Poly(2-oxazoline)s: The Versatile Polymer Platform

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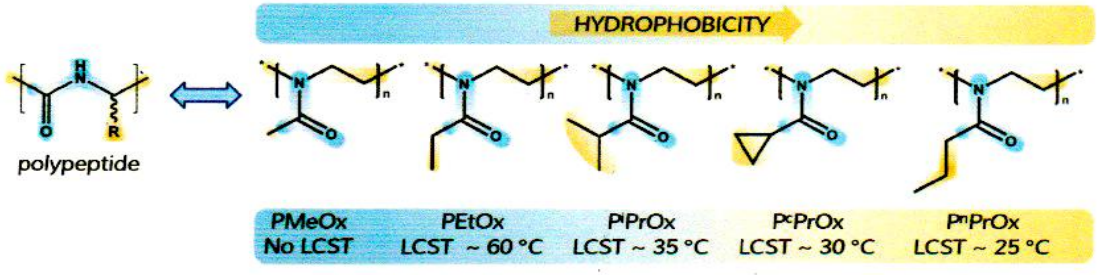
Abstract:
Poly(2-oxazoline)s (commonly abbreviated as PAOx, POZ, POx or POXA) represent an extraordinary polymer platform with highly tunable properties and excellent biocompatibility, making them interesting in a broad variety of applications. The ability to vary the solubility and properties of PAOx via the side-chains is a highly interesting feature to be exploited for determining structure property relationships. The polymer hydrophilicity can be tuned from superhydrophilic via thermoresponsive to hydrophobic.
End-functional PAOx can be used as macroinitiators for block copolymer synthesis, or to confer the polymer properties (anti-fouling, thermoresponsive, etc.) to a substrate of interest. The high stability of PAOx against degradation is an important advantage of this polymer class with respect to surface functionalization applications.
Besides surface and nanoparticle functionalization, clickable and amino end-functional PAOx allow further modification and conjugation to a wide range of moieties, e.g., probes or biomolecules, using a variety of highly efficient coupling chemistries. The present article intends to provide an overview of the aforementioned application possibilities of PAOx focusing on examples involving readily available PAOx derivatives.

Keywords: poly(2-oxazoline)s, polymer platform, biocompatibility, terminal modification, conjugation

Introduction

Poly(2-oxazoline)s (commonly abbreviated as PAOx, POZ, POx or POXA) represent an extraordinary polymer platform with highly tunable properties, making them interesting as basis for future materials. First reported 50 years ago, PAOx reemerged in the new millennium due to improved synthetic methodologies and excellent biocompatibility, allowing their use in a broad variety of applications.[1]
The structural analogy of PAOx with natural polypeptides accounts for their excellent biocompatibility and stealth-behavior i.e. PAOx can be used to suppress interactions with proteins and cells which, in fact, is the key property that was at the basis of the wide-spread use of poly(ethylene glycol) (PEG). The properties of PAOx can be adjusted by simply varying the polymer side-chains. Glass transition temperature (Tg) can be varied from -10 to 80 °C using simple monomers2 while solubility can be tuned from highly water soluble (poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl2-oxazoline) (PEtOx)) to thermoresponsive in water (poly(2-propyl-2-oxazoline) (PPrOx) derivatives) or water insoluble (PAOx with butyl of longer side chains) (Figure 1).

Figure 1. A series of PAOx derivatives displaying their structural analogy with polypeptides and their amphiphilic character. PAOx cover a broad lower critical solution temperature (LCST) range that can be finely tuned by copolymerization. PiPrOx and PnPrOx are structural isomers and potential alternatives to PNIPAM (LCST = 32 °C) (Adapted with permission from ref. 3).



PAOx can be prepared via living cationic ringopening polymerization resulting in well-defined polymers with controlled end-groups that can be installed through initiation and termination (Figure 2). Under appropriate polymerization conditions, each initiator molecule initiates one polymer chain and all chains grow with a similar rate while chain transfer and chain termination do not occur, or are strongly suppressed. As a result, all polymer chains will have similar chain length and the ratio of monomer to initiator will determine the degree of polymerization (DP) at a certain monomer conversion.

Figure 2. Overview of the cationic ring-opening polymerization (CROP) of 2-substituted-2-oxazolines, displaying the facile introduction of functionality at both the polymer chain-ends and side-chains.

Structure-property screening and formulation

The ability to vary the solubility and properties of PAOx via the side-chains is a highly interesting feature to be exploited for determining structure property relationships. Especially, the comparison of PMeOx, PEtOx and PnPrOx allows screening over a wide range of aqueous solubility, from PMeOx that is more hydrophilic than PEG, via PEtOx that has similar aqueous solubility as PEG to PnPrOx that is only soluble in water below 25° C, above which it undergoes an LCST transition. PMeOx-OH, PEtOx-OH and PnPrOx-OH with a DP of 100 and a hydroxyl group at the omega-terminus are available in the TCI catalog (Figure 3), and provide an excellent platform for deriving fundamental structure property relationships, either for direct formulation or for further modification and coupling reactions.

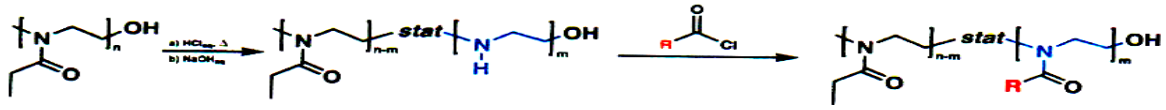


Figure 3. Hydroxy-terminated poly(2-oxazoline)s available in the TCI catalog.

The hydrogen bonding layer-by-layer assembly of PAOx with tannic acid was reported to be strongly dependent on the hydrophilicity of the PAOx, as PMeOx revealed purely enthalpic, hydrogen bonding driven assembly while PnPrOx showed a purely entropy driven assembly based on the release of hydrating water molecules. PEtOx exhibited an intermediate behavior.[4] Furthermore, Khutoryanskiy et al. functionalized SiO_2 nanoparticles with PMeOx, PEtOx and PnPrOx and investigated their permeation and diffusion through mucosal tissue.[5] The authors found a clear correlation between polymer hydrophilicity and permeability through the mucosal barrier, whereby the most hydrophilic PMeOx-grafted SiO_2 nanoparticles permeated significantly faster and deeper into the mucosa than their more hydrophobic PEtOx and PnPrOx-grafted counterparts. A final example consists of the grafting of PMeOx, PEtOx or PnPrOx on gold nanoparticles, revealing that their aggregation behavior can be strongly altered by changing the PAOx side chains.[6]

Poly(2-oxazoline) partial hydrolysis

Defined PAOx homopolymers can also be used for (partial) hydrolysis,[7] yielding poly(2-oxazoline)-copolyethylenimine copolymers or linear polyethylenimine (L-PEI).[8] Partially hydrolyzed PAOx may serve as functional materials in which the secondary amine units in the main chains can be further modified to, e.g., install methyl ester functionalities as additional reactive handles (see Figure 4).[9] Full hydrolysis followed by full reacylation has also been demonstrated to yield novel PAOx that are not easily attainable via CROP.[10] Furthermore, partially hydrolyzed PnPrOx has been exploited as thermoresponsive gene delivery vector.[11]

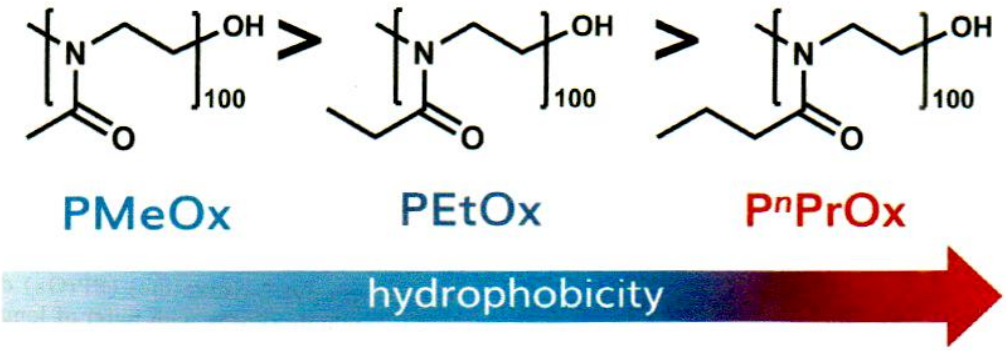


Figure 4. Partial hydrolysis of poly(2-ethyl-2-oxazoline) and subsequent functionalization.

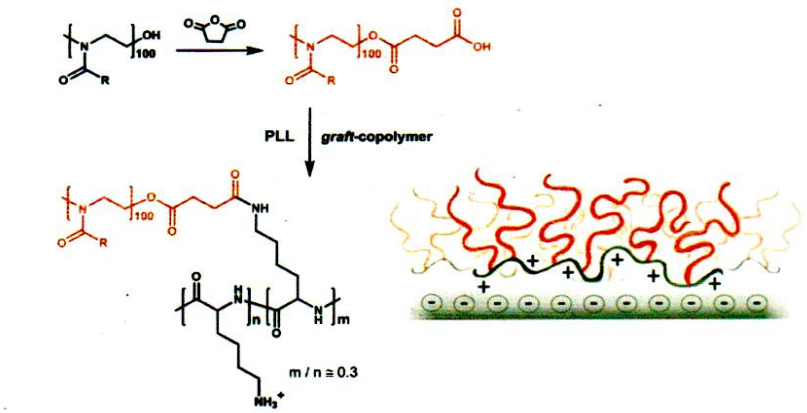
End-group modification

Chain-end functionalized PAOx offer an excellent platform for derivatization at the polymer termini allowing, e.g., facile grafting to (bio)molecules, surfaces and particles. In virtue of their high stability and biocompatibility, PAOx-functionalized surfaces[12] and nanoparticles[6] have potential uses in a variety of applications including implants, biosensors, imaging, or drug delivery.[3]

In analogy to PEG, end-functional PAOx have been successfully conjugated to biologicals for halflife extension, protection against degradation and immunogenicity prevention.[3,13] With over fifteen PEGylated pharmaceuticals in the market, PEG has proven extremely effective; however, its immunogenicity has become a significant issue, limiting further development of novel PEGylated therapeutics.[14] Thus, considering the biocompatibility and versatility of PAOx, PAOxylation or POZylation has been proposed as the new generation PEGylation.[14a,15]

The previously mentioned PEtOx and PMeOx-OH have been used for conjugation to polylysine (PLL), after conversion of the hydroxyl group to a carboxyl group via ring-opening of succinic anhydride. Subsequent coating of the PAOx-PLL induced efficient non-fouling properties to the substrate, whereby the PMeOx-g-PLL resulted in more efficient suppression of protein and cell adhesion compared to PEG-PLL and PEtOx-PLL (Figure 5).[16]

Figure 5. Surface functionalization with brush-forming PLL graft copolymers with different side-chain compositions (Adapted with permission from ref. 16a).



PEtOx-OH has also been demonstrated as efficient initiator for the controlled ring-opening of cyclic esters, directly yielding amphiphilic block copolymers.[17] Such block copolymers may be utilized for the encapsulation of drugs and their slow release based on hydrolysis of the polyester block.

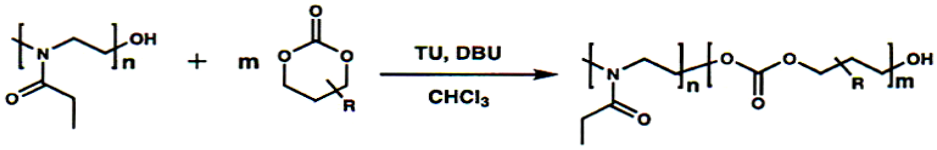


Figure 6. Schematic representation of the synthetic method for the preparation of block copolymers composed of 2-oxazolines and (functional) 6-membered cyclic carbonates.[17]

Besides the hydroxyl end-groups, azides and amino end-groups can be installed in PAOx through termination and post-polymerization functionalization, further expanding the conjugation possibilities.[18] Clickable PAOx-N_3 polymers enable efficient further modification via copper(I) catalyzed azide-alkyne cycloadditions with alkyne functionalized compounds, substrates or materials, as well as through strain-promoted azide-alkyne cycloadditions with strained alkynes.[19]

PMeOx and PEtOx with amine (-NH_2) endfunctionalities allow the conjugation of the polymer to a wide range of moieties and substrates. PAOx-NH_2 can be easily reacted through a variety of chemistries such as activated esters, or iso(thio)cyanates. For example, substrates decorated with epoxides have been rendered protein repellent or antifouling by reaction with PEtOx-NH_2. [20] The distinctly high chemical stability of PAOx makes them especially interesting for surface functionalization.[21]

Figure 7 showcases some of the chemistries that enable the formation of stable poly(2-oxazoline) conjugates based on these functional hydrophilic polymers, which are currently available in the TCI catalog.

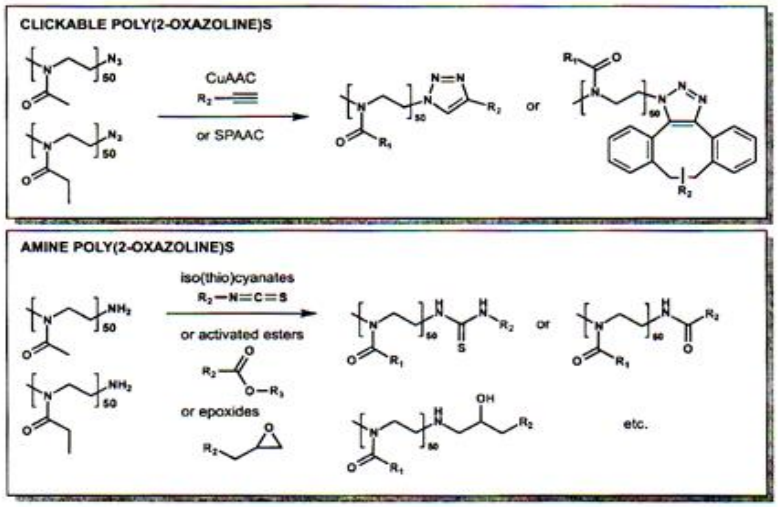


Figure 7. Conjugation reactions involving clickable and amine-functional poly(2-oxazoline)s. Amine-terminated poly(2-oxazoline)s can be used in combination with multiple other functional groups such as anhydrides, carbonates, aldehydes, etc.

Conclusions

The biocompatibility, tunable properties and high functionalization possibilities of PAOx make them a very attractive polymer platform for a broad spectrum of applications, ranging from biomedicine to smart materials and from personal care, via cosmetics to pharmaceuticals. The availability of PMeOx-OH, PEtOx-OH and PnPrOxOH with DP100 at TCI allows fast and efficient screening of the effect of polymer solubility on their formulation behavior and effectiveness for various applications. Moreover, they may serve as starting materials for the controlled (partial) hydrolysis towards functional PAOx. The chain-end-functionalized PAOx that are available with hydroxyl, azide and amino end-groups allow further modification and conjugation to a wide range of moieties, e.g., biomolecules such as proteins and surfaces or (nano)particles.

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