

Poly(2-oxazoline)s: A comprehensive overview of polymer structures and their physical properties

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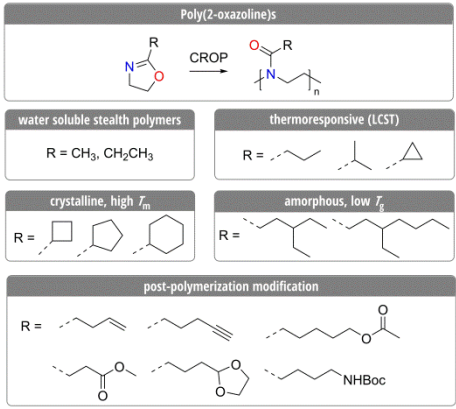
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Abstract

Poly(2-oxazoline)s (PAOx) are of increasing importance for a wide range of applications, mostly in the biomedical field. This review describes the synthesis of 2-oxazoline monomers, their cationic ring-opening polymerization (CROP) and gives a comprehensive overview of all reported PAOx homopolymers. In the second part of the review, the polymer properties of these PAOx homopolymers with varying side-chain structures are discussed. Altogether, this review intends to serve as encyclopedia for poly(2-oxazoline)s enabling the straightforward selection of a polymer structure with the desired properties for a certain application.

Keywords: Poly(2-oxazoline)s, cationic ring-opening polymerization, thermal properties, mechanical properties, surface properties, solution properties

Graphical abstract:



1. Introduction

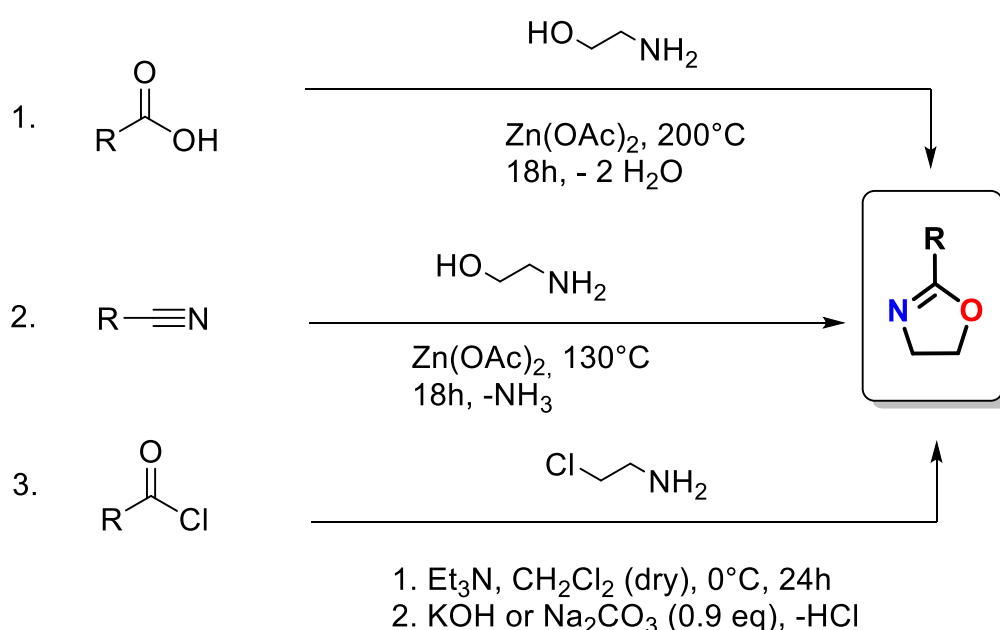
Over the years numerous 2-oxazolines have been used in the cationic ring-opening polymerization (CROP) to obtain the corresponding poly(2-oxazoline)s (PAOx, also referred to as POx, POz), since 1966, when they were reported for the first time by four independent research groups.¹⁻⁴ Besides their use as monomers, 2-oxazolines are also commonly used as ligands in asymmetric catalysis.⁵⁻⁷ In the last decade PAOx have received increasing interest, especially for biomedical applications. Several reviews on this topic have recently been published providing an excellent overview of the current state-of-the-art.⁸⁻¹⁴ Even though the application potential of PAOx is tremendous and has been the focus of many review articles, it is relatively difficult to get a complete overview of the different PAOx structures that have been reported as well as a systematic insight in the properties of the different PAOx.

Therefore, the present review aims to provide a comprehensive overview of PAOx homopolymers. The review will start with a brief overview of the different methods to synthesize 2-oxazoline monomers and the CROP mechanism leading to PAOx. The second part of the review comprises an as complete as possible overview of all reported 2-oxazoline monomers that have been polymerized via CROP followed by sections discussing the thermal, mechanical, surface and solution properties of the resulting PAOx homopolymers. We hope that this review will serve as guide for the selection of a specific PAOx for various future applications.

2. Synthesis of 2-oxazoline monomers

Except for some 4- and 5-substituted 2-oxazolines, which are not always polymerizable,¹⁵⁻¹⁸ 2-substituted 4,5-dihydrooxazoles, *i.e.* 2-substituted-2-oxazolines, referred to as 2-oxazolines in the following paragraphs, are the most commonly used cyclic imino ether monomers in

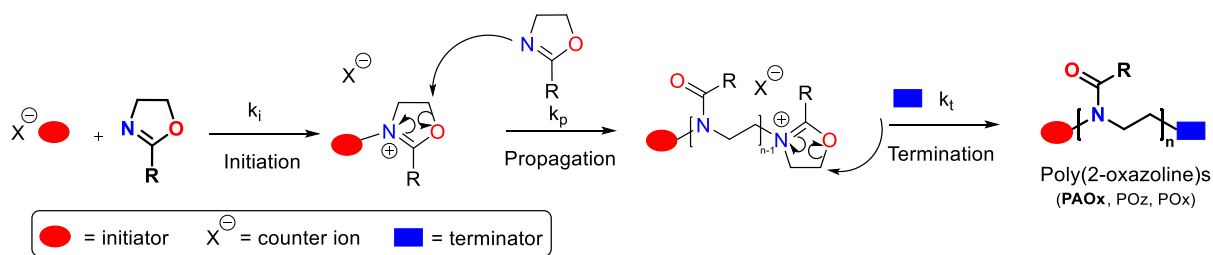
CROP. Typically 2-oxazolines are synthesized *via* the direct synthesis from non-activated carboxylic acids,¹⁹ the Witte-Seeliger synthesis from nitriles^{20, 21} or the Wenker method²², *i.e.* a two-step synthesis *via* cyclization of β -halo amides (see scheme 1). Other less common synthesis routes, *e.g.* α -deprotonation of 2-methyl-2-oxazoline followed by alkylation towards more complex 2-oxazolines, are also reported.^{23, 24} For a more detailed overview and description of the synthesis of 2-oxazolines one can refer to the recent review by Verbraeken *et al.*²⁵



Scheme 1. Overview of the synthesis of 2-oxazolines monomers. 1. Direct synthesis *via* non-activated carboxylic acids, 2. The Witte-Seeliger method starting from nitriles and 3. The (modified) Wenker method.

3. Cationic ring-opening polymerization of 2-oxazolines

The first CROP of 2-oxazolines was reported 50 years ago by four independent research groups, resulting in a new class of polymers, *i.e.* the PAOx.¹⁻⁴ The CROP mechanism consists of three steps, initiation, propagation and termination (scheme 2).



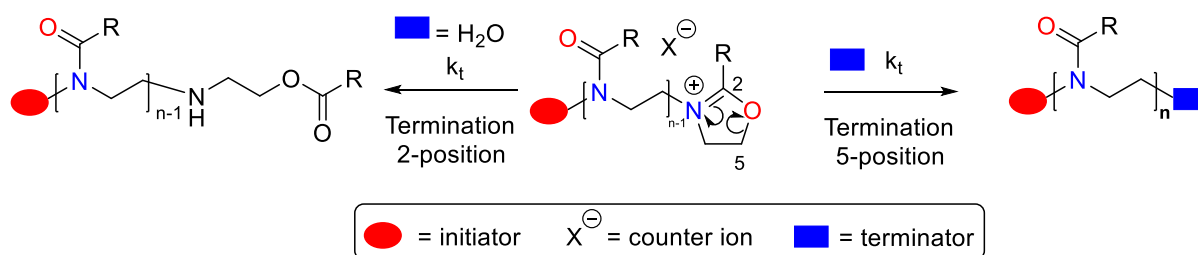
Scheme 2. The cationic ring-opening polymerization of 2-oxazolines, three-step mechanism with initiation, propagation and termination step.

In the first step a nucleophilic attack of the nitrogen lone pair of the 2-oxazoline monomer onto an electrophilic initiator forms an oxazolinium cation, initiating the polymerization reaction. Different initiator systems can be used including alkyl sulfonates such as methyl *p*-toluenesulfonate (MeOTs), which is most frequently found in literature, *p*-nitrobenzenesulfonates (nosylates) and trifluoromethanesulfonates (triflates), alkyl, benzyl and acetyl halides, oxazolinium salts and lewis acids.²⁶⁻³⁴ Also functional initiators can be used as long as they don't bear any nucleophilic character that could interfere with the CROP. An overview of various functional initiators that have been reported can be found in a review by Lapinte *et al.*³⁵

Subsequently, in the propagation step the 2-oxazoline monomer attacks the cationic oxazolinium intermediate, forming the poly(2-oxazoline) backbone by ring-opening and the formation of an amide while remaining the living oxazolinium chain-end. In an ideal polymerization no chain coupling, transfer or termination reactions occur resulting in the living character of the CROP of 2-oxazolines. The livingness of the polymerization results in control over molecular weight and narrow molar mass distribution, *i.e.* dispersity (\mathcal{D}), if the initiation is fast and quantitative. Unfortunately chain transfer reactions, such as β -elimination, and coupling reactions have been reported, which become especially important when aiming for high molar mass PAOx.³⁶⁻⁴⁰ A detailed overview of the CROP mechanism and chain transfer mechanism can be found in a recent review by Verbraeken *et al.*⁴¹ Furthermore,

the synthesis of well-defined PAOx with a narrow molar mass distribution requires thorough purification of the initiator, monomer and solvent used for the polymerization, to avoid the presence of nucleophilic impurities, including traces of moisture, that induce chain transfer and termination reactions. A recent patent, by Monnery *et al.*, shows the ability of synthesizing defined high molar mass poly(2-oxazoline)s by excluding these side reactions under critical reaction conditions, including specialized vacuum techniques and low temperature polymerization.⁴²

Finally, termination of the CROP of 2-oxazolines occurs *via* nucleophilic attack of an added termination agent on the living cationic chain-end. Most strong nucleophiles, such as methanolic potassium hydroxide, carboxylates and amines, can be used to terminate the polymerization reaction onto the 5-position of the activated 2-oxazoline ring (scheme 3). Termination on the 2-position – where the side-chain is located – has also been reported for other, weaker nucleophiles, particularly water as most important example.^{43, 44} With the CROP being a living/controlled polymerization mechanism, functionalities can be easily introduced upon termination with high end-group fidelity.



Scheme 3. Example of termination reaction respectively on the 2-position, *e.g.* with water, and on the 5-position of the oxazolinium chain-end.

Oxygen, nitrogen, sulfur and carbon centered nucleophiles, which exclusively terminate via reaction at the 5-position, can be used to introduce functional groups at the ω -chain-end as illustrated in table 1.

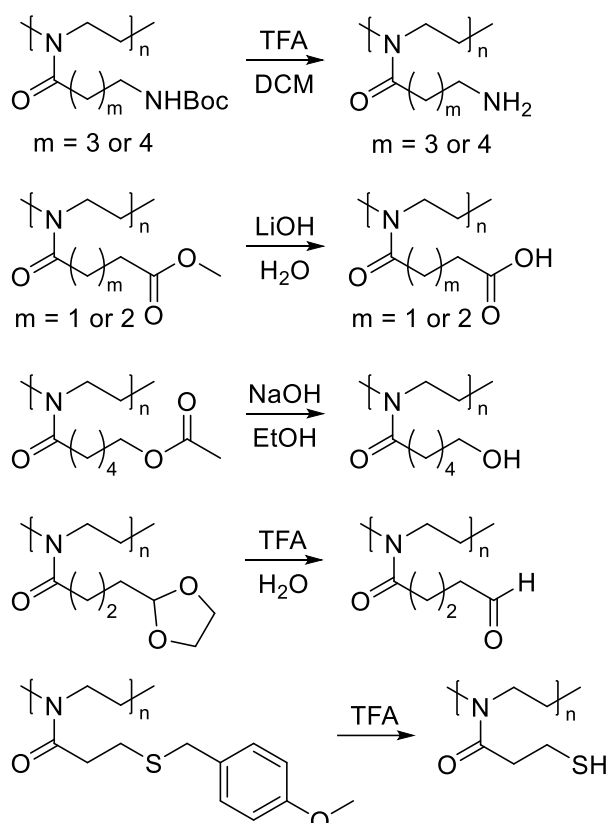
4. Poly(2-oxazoline) homopolymers

In the last 50 years an enormous range of PAOx with varying side-chain structures has been reported in the literature. Tables 1-6 provide a comprehensive overview of all reported 2-oxazoline monomers whose respective PAOx homopolymers have been prepared by CROP. The simplest and most widely studied PAOx are those with linear or branched alkyl side-chain (Tables 2 and 3). Table 4 shows reported 2-oxazolines with a phenyl or benzyl substituent. The propagation rate constants (k_p ; strictly speaking apparent k_p 's are listed as on information is provided on percentage of cationic propagating species (close to 100% with methyl tosylate) nor initiation efficiency) of 2-alkyl-2-oxazolines decrease with an increase of the inductive electron donating character of the 2-substituent. Therefore k_p decreases in the order MeOx > EtOx > *i*-PrOx. It is noteworthy that an increase of the side chain length for linear alkyl chains from ethyl to *n*-nonyl has a minimal influence on the k_p .⁸³ Amongst 2-oxazolines with a propyl side-chain k_p decreases in the order *c*-PrOx > *n*-PrOx > *i*-PrOx.⁸⁴ The CROP of 2-aryl-2-oxazolines is generally slower compared to 2-alkyl-2-oxazolines. Electron withdrawing *para*-substituents such as Cl or NO₂ slightly increase the k_p of 2-phenyl-2-oxazoline derivatives which can be explained by an increased reactivity of the cationic propagating species.⁸⁵ An exception to this general trend are *ortho*-fluoro substituted PhOx, whereby 2,6-DFOx is the fastest 2-oxazoline monomer in the living CROP reported to date.⁸⁶ This acceleration of the CROP of orthofluoro substituted PhOx is due to loss of the conjugation by out of plane twisting of the aryl substituent.

An important feature of PAOx is that functional groups can easily be incorporated in the polymer side-chains by employing functional monomers. The 2-oxazolines with a group 15 (N or P) or group 16 (O or S) heteroatom in the substituent that have been used for CROP are collected in Tables 5 and 6 respectively. It should be noted that for some of these monomers

the polymerization conditions have to be selected more carefully than for simple 2-alkyl-2-oxazolines. The monomers with a Boc protected amino group (C₄NHBocOx) could only be polymerized using an oxazolinium salt as initiator while the use of methyl triflate resulted in the formation of undefined low molar mass products.¹²⁷ Monomers with cyclic amines can be polymerized via the CROP mechanism yielding the corresponding PAOx with initiators such as methyl tosylate or methyl triflate resulting in a cationic propagating species, with the risk of termination by attack of the living chain end on the tertiary amine group. However initiators such as benzyl chloride, or methyl iodide result in covalent propagation that gives rise to a double isomerization ring-opening polymerization yielding polymers with a completely different structure having a cyclic urea in the main chain.^{128, 129} The CROP of the diethyl phosphonate functional monomer PhosOx gives polymers with two distinct molar masses. The underlying mechanism for this is not yet understood.¹³⁰ All the thioether containing monomers were found to show a limited polymerizability. Only well-defined polymers of relatively low molar mass could be obtained by keeping the conversion low, which could be due to attack of the sulfur on the propagating oxazolinium species resulting in termination and chain-transfer.^{99, 131} Similarly, the CROP of FuOx yielded a poorly defined polymer ascribed to unknown interfering side reactions.⁹⁹

The choice of monomers is only limited by the incompatibility of nucleophilic reactive groups, such as hydroxyls, amines, aldehydes, thiols and carboxylic acids, with the CROP process. However, PAOx with these functional groups can be prepared by the CROP of protected monomers followed by post-polymerization deprotection as shown in Scheme 4.



Scheme 4. Synthesis of PAOx with amino, carboxy, hydroxyl, aldehyde and thiol groups in the side-chains by post-polymerization deprotection. For references see the respective entries in tables 4 and 5. The synthesis of PAOx with thiol side-chains has only been reported for copolymers with EtOx. TFA = trifluoroacetic acid.

Table 7 shows 2-oxazolines with perfluoroalkyl substituents which can be used for the preparation of very hydrophobic PAOx. 2-Perfluoroalkyl-2-oxazolines were found to be much less reactive than 2-alkyl-2-oxazolines and therefore difficult to polymerize. Well-defined polymers of relatively low molar mass could only be obtained by using methyl triflate as initiator and not with methyl tosylate or methyl *p*-nitrobenzene sulfonate.¹⁴⁷ This limitation can be overcome by the introduction of an ethyl spacer between the 2-oxazoline ring and the perfluoroalkyl group to decouple the electron withdrawing effect of the perfluoroalkyl chain from the 2-oxazoline ring.⁹⁸

5. Thermal properties of poly(2-oxazoline) homopolymers

PAOx with hydrocarbon side-chains are stable up to temperatures of (at least) 300 °C^{87, 117} enabling applications over a broad temperature range. Poly(2-*n*-alkyl-2-oxazoline)s with varying length of the side-chains are ideal to study structure-property relationships. Figure 1 shows the glass transition temperatures (T_g) and melting temperatures (T_m) obtained from differential scanning calorimetry (DSC) of poly(2-*n*-alkyl-2-oxazoline)s with 1-17 carbon atoms in the side-chain.

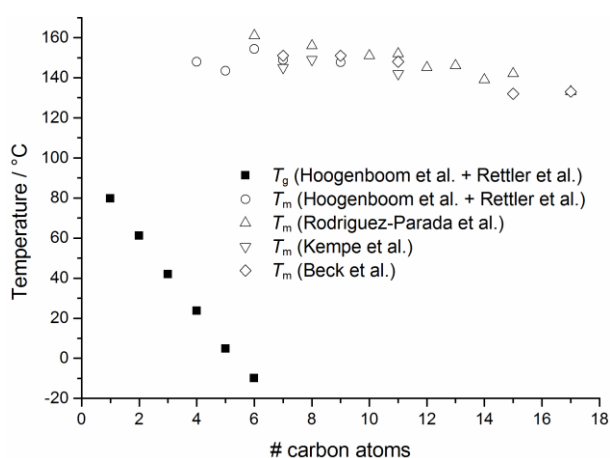
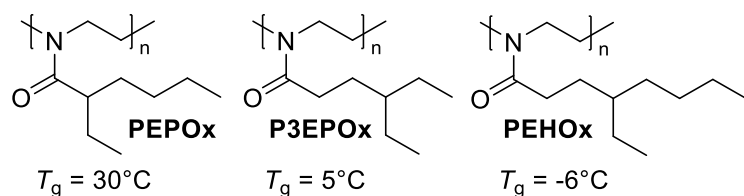


Figure 1. Glass transition and melting temperatures of poly(2-*n*-alkyl-2-oxazoline)s with varying side-chain length obtained from DSC. Data are taken from refs. 19, 83, 89, 98, 99

Polymers with 1-5 carbon atoms in the side-chain (PMeOx to *Pn*-PentOx) show a T_g that decreases linearly with increasing side-chain length which can be explained by increasing flexibility of the side-chains. For PMeOx, PEtOx and *Pn*-PrOx no melting peaks were observed by differential scanning calorimetry, while polymers with 4 or more carbon atoms in the side-chain were found to be semi-crystalline with a T_m around 150 °C independent of the side-chain length indicating side-chain crystallization. In contrast, Litt and co-workers³ reported melting temperatures also for PMeOx and *Pn*-PrOx by differential temperature analysis (DTA) based on a difference in birefringence. This discrepancy might originate from different processing resulting in alignment of the main-chains if enough time is given.^{150, 151} The fatty-acid based

PSoyOx revealed a much lower T_m (88.4 °C) than PAOx with long linear saturated alkyl side-chains due to the *cis*-double bonds in the side-chains that disturb the crystallization.¹⁰³ Fully amorphous PAOx with a low T_g can be prepared using monomers with branched alkyl side-chains as demonstrated for PEPOx, P3EPOx and PEHOx (Scheme 5), the latter being the amorphous poly(2-oxazoline) with the lowest reported T_g to date, being -6 °C.



Scheme 5. Structures and T_g s of PEPOx, P3EPOx and PEHOx.

PAOx with cycloalkyl side-chains are an interesting class of polymers. While Pc-PrOx is amorphous with a higher T_g (79 °C) than its linear analogue P*n*-PrOx,¹¹⁵ Pc-BuOx, Pc-PentOx and Pc-HexOx are semi-crystalline high performance polymers with a T_m of 243, 251 and 306 °C, respectively.¹¹⁷ Similarly high melting points have been reported for adamantyl-containing PAOx.¹¹⁸ Poly(2-*n*-perfluoroalkylethyl)-2-oxazoline)s represent very hydrophobic PAOx. Interestingly, their melting temperatures are much higher compared to their hydrocarbon analogues and unlike them, the melting points increase as the side-chain length increases (Figure 2).⁹⁸

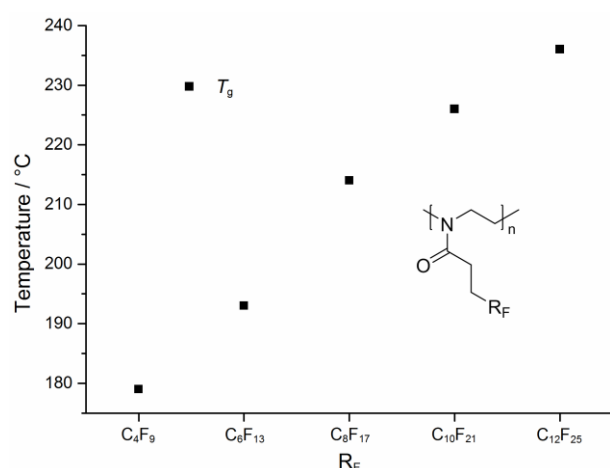


Figure 2. Glass transition temperatures of poly(2-*n*-perfluoroalkylethyl)-2-oxazoline)s obtained from DSC. Data are taken from ref. 98

The presence of the rigid aromatic phenyl ring in PPhOx leads to a higher T_g (103 – 107 °C)^{3, 19, 87} compared to poly(2-*n*-alkyl-2-oxazoline)s such as PMeOx or PEtOx. Significantly higher T_g values were found for polymers with two *ortho*-fluoro substituents on the phenyl ring with the highest values for P2,4,6-TFOx (T_g = 133 °C) and P2,3,4,5,6-PFOx (T_g = 135 °C).¹²³ All PAOx with functional groups in the side-chains whose thermal properties have been investigated were found to be amorphous and their glass transition temperatures are collected in table 8.

6. Mechanical properties of poly(2-oxazoline) homopolymers

There are only very few reports on the mechanical properties of PAOx as the majority of polymers have a rather low molar mass leading to very poor (brittle) mechanical properties, thereby obstructing mechanical testing. The mechanical properties of low molar mass poly(2-*n*-alkyl-2-oxazoline)s (DP = 60) have been reported based on nano-indentation on spin-coated polymer films. These measurements revealed that the mechanical properties are closely related to the thermal properties. Upon increasing the length of the alkyl side-chain from methyl to butyl, the elastic modulus decreases almost linearly^{89, 151} (Figure 3) related to the decrease in T_g (Figure 3).

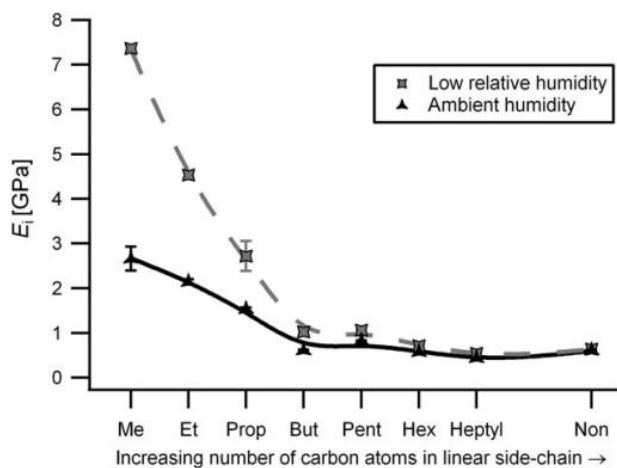


Figure 3. Indentation moduli of poly(2-*n*-alkyl-2-oxazoline)s with DP ~ 60 at low and ambient humidity. The lines are added to guide the eye only. Reproduced from Ref. 151 with permission from The Royal Society of Chemistry.

The polymers with more than 4 carbon atoms in the side-chain are semi-crystalline and have a T_g below ambient temperature and therefore the measurements were performed above their respective T_g resulting in moduli of ca. 0.8 GPa which is common for polymers tested between their glass transition and melting temperatures.¹⁵² It should be noted that the mechanical properties of PMeOx, PEtOx and P*n*-PrOx strongly depend on the humidity due to the hygroscopic nature of these polymers. As can be seen from Figure 3, the plasticizing effect of incorporated water reduces the indentation moduli.¹⁵¹ It is expected that more in depth mechanical properties of PAOx will become available in the near future based on the fact that well-defined high molar mass PAOx have become synthetically accessible recently.

7. Surface properties of poly(2-oxazoline) homopolymers

The surface properties of poly(2-*n*-alkyl-2-oxazoline)s are related to their thermal properties in a similar manner as their mechanical properties. Figure 4 shows the surface energies of poly(2-*n*-alkyl-2-oxazoline) thin films calculated from the surface angles using Neumann's equation of state.⁸⁹

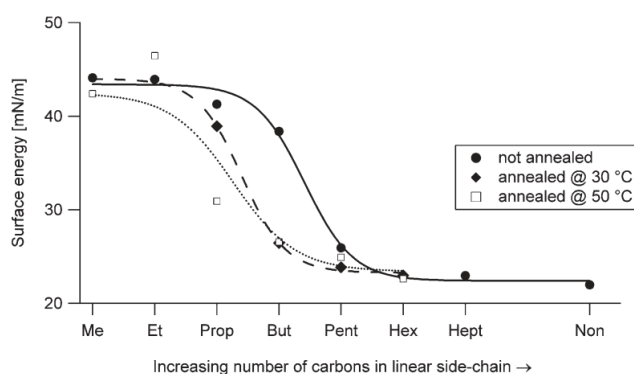


Figure 4. Surface energies of poly(2-*n*-alkyl-2-oxazoline)s with M/l = 100. The lines are sigmoidal fits to the data points. Reproduced from Ref. 89 with permission from WILEY-VCH.

Inspection of Figure 4 reveals a clear change in materials properties of the not annealed samples at *Pn*-BuOx which has a T_g close to ambient temperature. The polymers with 5 or more carbon atoms in the side-chain were measured above their respective T_g and show low surface energies, due to segregation of the longer side-chains to the surface, which is favored by the higher flexibility of the polymer chains. PMeOx, PEtOx and *Pn*-PrOx were measured below their respective T_g and cannot orient the side-chains to the surfaces, resulting in higher surface energies.⁸⁹ The surface energy of *Pn*-PrOx can be reduced by thermal annealing while no change was found for PMeOx and PEtOx even after annealing at 90 °C indicating that the methyl and ethyl side-chains are too short to fully cover the surface.⁸⁹ A similar surface energy as for poly(2-*n*-alkyl-2-oxazoline)s measured above their T_g was found for PPhOx (42.6 mNm⁻¹).¹²³ PAOx based on fluorophenyl oxazolines exhibited lower surface energies than PPhOx.¹²³ However, the surface energy does not continuously decrease with increasing fluorine substitution. A detailed look at the effect of the substitution pattern on the surface energy (Figure 5) demonstrates the importance of especially the *para*-fluoro substituent in lowering the surface energy.

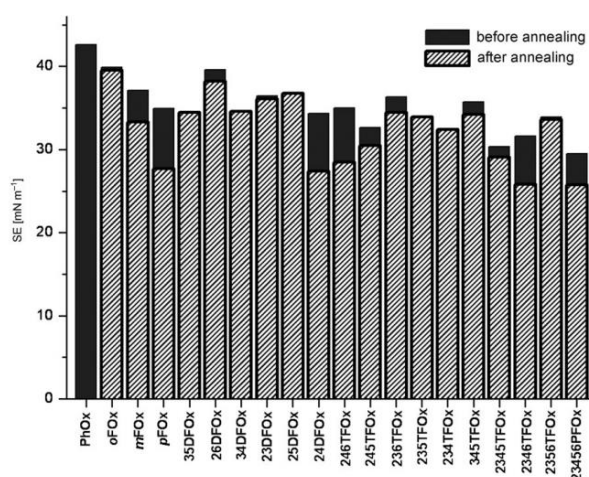


Figure 5. Surface energies (SEs) of the polymers of fluorophenyl oxazolines and PhOx before and after annealing (16 h, 140 °C). Reproduced from ref.123 with permission from WILEY-VCH.

Rodriguez-Parada et al.⁹⁸ investigated the behavior of PAOx with linear hydrocarbon and fluorocarbon side chains varying in length from 6 to 17 carbon atoms at the air-water interface in a Langmuir trough. Polymers with short hydrocarbon side chains (6-11 carbon atoms) were found to form fluid liquid like condensed monolayers in which the polymer backbone is at the water surface and the side chains are tilted toward the air. Polymers with longer side chains formed only rigid monolayers which tend to crystallize after the initial compression and Langmuir-Blodgett films of these materials could be prepared only with difficulty. Similar behavior was observed for polymers with fluorocarbon side chains, with the only difference that the same effects were observed at shorter side-chain lengths (usually 3 carbon atoms less), which can be explained by the higher hydrophobicity and rigidity of the fluorocarbon chains.⁹⁸

8. Solution properties of poly(2-oxazoline) homopolymers

The variation of the side-chain structure of PAOx enables the tuning of the properties from very hydrophilic (PMeOx) to very hydrophobic (long alkyl or perfluoro alkyl side-chains) polymers. Consequently, the solution behavior of PAOx strongly depends on the side-chain structure. Table 9 gives an overview of the solubility of various PAOx with hydrocarbon side-chains in water and common organic solvents.

In addition to the solvents listed in Table 9, sulfolane was found to be a good solvent for high molar mass PMeOx.¹⁵³ The semi-crystalline polymers Pc-BuOx, Pc-PentOx and Pc-HexOx show poor solubility in many common organic solvents, but are soluble in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and formic acid at ambient temperature that disrupt interchain interactions.¹¹⁷ The behavior of PAOx in aqueous solutions is influenced by the hydration of the polymer and the accompanied loss in entropy. With increasing temperature the entropy

loss increases and at the phase transition temperature it becomes more favorable to release the water molecules into the bulk water resulting in agglomeration of the polymers chains (Figure 6). Therefore many PAOx exhibit a lower critical solution temperature (LCST). Two comprehensive reviews about thermoresponsive PAOx by Weber et al¹⁵⁴ and Hoogenboom and Schlaad¹⁵⁵ give an excellent overview on these polymers and their solution behavior.

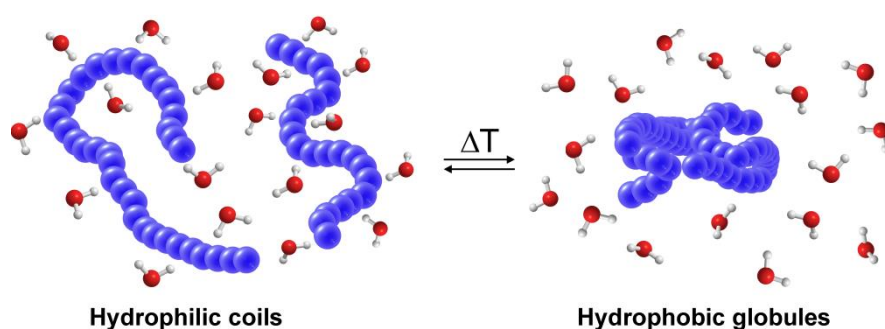


Figure 6. Schematic representation of a polymer phase transition in aqueous solution. Adapted from ref. 156 with permission from Elsevier.

While PMeOx, which has been claimed to be even more hydrophilic than PEG based on HPLC analysis⁷⁹ as well as based on the poor solubility of higher molar mass PMeOx in organic solvents like acetonitrile in which higher molar mass PEG is well soluble,¹⁵³ is fully water soluble from 0-100 °C, PAOx with longer alkyl side chains exhibit LCST behavior. Figure 7 shows the cloud point temperatures (T_{CP} , the temperature where the transmittance rapidly decreases due to agglomeration of the polymer chains) of PAOx with increasing hydrophobicity. It should be noted that the T_{CP} depends on the molar mass, the concentration, the polymer end-groups and the conditions of the measurement¹⁵⁷ and therefore comparisons of T_{CP} 's reported in the literature should be handled with care.

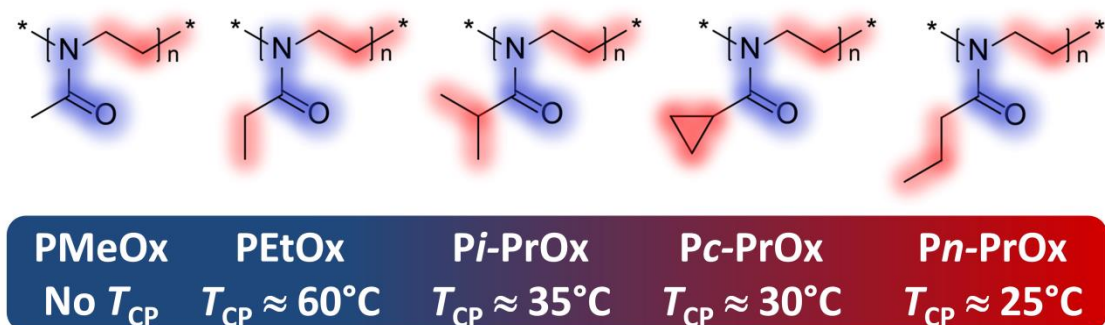


Figure 7. PAOx with hydrocarbon side-chains with increasing hydrophobicity (from left to right) and consequently decreasing cloud point temperature.

The LCST behavior of high molar mass PEtOx was first reported in 1988 by Lin et. al. with T_{CP} 's from 61-69 °C dependent on the concentration.⁹¹ Lowering the molar mass of PEtOx homopolymers results in a significant increase of the T_{CP} in aqueous solution.^{92, 93} Amongst thermoresponsive polymers those with a LCST close to body temperature are of special interest for applications in drug delivery or bioengineering.^{158, 159} Interestingly, PAOx with propyl side-chains namely *Pn*-PrOx, *Pc*-PrOx and *Pi*-PrOx belong to this class of polymers. It was first reported in 1992 that *Pi*-PrOx exhibits LCST behavior with the T_{CP} decreasing from 39 to 35 °C with increasing polymer concentration (0.1 – 1 wt%).¹⁰⁸ More detailed investigations of *Pi*-PrOx with varying molar mass revealed that the T_{CP} decreases with increasing molar mass and that the concentration dependence becomes less pronounced with increasing molar mass.^{107, 110, 160} All of these studies found the phase transition to be reversible with a small heating-cooling hysteresis. However, it was later discovered that the transition becomes irreversible after keeping the dispersion longer above the cloud point due to isothermal crystallization of the (partially) dehydrated polymer chains.^{106, 109} It was recently shown that cyclic *Pi*-PrOx exhibits a much higher T_{CP} compared to linear *Pi*-PrOx with the same molar mass.¹⁶¹ As much as 15 years after the LCST behavior of *Pi*-PrOx was discovered, it was

reported that *Pn*-PrOx also exhibits LCST behavior in aqueous solutions.⁹⁵ The T_{CP} was found to be more than 10 °C lower compared to *Pi*-PrOx with a similar molar mass which is in accordance with the higher hydrophobicity. As previously observed for *Pi*-PrOx, the T_{CP} of *Pn*-PrOx also decreases with increasing molar mass.⁹³ The cyclic side-chain structure of *Pc*-PrOx results in an intermediate hydrophobicity compared to *Pi*-PrOx and *Pn*-PrOx and consequently its T_{CP} in aqueous solution was found to be in between the T_{CP} 's observed for *Pi*-PrOx and *Pn*-PrOx.^{115, 116} In contrast to *Pi*-PrOx the phase transitions of the amorphous *Pn*-PrOx and *Pc*-PrOx are fully reversible, even when kept above T_{CP} for a prolonged time. PAOx with methyl ester side-chains were first reported 1968,³⁸ but it was only recently reported that these polymers exhibit thermoresponsive LCST behavior in aqueous solution.¹⁴² Their T_{CP} 's strongly depend on the length of the alkyl spacer. PC2MestOx shows a very similar solution behavior as PEtOx with a T_{CP} around 100 °C for a polymer with DP 100 while PC3MestOx exhibits a T_{CP} around 25 °C similar to *Pn*-PrOx. In contrast to the LCST behavior, there are no poly(2-oxazoline)s reported that show an upper critical solution temperature (UCST) in water. However, UCST behavior was observed for PAOx with phenyl, benzyl or alkyl side-chains longer than propyl in ethanol-water mixtures,¹¹² which results from the change in polarity of these non-ideal solvent mixtures upon heating.¹⁶² Figure 8 shows an overview of the solubility of various PAOx in ethanol-water mixtures.

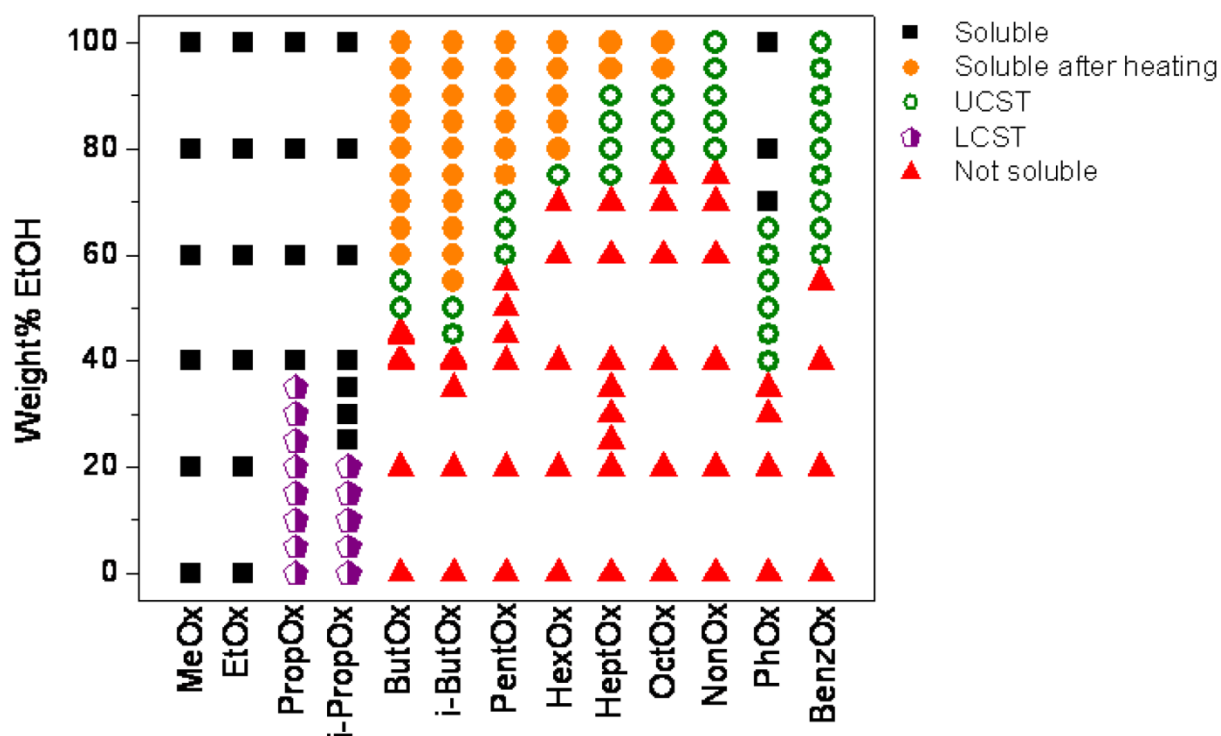


Figure 8. Solubility overview for poly(2-oxazoline)s with hydrocarbon side-chains in water-ethanol mixtures (5 mg/mL). Reproduced from ref. 112 with permission from MDPI AG.

9. Conclusions and outlook

In the last years PAOx have emerged as materials for biomedical and pharmaceutical applications, such as polymer-drug and polymer-protein conjugates, self-assembled carriers for drug delivery, solid dispersions, hydrogels, antibiofouling and antimicrobial surfaces, and wound healing.^{9, 11-14, 163} In the 50 years since the first reports on PAOx the CROP of more than one hundred different 2-oxazolines has been reported. In combination with the straightforward introduction of functional groups at the chain-ends, this allows the synthesis of a wide range of PAOx homo and copolymers with fine-tuned physical properties and chemical structures that can be further extended by post-polymerization modifications. The properties of PAOx range from amorphous polymers with glass transition temperatures well below ambient temperature to semi-crystalline polymers with melting points well above 200 °C. Some PAOx are very hydrophilic water-soluble polymers while others are very

hydrophobic. The toolbox for the construction of tailor-made PAOx that has been developed in the last decades should enable researchers to develop exciting new applications especially, but not exclusively, in the biomedical field. We hope that this review will serve as a reference guide for the selection of 2-oxazoline monomers for the preparation of PAOx with the desired physical properties and/or chemical functionality, by providing a comprehensive overview of the different monomers and corresponding polymer properties.

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Table 1 Terminating agents for the CROP of 2-oxazolines and structures of the resulting end-functionalized PAOx. The α -chain-end is shown as methyl group for reasons of brevity.

Terminating agent	Resulting PAOx	Refs.
MOH (M = Na or K)/MeOH or Na ₂ CO ₃ /H ₂ O/ Δ or (CH ₃) ₄ NOH/MeOH		44-46
+ base		47-51
		52
H ₂ N-R ¹		53-56
		57-60
		X = CH ₂ : 60-62 X = O: 63 X = NH: 64, 65 X = NBoc: 66, 67 X = NR ¹ : 65, 68
		69, 70
		29, 43
		71
base +		72
		73

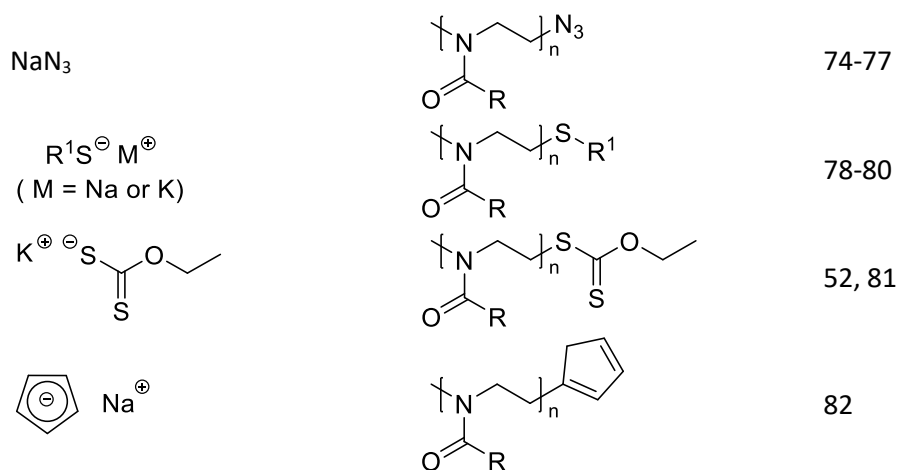


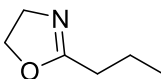
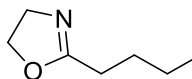
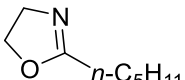
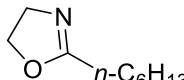
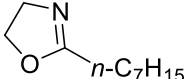
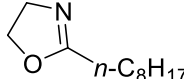
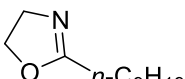
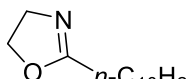
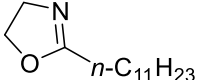
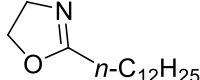
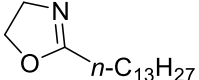
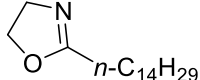
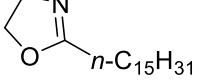
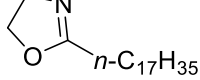
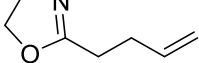
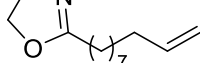
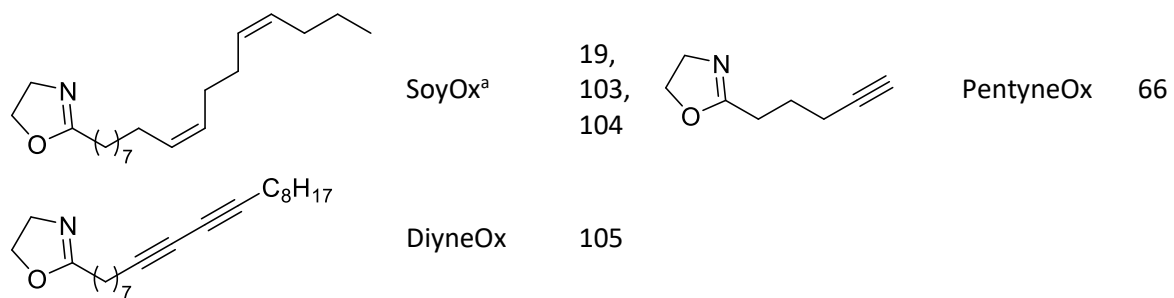


Table 2 2-Oxazolines with linear alkyl substituents without heteroatoms. References refer to the preparation and properties of the respective homopolymers. For DiyneOx only copolymerization has been reported.

Monomer	Abbr.	Ref.	Monomer	Abbr.	Ref.
	MeOx	3, 83, 87-89		EtOx	3, 83, 87-93
	<i>n</i> -PrOx	83, 84, 89, 93-97		<i>n</i> -BuOx	83, 89
	<i>n</i> -PentOx	83, 89		<i>n</i> -HexOx	89, 98
	<i>n</i> -HeptOx	19, 83, 89, 99		<i>n</i> -OctOx	98, 99
	<i>n</i> -NonOx	19, 83, 88, 89		DecOx	98
	UndecOx	19, 98-100		DodecOx	98
	TridecOx	98		TetradecOx	98
	PentadecOx	19, 98		HeptadecOx	19, 98
	ButenOx	101		DecenOx	102



^aSoyOx is based on soy-bean fatty acids and has on average 17 carbon atoms and 1.5 double bonds per monomer unit.

Table 3 2-Oxazolines with branched or cyclic alkyl substituents without heteroatoms. References refer to the preparation and properties of the respective homopolymers.

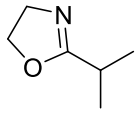
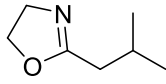
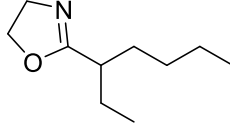
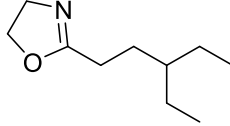
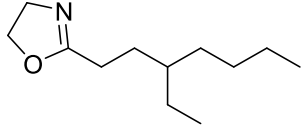
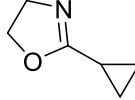
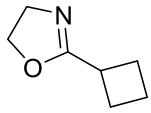
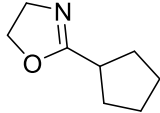
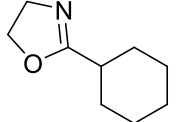
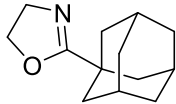
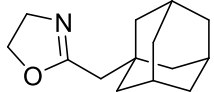
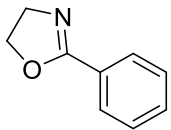
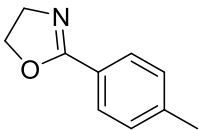
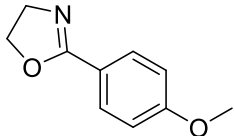
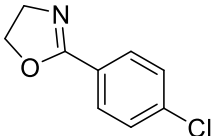
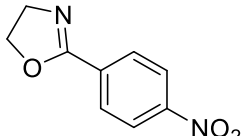
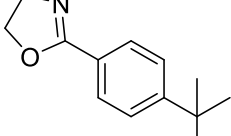
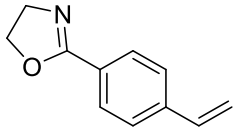
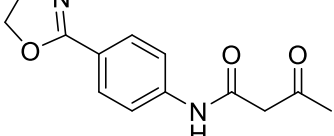
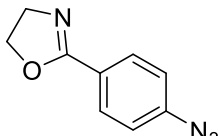
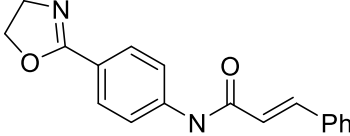
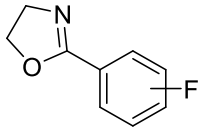
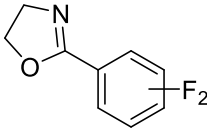
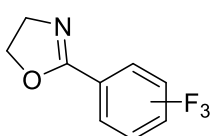
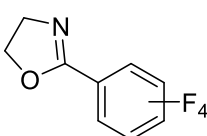
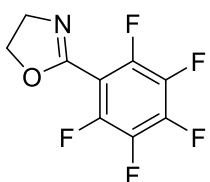
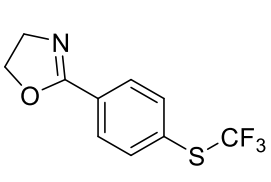
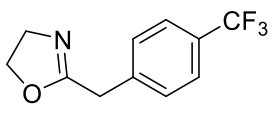
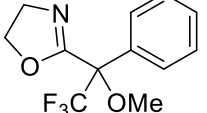
Monomer	Abbr.	Ref.	Monomer	Abbr.	Ref.
	<i>i</i> -PrOx	45, 84, 95, 106-110		<i>i</i> -BuOx	99, 111, 112
	EPOx	113		3EPOx	113
	EHOx	114		<i>c</i> -PrOx	84, 115, 116
	<i>c</i> -BuOx	117		<i>c</i> -PentOx	117
	<i>c</i> -HexOx	117		AdamOx	118
	MeAdamOx	118			

Table 4 2-Oxazolines with phenyl or benzyl substituents. References refer to the preparation and properties of the respective homopolymers. For *p*-N₃PhOx and CinamPhOx only copolymerizations have been reported.

Monomer	Abbr.	Ref.	Monomer	Abbr.	Ref.
	PhOx	3, 19, 85, 87, 88, 119, 120		<i>p</i> -MePhOx	85
	<i>p</i> -MeOPhOx	85		<i>p</i> -ClPhOx	85
	<i>p</i> -NO ₂ PhOx	85		<i>p</i> - <i>t</i> BuPhOx	99
	StyOx	121		AcAniOx	122
	<i>p</i> -N ₃ PhOx	105		CinamPhOx	105
	<i>o</i> -FOx <i>m</i> -FOx <i>p</i> -FOx	86, 123		2,3-DFOx 2,4-DFOx 2,5-DFOx 2,6-DFOx 3,4-DFOx 3,5-DFOx	86, 123
	2,3,4-TFOx 2,4,5-TFOx 2,4,6-TFOx 2,3,5-TFOx 2,3,6-TFOx 3,4,5-TFOx	123		2,3,4,5-TFOx 2,3,4,6-TFOx 2,3,5,6-TFOx	123
	2,3,4,5,6-PFOx	123		<i>p</i> -CF ₃ SPhOx	99
	<i>p</i> -CF ₃ BnOx	99		CF ₃ OMePhOx	99

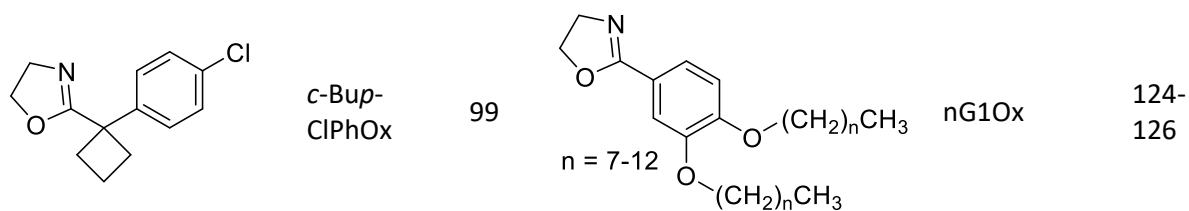


Table 5 2-Oxazolines with a nitrogen or phosphorous heteroatom in the substituent. References refer to the preparation and properties of the respective homopolymers.

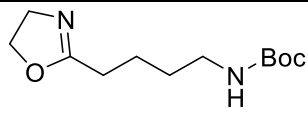
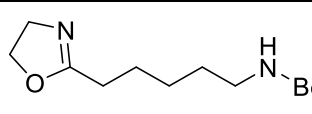
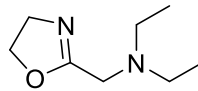
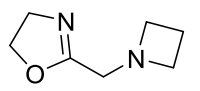
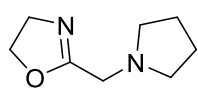
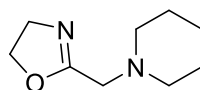
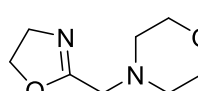
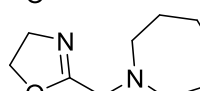
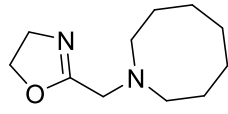
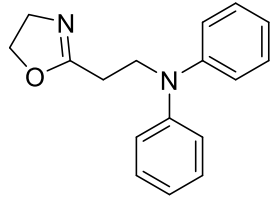
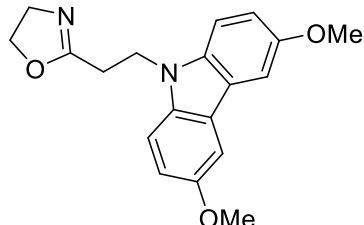
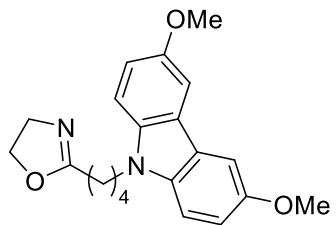
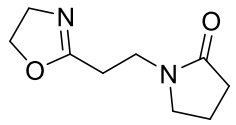
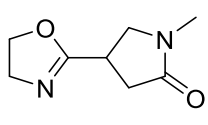
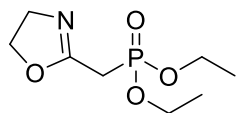
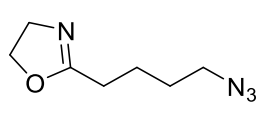
Monomer	Abbr.	Ref.	Monomer	Abbr.	Ref.
	C4NHBocOx	132		C5NHBocOx	127
	DEAOx	129		AzetOx	128
	PyrOx	128, 129		PipOx	128
	MorphOx	128		AzepOx	128
	AzocOx	128		EDPAOx	133
	C2CarbOx	134		C4CarbOx	134
	PyOx	135		MePyOx	136
	PhosOx	130		N3PentOx	137, 138

Table 6 2-Oxazolines with oxygen or sulfur heteroatoms in the substituent. References refer to the preparation and properties of the respective homopolymers. For HeptArIOx and MobsOx only copolymerizations have been reported.

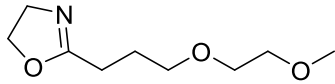
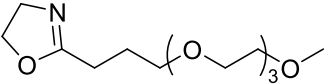
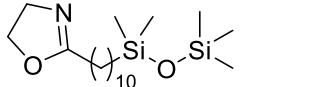
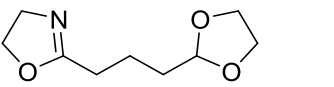
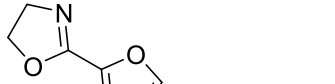
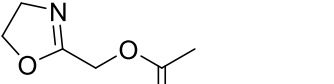
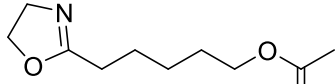
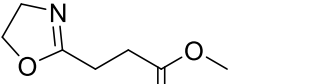
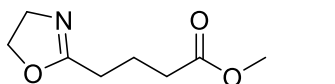
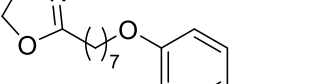
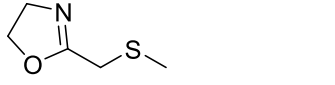
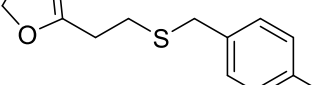
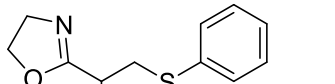
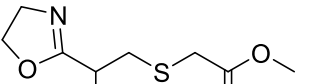
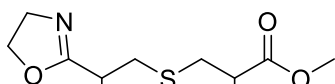
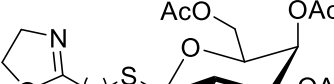
Monomer	Abbr.	Ref.	Monomer	Abbr.	Ref.
	MEGOx	135		TEGOx	135
	DecSiOx	139, 140		DPOx	23
	FuOx	99		C1AcOx	38
	C5AcOx	38		C2MestOx	38, 141, 142
	C3MestOx	142, 143		HeptArIOx	144
	MeSMeOx	99		MobsOx	145
	<i>i</i> -PrSPhOx	131		<i>i</i> -PrSMestOx	131
	CysOx	131		C2SGlycOx C10SGlycOx	146
			$n = 2 \text{ or } 10$		

Table 7 2-Oxazolines with a perfluoroalkyl substituent. References refer to the preparation and properties of the respective homopolymers.


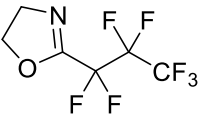
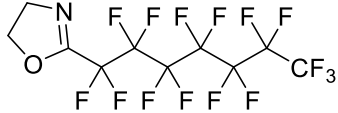
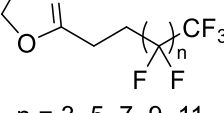
Monomer	Abbr.	Ref.	Monomer	Abbr.	Ref.
	C2F5Ox	147, 148		C3F7Ox	147, 148
	C7F15Ox	148		C2CnF(2n+1)Ox	98, 149
			n = 3, 5, 7, 9, 11		

Table 8. Glass transition temperatures of miscellaneous PAOx homopolymers

Polymer	$T_g / ^\circ\text{C}$	Ref.
PButenOx	17	101
PAcAniOx	35	122
P <i>p</i> -CF ₃ SPhOx	100	99
P <i>p</i> -CF ₃ BnOx	75	99
PCF ₃ OMePhOx	89	99
P <i>c</i> -Bu- <i>p</i> -ClPhOx	112	99
PC4NHBocOx	47	132
PC2CarbOx	130	134
PC4CarbOx	99	134
PC2MestOx	39	142
PC3MestOx	-1	142
PMeSMeOx	39	99

Table 9. Solubility of PAOx with hydrocarbon side-chains in water and various organic solvents. MeOH = methanol, CHCl₃ = chloroform, MeCN = acetonitrile, DMF = *N,N'*-Dimethylformamide, PhCl = Chlorobenzene, DMAc = *N,N'*-Dimethylacetamide. + = soluble, - = insoluble, +/- = partially soluble, LCST = lower critical solution temperature

	Water	MeOH	CHCl ₃	MeCN	DMF	PhCl	DMAc
PMeOx	+	+	-	+/- ^a		-	+
PEtOx	LCST	+	+	+	+	+	+
P <i>n</i> -PrOx	LCST	+	+	+		+	+
P <i>n</i> -NonOx	-		+	-	-		+
PPhOx	-		+	+	+		+
P <i>c</i> -BuOx	-	-		+/- ^b		+/- ^b	+/- ^b
P <i>c</i> -PentOx	-	-		-		-	-
P <i>c</i> -HexOx	-	-		-		+/- ^c	+/- ^c

^apoor solubility for molar mass >~ 20kDa, ^bsoluble after heating, precipitated on cooling. ^csoluble after heating