transitions and turbidity already below T_{cp}. These observations indicate that thionation does not simply reduce hydration stability but fundamentally perturbs the hydration state and aggregation pathway of the polymer chains. Unlike thioether incorporation, which primarily shifts the hydrophilic–hydrophobic balance through side-chain modification, thionation simultaneously alters polarity, hydrogen-bonding capability, and chain dynamics of the amide-containing repeat units. Consequently, the phase behavior of partially thionated systems increasingly deviates from classical LCST behavior and instead reflects more complex pre-aggregation and dehydration processes already occurring below the macroscopic phase transition.

Closer inspection of the turbidity profiles further revealed pronounced mechanistic differences between gradient and partially thionated copolymers. Grad-S25 exhibited sharp and well-defined LCST transitions similar to pristine PMeOMeOx, indicating that thioether incorporation primarily shifts the overall hydrophobicity without altering the dehydration mechanism. [III] In contrast, below 0.4 M Na_2SO_4 concentration PMeOMeOx-S24 showed broader phase transitions over a wider temperature range, and lower initial transmittance below T_{cp} (Figure 31). Although both thioether incorporation and thionation increase sulfur content and reduce overall polymer hydrophilicity, they affect solution behavior through fundamentally different structural mechanisms. In thioether-containing copolymers, sulfur is introduced within the side chain and primarily increases hydrophobicity, while preserving the amide motif. In contrast, thionation directly converts amides into thioamides, decreasing overall polarity, reducing hydrogen-bonding capability, and affecting chain dynamics through increased C–N double-bond character. Consequently, thionation fundamentally changes the hydration and dehydration behavior of the polymer chains. In line with previous reports,[I,II] these combined effects appear to alter the pathway of phase separation compared to the more classical LCST-type behavior observed for thioether-containing copolymers. For PMeOMeOx-S24, increasing Na_2SO_4 concentration up to approximately 0.4 M initially decreased T_{cp}, narrowed the phase transition interval, and increased transition cooperativity, consistent with classical kosmotropic

salting-out behavior. In this concentration regime, sulfate-induced dehydration likely enhances interchain interactions and promotes compaction of the loosely associated aggregates already present below T_{cp}. As a consequence, less thermal energy is required to induce macroscopic phase separation, leading to a decrease in T_{cp}. Simultaneously, aggregate restructuring toward more homogeneous and compact states plausibly reduces structural heterogeneity, resulting in sharper and more cooperative LCST transitions.

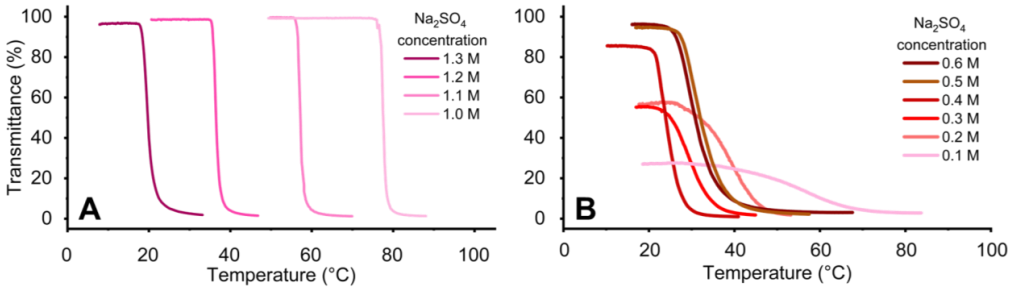

Figure 31 Turbidity heating curves of (A) PMeOMeOx and (B) PMeOMeOx-S24 in aqueous Na_2SO_4 solutions at varying salt concentrations. Increasing kosmotropic salt concentration progressively lowers the cloud point temperature (T_{cp}) for PMeOMeOx through salting-out effects. In contrast to pristine PMeOMeOx, the partially thionated polymer exhibits non-monotonic salt dependency.

Interestingly, above approximately 0.4 M Na_2SO_4, the behavior deviated from conventional LCST-type salting-out. Further increases in salt concentration resulted in increased transmittance below T_{cp} together with a slight increase of T_{cp}. This observation suggests a shift in the dominant mechanism governing solution behavior. At sufficiently high ionic strength, direct ion–polymer interactions likely become increasingly important in addition to indirect water-structuring effects especially for Na_2SO_4.[207] In particular, the highly polarizable thioamide sulfur atoms may participate in specific ion–dipole interactions, plausibly with soft Na^+ cations, thereby stabilizing dispersed aggregate states and partially counteracting dehydration-driven collapse.

Simultaneously, increased ionic strength may alter the internal organization of the aggregates, favoring formation of more compact and structurally defined colloidal assemblies with improved colloidal stability below T_{cp}. Such restructuring is consistent with the observed increase in transmittance and sharper phase transitions at elevated salt concentrations. Together with our previous observations for partially thionated POx systems,[I,II] these findings indicate that thionation fundamentally alters not only the hydration strength, but also the aggregation pathway and phase separation mechanism of POx in aqueous solution. For more accurate interpretation, further characterization including temperature-dependent NMR studies should be performed.

Overall, the observed phase behavior demonstrates that both increased hydrophobicity and modulation of hydrogen-bonding interactions can shift highly hydrophilic PVP, PMeOMeOx and possibly PMeOMeOzi systems toward thermoresponsive behavior. Importantly, the extent and mechanism of this shift strongly depend on the precise structural position of sulfur incorporation. Whereas thioether-containing sidechains gradually tune hydration primarily through hydrophobic effects, amide thionation perturbs polymer–water interactions far more profoundly by simultaneously altering polarity, hydrogen bonding, and chain dynamics. These findings therefore establish thionation as a post-polymerization approach capable of shifting highly hydrophilic polymers across the thermoresponsive boundary and revealing LCST-type behavior.

5 Conclusion & Outlook

In this thesis, thionation was established as a post-polymerization modification strategy for systematically tuning polymer–water interactions and thermoresponsive behavior in amide-containing polymers. By partially converting amide functionalities into thioamides, substantial changes in hydration, aggregation behavior, thermomechanical properties, and phase separation could be induced. The results demonstrate that amide modifications can profoundly perturb aqueous solution behavior through simultaneous changes in polarity, hydrogen-bonding capability, and conformational rigidity.

The presented work furthermore expands the currently accessible chemical space of thermoresponsive and highly hydrophilic poly(2-oxazoline) (POx) and poly(2-oxazine) (POzi) systems. Novel ether-functionalized monomers, namely 2-methoxymethyl-2-oxazoline (MeOMeOx) and 2-methoxymethyl-2-oxazine (MeOMeOzi), were successfully synthesized and polymerized via direct cationic ring-opening polymerization. These systems provided exceptionally hydrophilic POx/POzi platforms in which the hydration behavior could subsequently be modulated through sulfur incorporation either via thioether-containing copolymerization or direct thionation. In this regard, the work demonstrates that highly hydrophilic polymers may still possess “hidden” thermoresponsive behavior that becomes accessible upon perturbation of polymer–water interactions.

Across all investigated polymer systems, thionation generally reduced hydration stability and shifted phase transitions toward lower temperatures or lower salt concentrations. However, the resulting behavior was found to be strongly polymer-specific rather than universally transferable. The magnitude and mechanistic consequences of thionation depended sensitively on amide type, backbone structure, chain flexibility, side-chain hydrophobicity, and the intrinsic aggregation mechanism of the parent polymer. This became particularly evident through comparison of the structurally isomeric thermoresponsive polymers PNIPAM, P*i*PrOx, and PEtOzi, which possess identical repeat unit compositions but fundamentally different phase transition characteristics.

For PNIPAM, thionation weakened inter- and intramolecular hydrogen bonding interactions responsible for its cooperative LCST-Type II behavior, leading to suppression of thermal hysteresis, reduced transition cooperativity, and formation of comparatively small and well-defined mesoglobules upon phase separation. In

contrast, the LCST behavior of pristine P*i*PrOx is regulated by chain packing and side-chain organization. Here, thionation disrupted the conformational mobility necessary for ordered packing due to increased rigidity and effectively suppressed crystallization both in bulk and in aqueous solution, although residual slow ordering processes remained observable over extended timescales. PEtOzi, on the other hand, largely preserved its original solution behavior upon thionation while displaying phase transition shifts comparable to those observed previously for PEtOx. These observations indicate that side-chain identity predominantly governs the magnitude of LCST shifts, whereas backbone structure and amide type determine the qualitative nature of the phase transition itself, including hysteresis, cooperativity, aggregation pathways, and crystallization tendencies.

The studies on highly hydrophilic systems further demonstrated that thionation does not universally induce thermoresponsiveness, but rather shifts the balance between hydration and hydrophobic association toward the solubility limit of the polymer. Whereas partial thionation successfully introduced LCST-type behavior into otherwise fully water-soluble PVP, thionated PMeOx lost hydration stability without exhibiting reversible thermoresponsive phase separation. These findings establish that a minimum degree of side-chain hydrophobicity is required for LCST behavior. Comparison between thioether-containing copolymers and directly thionated analogues further revealed that thionation perturbs polymer hydration substantially stronger than side-chain sulfur incorporation alone. While thioether-containing systems primarily altered overall hydrophobicity, thionation simultaneously modified polarity, hydrogen-bonding capability, and chain rigidity, resulting in fundamentally different aggregation pathways and phase behavior.

Thermomechanical characterization demonstrated that thionation generally increased glass transition temperatures while decreasing thermal stability. The increase in T_g was attributed primarily to the enhanced double-bond character and higher rotational barrier of the thioamide C–N bond rather than simply to the presence of sulfur atoms. In agreement with this interpretation, molecular dynamics simulations indicated reduced polymer hydration, decreased solvent-accessible surface area, and more compact chain conformations upon thionation, corroborating the experimentally observed reduction in hydrogen bonding between the polymers and surrounding water molecules.

Taken together, the results of this thesis establish several broader design principles for thionated amide-based polymers. Thionation consistently weakens polymer–water hydrogen bonding and promotes dehydration and pre-aggregation. However, the resulting thermoresponsive behavior is ultimately dictated by the interplay between backbone structure, side-chain hydrophobicity, hydrogen bonding, chain packing, and conformational mobility. Consequently, thionation emerges not simply as another hydrophobic modification strategy, but as a

conceptually distinct molecular tool for directly perturbing the hydrogen-bonding landscape and chain dynamics of thermoresponsive polymers.

Despite the versatility demonstrated throughout this work, several limitations remain. Precise control over low thionation degrees proved challenging for many systems due to steric accessibility, solvent effects, and limitations associated with Lawesson's reagent. Furthermore, higher thionation degrees frequently pushed polymers beyond their solubility limits, restricting the accessible thermoresponsive window. Alternative thionation reagents may therefore provide important opportunities for future development.

Beyond the polymer systems investigated in this thesis, extending thionation concept toward other classes of thermoresponsive polymers represents a particularly promising direction. Thermoresponsive polypeptoids are especially attractive targets because hydrophilic members of this polymer class may possess "hidden" LCST behavior similar to PVP or PMeOMeOx systems. Partial thionation may therefore provide a powerful strategy for systematically perturbing hydration and revealing otherwise experimentally inaccessible thermoresponsive transitions in water-soluble polypeptoids. Likewise, extension of thionation strategies toward UCST-type polymers could open fundamentally new directions for responsive polymer design. In particular, poly(N-acryloyl glycinamide) (PNAGA), in which its UCST behavior is dominated by intermolecular hydrogen bonding, represents a highly intriguing candidate. Partial thionation of PNAGA-type systems could directly perturb these intermolecular interactions and thereby affect UCST behavior, cooperativity, and association strength in aqueous media.

Beyond the fundamental insights into aqueous solution behavior, the results presented here also open several promising directions for future research and applications. Owing to their enhanced metal-binding capability, thioamide-containing thermoresponsive polymers may represent attractive candidates for selective metal ion capture, water purification, or responsive separation materials. Moreover, thioamides may serve as versatile reactive intermediates for accessing additional functional polymer architectures inaccessible through conventional amide chemistry. The newly established MeOMeOx- and MeOMeOzi-based systems furthermore expand the toolbox of highly hydrophilic POx/POzi building blocks available for the design of amphiphilic block copolymers, nanostructured assemblies, and responsive biomaterials. More broadly, the findings of this thesis demonstrate that direct modulation of hydrogen bonding and hydration through selective sulfur incorporation constitutes a powerful and largely unexplored strategy for tailoring thermoresponsive behavior in aqueous polymer systems.

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