Poly(2-oxazoline)s

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Poly(2-oxazoline)s: A Polymer Class with Numerous Potential Applications

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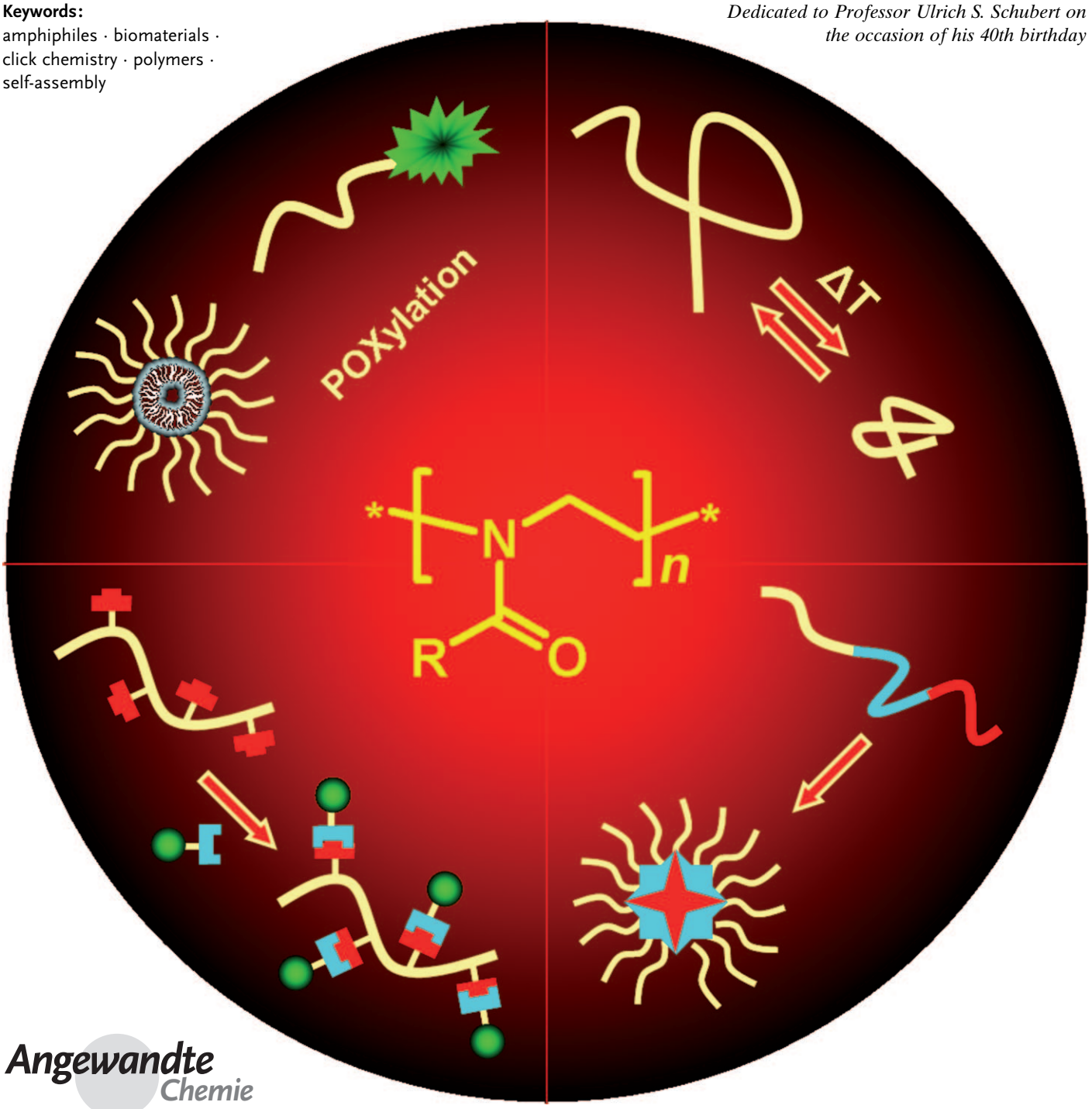
amphiphiles · biomaterials · click chemistry · polymers · self-assembly

Dedicated to Professor Ulrich S. Schubert on the occasion of his 40th birthday



The living cationic ring-opening polymerization of 2-oxazolines has been studied in great detail since its discovery in 1966. The versatility of this living polymerization method allows copolymerization of a variety of 2-oxazoline monomers to give a range of tunable polymer properties that enable, for example, hydrophilic, hydrophobic, fluorophilic, as well as hard and soft materials to be obtained. However, this class of polymers was almost forgotten in the 1980s and 1990s because of their long reaction times and limited application possibilities. In the new millennium, a revival of poly(2-oxazoline)s has arisen because of their potential use as biomaterials and thermoresponsive materials, as well as the easy access to defined amphiphilic structures for (hierarchical) self-assembly. Recent developments that illustrate the potential of poly(2-oxazoline)s are discussed in this Review. In addition, the promising combination of poly(2-oxazoline)s and click chemistry is illustrated.

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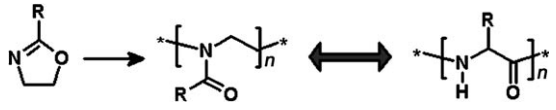
1. Introduction

The synthesis of well-defined polymer structures is essential for the study of interactions between macromolecules and biological systems, tuneable stimuli-responsive materials, as well as hierarchical self-assembly. In an ideal case, a one-pot synthetic procedure allows accurate control over a wide range of polymer architectures, monomer composition, and distribution as well as polymer properties such as the hydrophilic/hydrophobic ratio. The most commonly used polymerization methods in contemporary research are controlled radical polymerization techniques, which, unfortunately, do not meet this ideal case, since intermediate purification is required for the preparation of well-defined block copolymers. In contrast, living ionic polymerizations remain living up to near-quantitative conversion as a consequence of repulsion between the charged living chain ends, which allows the sequential addition of different monomers for the preparation of block copolymers.

The cationic ring-opening polymerization of 2-oxazolines was discovered in the middle of the 1960s by four independent research groups.[1–4] The resulting polyamides can be regarded as analogues of poly(amino acid)s, that is, pseudopeptides, as shown in Scheme 1. The living cationic ring-opening polymerization of 2-oxazolines provides easy and direct access to a wide variety of well-defined polymers, in which the end-group functionality can be controlled during the initiation and termination steps. Furthermore, the properties of poly(2-oxazoline)s can be tuned simply by varying the side chain of the 2-oxazoline monomer. The synthesis and polymerization mechanisms of a wide variety of 2-oxazoline monomers have been discussed in excellent reviews by Kobayashi,[5] Aoi and Okada,[6] as well as Kobayashi and Uyama.[7] Furthermore, the early possible applications of poly(2-oxazoline)s as stabilizers/surfactants, compatibilizers, and thermosettings were addressed by Kobayashi and Uyama.[8] The reader is also directed to more recent overviews of synthetic aspects of poly(2-oxazoline)s that focus on side-chain and end-group functionalization[9] as well as the synthesis and properties of block, gradient, and statistical copolymers.[10]

In recent years, the use of poly(2-oxazoline)s in biomedical applications[11] has evolved as a result of their biocompatibility as well as their stealth behavior (see Section 2.1) being similar to that of poly(ethylene oxide) (PEO). Furthermore, the discovery that poly(2-ethyl-2-oxazoline) (PEtOx) exhibits a lower critical solution temperature in water[12] opened up a completely new research area on thermoresponsive materials. Furthermore, the easy access to hydrophilic, hydrophobic, and fluorophilic polymers by simply changing the side chain of the monomer stimulated investigations into the synthesis and self-assembly of a range of amphiphilic copolymer structures.

These recently emerging applications of poly(2-oxazoline)s are discussed in this Review. In addition, an overview of recent efforts to use click chemistry to prepare functional poly(2-oxazoline)s and to combine poly(2-oxazoline)s with other polymer structures is provided.



Scheme 1. Polymerization of 2-oxazolines as well as the structural analogy with poly(amino acid)s.

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2. Biomedical Applications

2.1. Blood Clearance, Biodistribution, and Protein Adsorption

The biocompatibility of poly(2-methyl-2-oxazoline) (PMeOx) was demonstrated in 1989 by Goddard through intraveneous administration in mice.[13] ^{125}I-labeled polymers were found to be excreted from mice without significant accumulation in organs, although some, presumably high-molecular-weight, polymer was found in skin and muscle tissue. More recent studies by Jordan and co-workers on the biodistribution and excretion of well-defined radiolabeled PMeOx and PEtOx in mice demonstrated no accumulation in tissue and rapid clearance from the bloodstream.[14]

Dejardin and co-workers reported in 1989 that the adsorption of a poly(2-methyl-2-oxazoline)-*block*-poly(ethylene oxide)-*block*-poly(2-methyl-2-oxazoline) (PMeOx-*b*-PEO-*b*-PMeOx) triblock copolymer on silica particles suppressed platelet adhesion and fibrinogen adsorption.[15] However, at that time it could not be distinguished whether the protein-repellent properties were due to the PEO, PMeOx, or a combination of both. Nonetheless, this was a first indication of the potential "stealth" behavior of PMeOx, that is, suppression of all interactions with the body—such as with proteins and the immune system. Unambiguous proof of the biocompatibility and stealth behavior of PMeOx- and PEtOx-decorated liposomes was provided by Zalipsky and co-workers.[16,17] In vivo studies of these liposomes in rats and mice revealed enhanced circulation times, with similar blood-clearance rates being found for PMeOx and PEO, while PEtOx was removed somewhat faster (Figure 1). The liposomes accumulated mainly in the liver, kidney, and spleen, similar to PEO lyposomes.

The in vitro blood compatibility of PEtOx was demonstrated by Chung and co-workers.[18] A thin layer of PEtOx attached to a polyurethane film suppressed platelet adhesion to the same extent as a PEO layer, thereby indicating similar stealth behavior for PEtOx and PEO. In addition, Konradi et al. found that surfaces coated with PMeOx showed a similar adsorption of proteins and bacteria in vitro as PEO-coated surfaces.[19,20]

Furthermore, PEtOx was found to increase the biocompatibility of the hydrogels, thereby resulting in enhanced in vitro cell viability.[21] The importance of the molecular weight of the polymer is evident from a report by Rühe and co-workers, who demonstrated that a glass-surface-grafted layer of high-molecular-weight ($M_w = 380$ kDa; all previous studies were based on polymers with $M_n < 20$ kDa) PEtOx promotes the formation of a dense layer of healthy endothelial cells on the surface.[22]

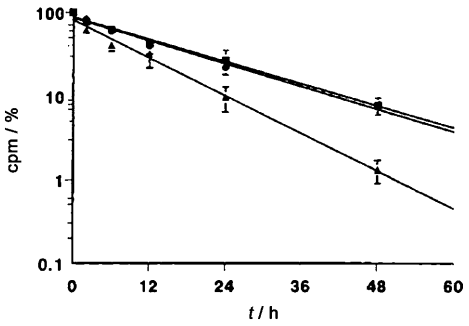

Figure 1. In vivo elimination of polymer-decorated liposomes from the blood of mice. The pharmacokinetic curves are similar and show enhanced circulation times for PMeOx (●) and PEO (■) as well as a somewhat faster clearance for PEtOx (▲). Reprinted from Ref. [17].

The biocompatibility, stealth behavior, and biodistribution of PMeOx closely resemble the beneficial properties of PEO that boosted its widespread use in biomedical applications. It should be noted that PMeOx is more hydrophilic than either PEtOx or PEO,[23,24] which might complicate conjugation reactions in apolar organic solvents. Nonetheless, PMeOx has great potential for use in biomedical applications, although in-depth studies have to be performed to further evaluate the fate and possible degradation pathways when used in vivo. The potential formation of poly(ethylene imine) residues by enzymatic degradation of the amide bonds of poly(2-oxazoline)s[25] have to be studied in detail in particular, since copolymers of 2-ethyl-2-oxazoline and ethylene imine are known to exhibit higher cytotoxicity than PEtOx.[26]

2.2. Drug and Protein Conjugates of Poly(2-oxazoline)

The conjugation of polymers to drugs is a well-established strategy in drug delivery to enhance the solubility of the drug and increase the circulation time in the body, while at the same time lowering the immunogenicity.[27] In addition, targeting groups can be included in the polymer to deliver the drug to a specific tissue or cell.

The first report of PMeOx–peptide conjugation dates back to the 1990 study by Saegusa and co-workers.[28] PMeOx was coupled to bovine liver catalase, and it was demonstrated that the remaining enzyme activity depended on both the molecular weight of the polymer as well as the extent of modification. The enzyme activity was also retained in organic solvents, such as chloroform and benzene, and results from the solubility of the polymer. Shortly after, the first PMeOx– and PEtOx–peptide conjugates were reported, and it was demonstrated that the affinity of the peptide for antibodies was retained in the conjugates.[29] As already stated in Section 2.1, Jordan and co-workers evaluated the biodistribution and excretion of PMeOx and PEtOx conjugates with an ^{111}In radiolabel.[14] A similar PEtOx polymer with a chelating end group was conjugated through its side chain

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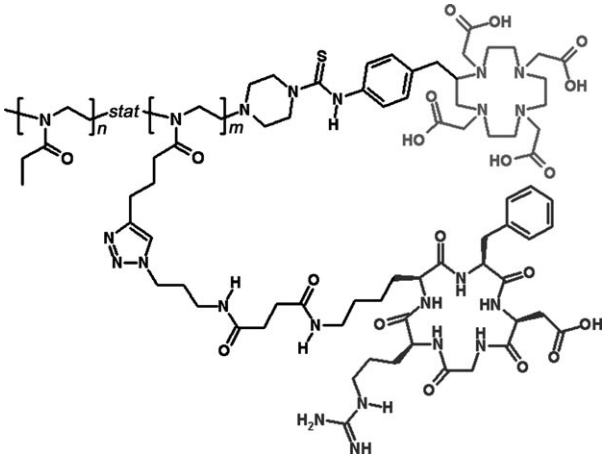
to a cyclic RGD peptide by a click reaction, which resulted in a polymer conjugate with a high potential for tumor cell diagnostics and therapeutics, depending on the radionuclides used (Scheme 2).[30] The versatility and potential of PEtOx as an alternative to PEO were also demonstrated by Hoogenboom and co-workers for both protein and small-drug conjugates; comparable results were obtained for PEtOx and PEO in regard to, for example, protein-rejecting properties, drug-release profile, and in vitro cytotoxicity.[31]



Scheme 2. Conjugate formed between poly(2-ethyl-2-oxazoline) and a cyclic RGD peptide; *stat* = statistical polymer.[30]

2.3. Poly(2-oxazoline)-Functionalized Drug Carriers

Nowadays, drug carriers are often functionalized with PEO (so-called PEGylation) to render them "invisible" to the human body by suppression of protein adsorption and recognition by the immune system.[32,33] As a result, such stealth particles have enhanced circulation times, which result in drug release over a longer time period. In addition, polymer-functionalized liposomes, polymer–lipid conjugate micelles, as well as block copolymer micelles are often used to enhance the solubility of hydrophobic drugs.[34,35]

Even though poly(2-oxazoline)-functionalized liposomes were demonstrated to have similar beneficial properties as PEGylated liposomes,[16,17] drug delivery using such poly(2-oxazoline) liposomes has, surprisingly, not been reported to date. Nonetheless, drug loading and release from micellar drug carriers formed from poly(2-oxazoline) block copolymers have been reported. Jeong and co-workers studied the use of PEtOx-*block*-poly(ε-caprolactone) micelles for the loading of paclitaxel, an anticancer drug with poor aqueous solubility.[36] The block copolymer micelles showed low cytotoxicity. In addition, loaded micelles showed a comparable in vitro inhibition of the proliferation of KB human epidermoid carcinoma cells as the current clinical formulation, while avoiding the side effects such as hypersensitivity and neurotoxicity. Wang and Hsiue studied the micellization of poly(L-lactide)-*block*-PEtOx-*block*-poly(L-lactide) (PLA-*b*-PEtOx-*b*-PLA) triblock copolymers and demonstrated that the middle PEtOx unit is both temperature and pH sensitive.[37] In particular, the protonation of the PEtOx below a pK_a value of 7.1 was identified as a potential targeted release mechanism in cancer cells, which are more acidic than healthy cells.[38] Thus, triblock copolymer micelles were loaded with the anticancer drug doxorubicin, and a faster release was found at pH 5 than at pH 7.4 (physiological value), because of the swelling of the micelles. In addition, the doxorubicin-loaded micelles successfully killed HeLa cells; the doxorubicin was located in the acidic compartments of the cells, thus suggesting an acid-triggered in vitro drug release. A similar low cytotoxicity and pH-induced release of doxorubicin was found for PEtOx-*block*-PLA block copolymer micelles.[39] However, the diblock copolymer micelles had better defined and smaller structures, while showing faster pH-induced release of doxorubicin.

Hsiue et al. also prepared PEtOx-*block*-PEI (PEI = polyethyleneimine) block copolymers for use as nonviral gene carriers.[40] This block copolymer formed polyplexes with DNA that dissociated at low pH values, thus indicating its potential to deliver DNA intracellularly. Furthermore, in vitro cell studies revealed low cytotoxicity as well as high transfection efficiency in gene expression, which makes this diblock copolymer a potential candidate for nonviral gene therapy.

2.4. Antimicrobial Poly(2-oxazoline)s

Antimicrobial polymers have evolved as attractive alternatives to low-molecular-weight antimicrobial agents.[41–43] The major advantage of antimicrobial polymers over low-molecular-weight alternatives is their lower toxicity as well as their lower tendency to lead to microbial resistance. Furthermore, the polymeric analogues have prolonged lifetimes and sometimes enhanced efficiency and selectivity.

Based on the low toxicity of poly(2-oxazoline)s, they were anticipated to be suitable as biocide end-functionalized polymers. Waschinski and Tiller reported that PEtOx end-functionalized with a quaternary ammonium salt had higher antimicrobial activity against *S. Aereus* than analogous end-functionalized PMeOx and PEO.[44] Surprisingly, the polymer chain length did not influence the activity, while the functionality at the other chain terminus (satellite group) strongly influenced the antimicrobial action. The effect of satellite groups was elucidated by further varying the structure, which revealed better antimicrobial activity when the quaternary ammonium salt and the satellite group aggregate in a unimolecular micelle. A subsequent joint attack of both groups on the phospholipid membrane (Figure 2) causes perforation of the membrane.[45,46]

Besides these soluble antimicrobial poly(2-oxazoline)s, the preparation of antimicrobial surfaces was reported by Tiller and co-workers through the use of two different approaches. In the first approach, an amphiphilic block copolymer consisting of poly(2-phenyl-2-oxazoline) (PPhOx) as the hydrophobic block and PMeOx as the hydrophilic block was prepared with a quaternary ammonium end group at the PMeOx terminus.[47] This polymer was subsequently used as a stabilizer for the emulsion polymerization of styrene/butyl acrylate mixtures to give poly(2-

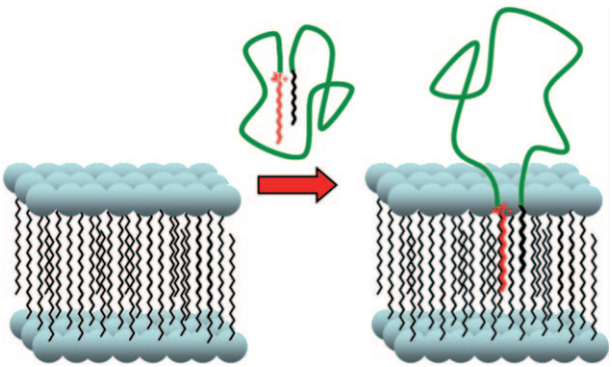


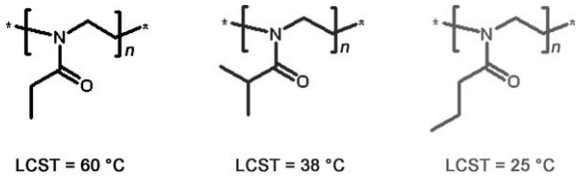
Figure 2. Bacterial action of a poly(2-oxazoline) bearing both quaternary ammonium and alkyl terminal groups. Modified from Ref. [45].

oxazoline)-modified latices. Polymer films that were cast from these latices were found to exhibit good antimicrobial properties agains *S. Aureus*, independent of the styrene/butyl acrylate ratio. In the second approach, a poly(2-oxazoline) bearing both a polymerizable end group and a antimicrobial quaternary ammonium end group was copolymerized with hydroxyethyl methacrylate and glycerol dimethacrylate to give a cross-linked polymer network.[48,49] The resulting polymer films were found to exhibit antimicrobial properties that required a lower amount of biocidal groups than low-molecular-weight copolymerizable additives, while having longer lasting activity.

3. Thermosensitive Poly(2-oxazoline)s

3.1. Thermoresponsive Polymers in Solution

The first study on the thermosensitivity of aqueous solutions of PEtOx, reported by Kwei and co-workers in 1988,[12] showed that the cloud points were dependent on the polymer concentration, and a lower critical solution temperature (LCST) in the range from 61 °C to 64 °C was found depending on the molecular weight of the polymer, which ranged from 500 kDa to 20 kDa. Later, Du Prez and co-workers reported that PEtOx with a molecular weight below 10 kDa does not exhibit a cloud point at 0.5 wt %.[50] In addition, Kwei and co-workers reported salting out (decrease of the LCST) on addition of sodium chloride, and salting in (increase of the LCST) on addition of tetrabutylammonium bromide to an aqueous solution of PEtOx.[12] In 1992, Uyama and Kobayashi reported that poly(2-isopropyl-2-oxazoline) (P*i*PrOx) also exhibits a cloud point in the range 36–39 °C, thus making it a promising candidate for biomedical purposes.[51] It was recently reported by Park and Katoaka that poly(2-*n*-propyl-2-oxazoline) (P*n*PrOx) also exhibits thermosensitivity in water, with a cloud point of 24 °C in a 1 wt % aqueous solution.[52] P*i*PrOx and P*n*PrOx are structural isomers of the most widely studied LCST polymer, namely poly(*N*-isopropylacrylamide) (PNIPAM; LCST = 32 °C),[53–55] with P*i*PrOx even having a similar LCST. Scheme 3 depicts the structures and LCSTs of PEtOx, P*i*PrOx, and P*n*PrOx.



Scheme 3. PEtOx (left), P*i*PrOx (middle), and PnPrOx (right) with their corresponding LCST values.

With regard to biomedical applications of thermosensitive polymers,[56–58] P*i*PrOx seems to be ideal because of its temperature transition close to body temperature.[51] Winnik and co-workers reported a differential scanning calorimetric study of the aqueous-phase transition of P*i*PrOx.[59] The sensitivity of the phase transition to the molecular weight of the P*i*PrOx was found to be more pronounced than for PNIPAM, thus making the latter superior for use in biomedical applications. In addition, it was demonstrated that the number of carbonyl groups available for hydrogen bonding, as well as the change in the solvation volume around the phase transition, increased as the chain length of P*i*PrOx increased. Katoaka and co-workers reported that acetal end-functionalized P*i*PrOx, which can be used for the preparation of bioconjugates, had similar cloud points as the nonfunctionalized analogue.[60] The introduction of larger hydrophilic or hydrophobic end groups into oligomeric P*i*PrOx leads to higher or lower cloud points, respectively.[23]

Even though the phase transition of P*i*PrOx has been reported to be fully reversible, Schlaad and co-workers observed the irreversible formation of coagulate particles when annealing a solution of P*i*PrOx for several hours at 60 °C, which is far above the cloud point temperature.[61] This observed coagulation was found to be a hierarchical self-assembly process based on the directional crystallization of P*i*PrOx into nanoribbons, which further assemble into nanofibers (Figure 3).[62] This isothermal crystallization process was very recently explored by Winnik and co-workers for the preparation of composite nanomaterials by heating a solution of P*i*PrOx-grafted pullulan (a natural water-soluble polysaccharide) above the cloud point.[63]

Besides P*i*PrOx homopolymers, there is significant interest in the copolymerization of different 2-oxazoline monomers to allow accurate control over the cloud points. Park and Katoaka reported the copolymerization of *i*PrOx with the more hydrophilic EtOx, which led to a linear increase of the cloud point as a function of the EtOx content up to 67 °C with 75 mol % EtOx.[64] This linear increase and absence of temperature-induced micellization was somewhat surprising considering the gradient monomer distribution in the polymer chains and the lower reactivity of *i*PrOx compared to EtOx. Copolymerizing *i*PrOx with the more hydrophobic *n*PrOx also resulted in a linear dependence of the cloud points on the composition.[52] Huber and Jordan further decreased the cloud point of P*i*PrOx down to 9 °C by gradient copolymerization of *i*PrOx with the hydrophobic 2-*n*-butyl-2-oxazoline and 2-*n*-nonyl-2-oxazoline (NonOx).[65] A versatile approach to tune the cloud point of P*i*PrOx was reported by Diehl and Schlaad.[66] Statistical copolymers of *i*PrOx and 2-(3-butenyl)-

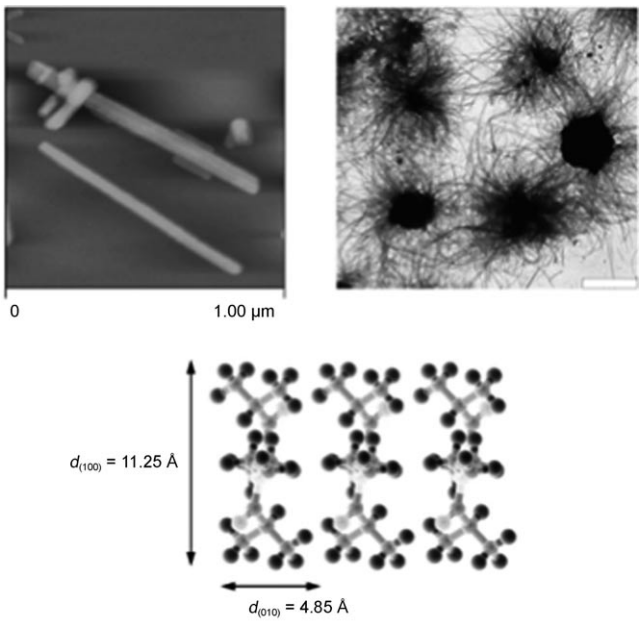


Figure 3. Top left: Nanoribbons formed by directed crystallization of P*i*PrOx upon annealing above the cloud point; top right: Coagulate particles resulting from hierarchical self-assembly of P*i*PrOx nanoribbons (scale bar: 2 μm); bottom: crystal structure of P*i*PrOx. Reprinted from Ref. [62].

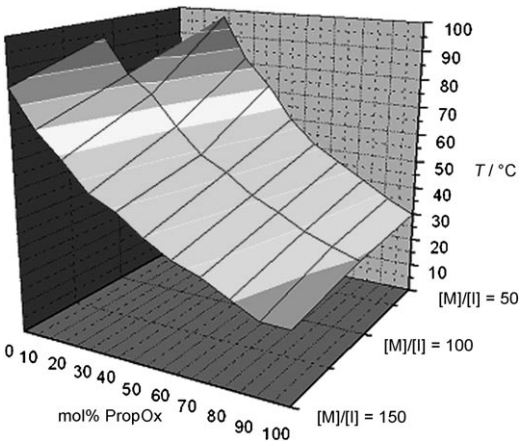


Figure 4. Cloud point of EtOx–*n*PrOx copolymers as a function of both composition and degree of polymerization (represented by the monomer to initiator ratio [*M*]/[*I*]). Reprinted from Ref. [67].

2-oxazoline) were prepared, and it was demonstrated that the cloud point could be tuned from 0 to 100 °C by incorporation of hydrophobic or hydrophilic side groups by using a thiol-ene "click" modification approach (see Section 5).

To avoid the complications induced by the gradient monomer distribution that are generally obtained with *i*PrOx, the copolymerization of EtOx and *n*PrOx, which have similar reactivity, was studied. Park and Kataoka reported initial studies demonstrating that the cloud points could be tuned between 24 and 75 °C, with a nonlinear relationship between the cloud points and the composition.[52] Extended investigations on EtOx–*n*PrOx copolymers were reported by Hoogenboom et al. which revealed that the cloud points could not only be tuned by composition, but also by the degree of polymerization (Figure 4).[67] As such, the cloud point could be kept constant while tuning other polymer properties, such as the hydrodynamic volume and glass transition temperature.

Very recently, two reports appeared on the synthesis and LCST behavior of poly(2-oxazoline) comb polymers.[68,69] Jordan and co-workers described both the free-radical polymerization and living anionic polymerization of 2-isopropenyl-2-oxazoline.[68] The resulting polymer was treated with an excess (based on the number of oxazoline units) of methyl triflate to provide the oxazolinium salt of the polymer, which was used as a macroinitiator for the cationic ring-opening polymerization of MeOx, EtOx, and *i*PrOx. The latter two comb copolymers showed LCST behavior, with cloud points significantly lower than linear analogues. The reverse synthetic route was demonstrated by Hoogenboom and co-workers.[69] First a methacrylate end-functionalized PEtOx macromonomer was prepared by end capping the living PEtOx chains with the ammonium salt of methacrylic acid.[70] In the next step, this macromonomer was polymerized by reversible addition fragmentation chain-transfer (RAFT) polymerization, which resulted in well-defined thermoresponsive comb copoly(2-oxazoline)s.

In contrast to the numerous studies on the LCST behavior of poly(2-oxazoline)s in solution, only a few recent reports have discussed an upper critical solution temperature (UCST). Schubert and co-workers found that PPhOx exhibited an UCST in ethanol.[71] Interestingly, the solubility of PPhOx increased on addition of water to the ethanol solution, leading to a solubility maximum in the range 6–25 wt% of water in ethanol. This maximum solubility was ascribed to the presence of monomeric water molecules in these solvent mixtures.[72] These water molecules form hydrogen bonds with the polymeric amide groups, thereby resulting in a "compatibilizing" hydration shell around the polymer. In addition, it was reported that $PEtOx_{80}$-*stat*-$PPhOx_{20}$ exhibits both LCST and UCST transitions when heated in a water/ethanol mixture with 40 wt% ethanol. Furthermore, copolymers of EtOx and NonOx also display UCST behavior in water/ethanol solvent mixtures, as demonstrated by Hoogenboom and co-workers.[73]

3.2. Thermoresponsive Hydrogels

Applications of thermoresponsive polymers are often based on hydrogels.[74,75] Thermoresponsive hydrogels can be divided into two types: polymers that undergo a sol–gel thermal transition, which can be used for thermally induced gelation,[74] and stable (cross-linked) hydrogels that undergo temperature-induced swelling/shrinking, which can be applied, for example, in pulsatile drug delivery.[75]

In 2000, Kim et al. reported that thermoresponsive PEtOx-*block*-poly(ε-caprolactone) (PCL) diblock and PCL-*b*-PEtOx-*b*-PCL triblock copolymers form micellar gels at low temperature and high concentration.[76] Increasing the temperature induced a gel–sol transition, followed by precip-

itation through collapse of the PEtOx. In contrast, PLA-*b*-PEtOx-*b*-PLA triblock copolymers form weak gels upon passing the phase transition temperature, that is, thermally induced gelation occurs, as demonstrated by Wang and Hsiue.[37] Interestingly, controlling the composition of the triblock copolymer allowed lowering the cloud point of PEtOx to 33 and 38 °C for polymers with a middle PEtOx block of 50–100 repeat units and outer PLA blocks with DP ≈ 5, which is ideal for in vivo applications. Cross-linked hydrogels consisting of PEtOx macromonomers and hydroxyethyl methacrylate (HEMA) or hydroxypropyl acrylate were reported by Du Prez and co-workers.[50] These hydrogels exhibit reversible swelling/deswelling behavior upon changing the temperature stepwise from 20 to 70 °C. Similarly, Kim et al. reported reversible temperature-induced swelling/deswelling cycles for interpenetrating networks of cross-linked PEtOx macromonomer with poly(vinyl alcohol)[77] or chitosan.[78] In a recent study, David et al. reported the synthesis and swelling behavior of ternary microgel particles consisting of NIPAM, HEMA, and PMeOx or PEtOx macromonomers.[79] Upon drying, the microgel particles self-assembled into colloidal crystals to form porous hydrogels with large uniform channels (Figure 5), presumably through hydrogen bonding between the poly(2-oxazoline) tertiary amides and the PNIPAM secondary amides. The presence of a channel-like microstructure resulted in a faster deswelling of the hydrogels compared to PNIPAM hydrogels.

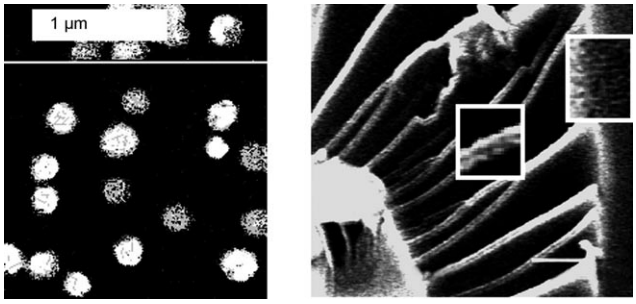


Figure 5. Left: Transmission electron microscopy (TEM) image of ternary microgel particles; right: scanning electron microscopy (SEM) image of a fractured ternary hydrogel (scale bar: 5 μm); the insets are enlargements that show that the hydrogel is composed of aggregated microparticles. Reprinted from Ref. [79].

4. Self-Assembly of Poly(2-oxazoline)s

Controlled and directed self-assembly forms the basis of living matter.[80] Prominent examples include the self-assembly of phospholipids into cell-membranes as well as the folding of proteins. In biological materials, these self-assembly processes result in functional materials with specific properties ranging from mechanical strength and flexibility to information storage in genes and brains.[81] The beauty of natural self-assembly has inspired chemists throughout the world to investigate the self-assembly of synthetic molecules.[82,83] Currently, the self-assembly of well-defined synthetic polymers is an important area of research,[84] focusing on structure formation by phase separation in the bulk phase[85] as well as structure formation in solution by selective solubility.[86] The latter is a particularly important area of research for poly(2-oxazoline)s, which will be discussed in the following section.

4.1. Self-Assembly of Homopoly(2-oxazoline)s

The self-assembly of homopolymers in solution can be induced by crystallization, as described in Section 3.1 for the formation of nanoribbons and fibers of P*i*PrOx (Figure 3).[62] A similar crystallization-driven hierarchical self-assembly was reported by Jin for six-arm PMeOx with a benzene core.[87] The hexakis(bromomethyl)benzene-initiated polymerization of MeOx led to the formation of an opaque suspension, which does not occur for linear PMeOx. A combination of optical micrography, wide-angle X-ray scattering, and differential scanning calorimetry revealed the formation of micrometer-sized spheres with a crystalline PMeOx wall. It was proposed that the spherical polymer consists of a rigid crystalline core surrounded by flexible sections that aggregate to give large spheres. Furthermore, Schlaad and co-workers reported the self-assembly in solution of a poly(2-oxazoline) with glucose units in the side chain into nanofibers.[88] In this case, the driving force for the self-assembly was found to be hydrogen bonding between the sugar moiety and the amide groups of the polymer backbone, which are proposed to result in sheetlike structures that form the wall of the nanofibers.

Alternatively, the self-assembly of homopoly(2-oxazoline)s can be induced by the introduction of bulky dendritic side chains, as was beautifully demonstrated by a number of research groups. Stebani and Lattermann reported that poly[2-{3,4-bis(*n*-decyloxy)phenyl}-2-oxazoline], which was prepared by living cationic ring-opening polymerization of the corresponding monomer, exhibits liquid-crystalline behavior in the melt.[89] Simultaneously, Ringsdorf and co-workers described the synthesis of the same polymer by functionalization of linear poly(ethyleneimine), and it was demonstrated that this polymer self-assembles in a hexagonal columnar mesophase.[90] Based on the similarity of the hexagonal phases of the polymer as well as cyclic and linear oligomeric analogues, it was speculated that the polymer arranges in a helical fashion. However, further investigations on polymers bearing chiral centers in either the dendritic side chain or the polymer backbone revealed destabilization of the hexagonal columnar mesophases, thus undermining the proposed helical arrangement of the polymer backbone.[91] In parallel to these examples, Percec et al. reported that poly[2-{3,4,5-tris(*n*-alkoxy)phenyl}-2-oxazoline]s, prepared by living cationic polymerization, form hexagonal columnar phases.[92] Reducing the degree of polymerization to 20 for polymers with dodecyloxy or undecyloxy chains attached to the dendritic groups led to the formation of the rarely observed lyotropic inverse micellar phase.[93,94] Furthermore, Percec et al. reported systematical variations in the molecular structure of poly[2-{3,4-bis(*n*-alkoxy)phenyl}-2-oxazoline]s in regard to the degree of polymerization as well as the length of the alkyloxy chain.[95,96] The polymers with alkyloxy chain lengths varying from octane to tridecane were found to form

columnar hexagonal lattices, in which the lattice dimensions depended on both the length of the alkyloxy chain and the degree of polymerization.[95] In contrast, the polymers with tetradecane and pentadecane alkoxy chains were found to undergo a transition from a 3D cubic phase at a low degree of polymerization to a 2D hexagonal columnar phase at a higher degree of polymerization (Figure 6).[96] Interestingly, polymers with intermediate chain lengths showed a thermal transition between the two phases.

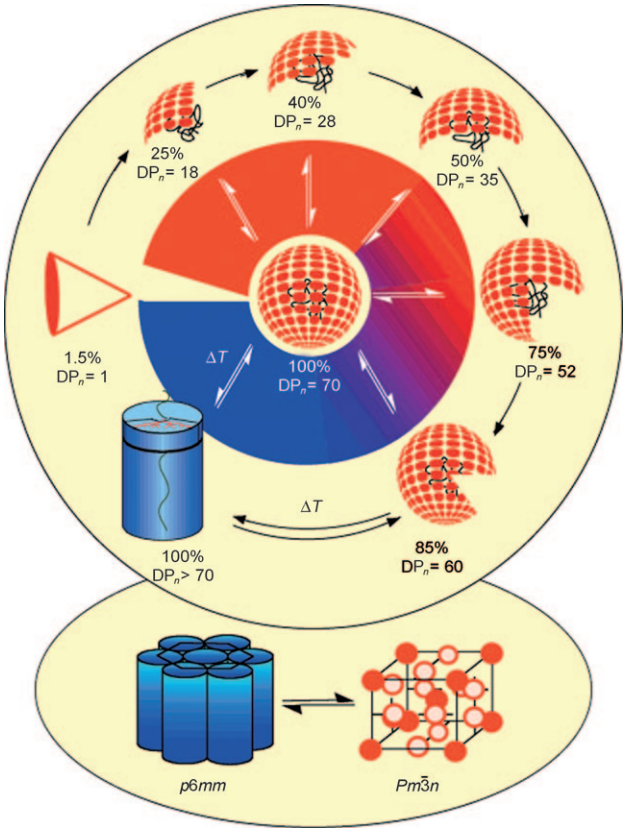


Figure 6. Effect of the degree of polymerization of poly[2-{3,4-bis(*n*-alkyloxy)phenyl}-2-oxazoline]s (alkyloxy = tetradecyloxy, pentadecyloxy) on the self-assembly into different lyotropic phases; DP_n = number average degree of polymerization. Reprinted from Ref. [96].

4.2. Self-Assembly of End-Functionalized Poly(2-oxazoline)s including Lipopoly(2-oxazoline)s

The self-assembly of monoalkyl end-functionalized PMeOx, prepared by initiation of the polymerization with alkyl iodides, was investigated by Volet et al.[97] The hydrophobic alkyl end group induces micellation. The resulting micelles could be dissociated by the addition of β-cyclodextrin which encapsulates the alkyl chain, thereby rendering it hydrophilic. In a very recent study, Winnik and co-workers reported the effect of temperature on the self-assembly of telechelic and semitelechelic octadecyl-functionalized PEtOx and P*i*PrOx.[98] Below the cloud points, the polymers self-assemble into micellar aggregates. Heating through the cloud point results in aggregation of the micelles, while retaining the flexibility of the poly(2-oxazoline) chains. At only 2 °C above the cloud point, rigid objects are formed that preserve their shape upon further heating. These poly(2-oxazoline)s behave rather differently from analogous poly(*N*-isopropylacrylamide)s because of the main-chain amide nitrogen atom.

Besides these monoalkyl end-functionalized polymers, a range of dialkyl-functionalized poly(2-oxazoline)s, that is, lipopolymers, have been studied. The formation of liposomes from such lipopolymers was already discussed in Section 2.1.[16,17] In addition, monolayers of lipopolymers at the air–water interface are often studied as model systems to investigate interactions in biological membranes.[99] Initial work by Bækmark et al. on monolayers of lipopoly(2-oxazoline)s revealed a plateau in the Langmuir–Blodgett monolayer isotherm.[100,101] Infrared reflection absorption spectroscopy as a function of the molecular area indicated a strong local ordering of the lipopolymer in the observed plateau region through van der waals interactions between the alkyl chains, that is, crystallization occurs. Helm and co-workers demonstrated unambiguously with grazing incident X-ray diffraction that the lipopoly(2-methyl-2-oxazoline) (lipoPMeOx) forms striped nanostructures with domains of weakly ordered alkyl chains embedded in the polymer matrix when the polymer floats on the air–water interface.[102] Further investigations on the conformation of lipoPMeOx monolayers at the air–water surface were reported by Lösche and co-workers, who used neutron and X-ray reflection in combination with a partially deuterated polymer[103–105] to show there was an increased density of the polymer close to the interface. Furthermore, the polymer did not undergo significant changes on increasing the lateral pressure of the monolayer, while the ordering of the alkyl chains increased and the lipid moieties became partially immersed into the aqueous phase (Figure 7).

In addition, surface rheological investigations by Naumann and co-workers revealed the formation of physical networks of dioctadecylglycerol/poly(2-methyl-2-oxazoline), which could be ascribed to microcondensation of the alkyl chains and possibly interactions between the adjacent polymer chains through hydrogen bonding.[106] The importance of alkyl-chain condensation was demonstrated by the absence of physical gelation when the alkyl chain was replaced by a short hydrophobic polymer.[107] The absence of physical gelation with other hydrophilic lipopoly(2-oxazoline)s with more bulky side chains indicated that hydrogen bonding between the polymer chains does not play an important role.[108] More recently, the two-dimensional diffusion of the center of mass of a single lipoPMeOx molecule in monolayers at the air–water interface was investigated by single-molecule fluorescence microscopy, which revealed different diffusion mechanisms at different surface concentrations of the polymer.[109]

Besides the self-assembly of pure lipopoly(2-oxazoline)s, the coassembly of phospholipids and silane-functionalized lipopoly(2-oxazoline)s at the air–water interface followed by transfer of the (condensed) monolayer onto a glass slide was reported by Jordan and co-workers.[110] Subsequent coupling of the silane end group of the lipopolymer to the glass slide and vesicle fusion enabled the preparation of solid-supported polymer-tethered membranes (Figure 8). The spontaneous

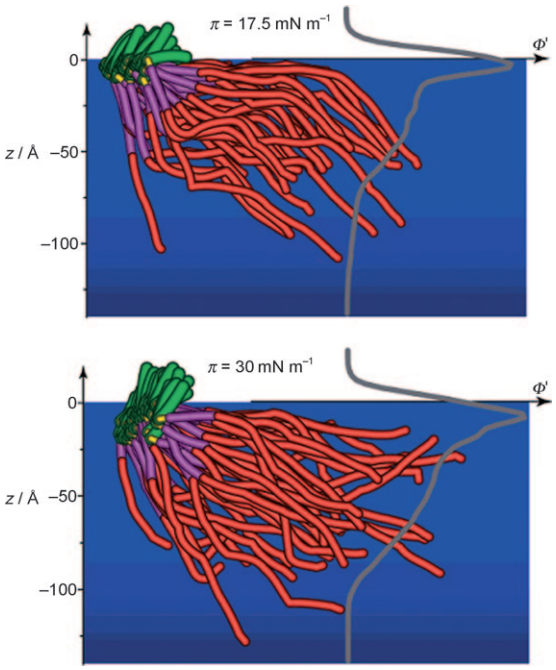


Figure 7. Ordering of a lipopoly(2-[{D_3}methyl]-2-oxazoline)-*block*-poly(2-methyl-2-oxazoline) monolayer at different lateral pressures π. Green: alkyl chains, purple: deuterated polymer, and red: hydrogenated polymer. The envelope volume density Φ' is indicated in gray. Reprinted from Ref. [105].

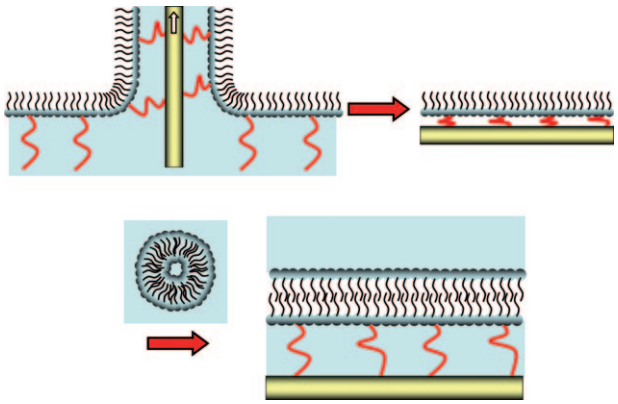


Figure 8. Formation of a solid-supported polymer-tethered lipid membrane by transfer of a mixed lipopolymer/phospholipid monolayer followed by annealing and vesicle fusion using a solution of phospholipid vesicles.[110]

formation of a striped pattern parallel to the transfer direction was observed during the transfer of the mixed phospholipids/lipopolymer monolayer.[111] The use of fluorescently labeled polymers revealed separation of the phospholipids and lipopolymer during the transfer process, driven by condensation of the alkyl chains. After covalent attachment of the polymer stripes to the glass substrate, the phospholipid monolayer was fused with integrin-containing phospholipid vesicles. This process resulted in a protein-functionalized polymer-tethered membrane, in which the proteins were preferably located in the lipopolymer-rich phase. The lipopolymer tethers were found to strongly enhance the adhesion of RGD-functionalized vesicles to the integrin-functionalized membrane compared to solid-supported membranes that were prepared by direct deposition of integrin-containing vesicles.[112] Jordan and co-workers also demonstrated that these polymer-tethered membranes can be used as models to study the diffusion of the integrin transmembrane protein.[113] Furthermore, Naumann and co-workers reported the effect of the polymer tethers on the phospholipid diffusion in the membrane.[114] Obstruction of the phospholipid diffusion was observed, which is most likely due to lipopolymer-induced membrane protrusion and/or clustering of the lipopolymer leading to membrane curvature.

4.3. Self-Assembly of Amphiphilic Copoly(2-oxazoline)s

The living cationic ring-opening polymerization of 2-oxazolines is ideally suited for the preparation of amphiphilic block copolymers that self-assemble in aqueous solution, since both hydrophilic and hydrophobic poly(2-oxazoline)s are readily accessible by varying the side-chain substituent of the monomer. The living cationic polymerization mechanism allows monomer conversions of greater than 99%, since the cationic propagation species repel each other and, thus, the second monomer can be added after full conversion of the first monomer, thereby resulting in well-defined block copolymers in a relatively simple one-pot procedure. This section will cover the self-assembly of nonfluorinated poly(2-oxazoline) block copolymers in which all the blocks are poly(2-oxazoline)s. Recent research on the self-assembly of block copolymers containing PMeOx and/or PEtOx as the hydrophilic block in combination with other hydrophobic polymer structures are beyond the scope of this Review. Nonetheless, the beautiful work by the research groups of Meier[115–117] as well as Montemagno[118–120] on polymersomes based on poly(2-oxazoline)-*block*-poly(dimethylsiloxane)-*block*-poly(2-oxazoline) triblock copolymers as biomimetic membranes should also be mentioned here.

4.3.1. Self-Assembly of Linear Block Copolymers in Solution

Since the initial report by Kobayashi et al. in 1986, amphiphilic poly(2-oxazoline) block copolymers have been recognized as non-ionic surfactants.[121] The properties of these surfactants, such as critical micelle concentration (CMC) and surface tension, as well as their use as stabilizers for emulsion polymerization have been discussed in earlier reviews.[6–8] Here we will discuss more recent studies on the self-assembled structures formed by poly(2-oxazoline)s.

Naka et al. reported the synthesis and micellization behavior of block copolymers having a PMeOx hydrophilic block and a 2-butyl-, 2-octyl-, or 2-phenyl-2-oxazoline hydrophobic block.[122] It was found by a combination of dynamic light scattering and transmission electron microscopy that the block copolymer with 2-phenyl-2-oxazoline formed spherical micelles with a diameter of 25 nm, while the other diblock copolymers formed a combination of spherical and rodlike micelles. Binder and Gruber similarly reported the synthesis

of a series of block copolymers with PMeOx as the hydrophilic block and 2-undecyl-, 2-phenyl-, 2-(4-azidophenyl)-, 2-cinnamoyl-, and 2-diyne-2-oxazolines as the hydrophobic block.[123] Most of the block copolymers showed the formation of large aggregates, which follows the general trends for block copolymer micelles, that is, the formation of larger aggregates as the hydrophobic content and molecular weight increases.

Papadakis and co-workers studied the self-assembly of fluorescently labeled poly(2-methyl-2-oxazoline)-*block*-poly(2-nonyl-2-oxazoline) (PMeOx-*b*-PNonOx) block copolymers with fluorescence correlation spectroscopy, and revealed the presence of individual chains at low concentration ($<2\times10^{-5}$), both individual chains and micelles at intermediate concentrations, and only micelles at high concentrations ($>10^{-2}$ M).[124] Even though the location of the tracer (at the hydrophobic or hydrophilic block) did not influence the results, the addition of a free tracer resulted in a similar CMC, but smaller hydrodynamic radius.[125] This discrepancy was attributed to partitioning of the free dye between the water phase and the micelles. Small-angle neutron scattering revealed that the PMeOx-*b*-PNonOx copolymers formed spherical core–shell micelles in which the PNonOx core block is stretched and the PMeOx corona block is coiled.[126] Nuyken and co-workers reported the use of amphiphilic poly(2-oxazoline) block copolymers for micellar catalysis, whereby the hydrophobic part of the block copolymer was functionalized with a catalyst so that the resulting micelles could be used as catalytic particles in aqueous solution (Figure 9).[127–129]

Such functionalized poly(2-oxazoline) block copolymers have been applied by the research groups of Nuyken and later Weberskirch to catalyze a wide range of chemical transformations. A bipyridine-functionalized polymer was used with copper(I) bromide to catalyze the atom-transfer radical polymerization of methyl methacrylate.[130] Ruthenium-functionalized polymers were used for micellar catalysis of alkyne polymerizations, thereby resulting in a poly(acetylene) latex,[131] as well as for ring-closing metathesis.[132] Furthermore, rhodium-functionalized poly(2-oxazoline)s was successfully used in a micellar catalysis protocol to catalyze hydrogenation,[133] hydroformylation,[134,135] and hydroaminomethylation reactions.[136] The final set of examples for poly(2-oxazoline)-supported micellar catalysis involves palladium-catalyzed Heck and Suzuki–Miyaura C–C coupling reactions, in which the micellar catalysts show high activity.[137–139]

The self-assembly of PEtOx-*b*-PNonOx block copolymers in water/ethanol mixtures was reported by Hoogenboom and co-workers.[73] The block copolymers were found to form mostly individual micelles, although a minor second population of larger aggregates was observed. The addition of ethanol resulted in the micelles increasing in size as a result of the expansion of the PEtOx chains in the corona. Furthermore, the formation of micellar aggregates in water and a hydrophobic ionic liquid was investigated.[140] It was demonstrated that the micelles could be reversibly shuttled between water and the ionic liquid in a biphasic system (Figure 10). The shuttling is based on the better solubility of PEtOx in water at low temperatures, while its LCST behavior causes a decreasing solubility in water as the temperature increases.

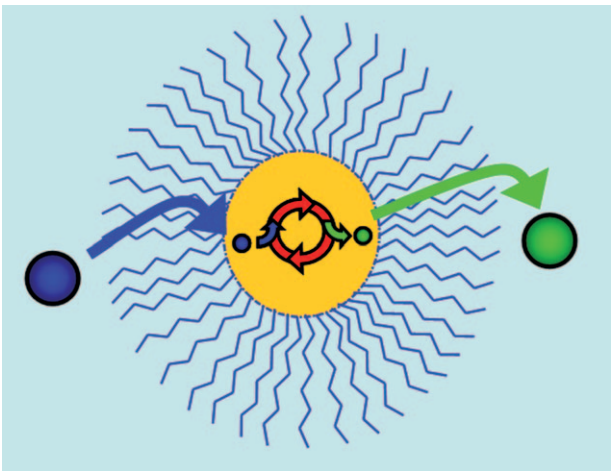


Figure 9. Principle of micellar catalysis in which a catalyst is coupled to the hydrophobic part (yellow circle) of an amphiphilic block copolymer, and the self-assembled micelles act as catalytic nanoparticles; blue circle: starting compound, green circle: product.

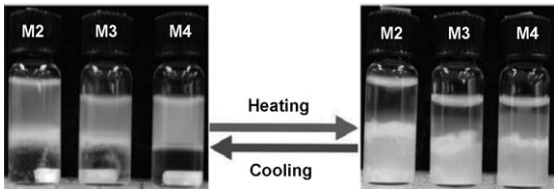


Figure 10. Pictures of the temperature-induced shuttling of PEtOx-*b*-PNonOx micellar aggregates between water (top layer) and a hydrophobic ionic liquid (bottom layer). Reprinted from Ref. [140].

These effects lead, eventually, to better solubility in the ionic liquid, thereby causing a transfer of the micellar aggregates.

Schubert and co-workers reported the synthesis and self-assembly behavior of block copoly(2-oxazoline)s consisting of an EtOx hydrophilic block and a 2-"soy-alkyl"-2-oxazoline hydrophobic block, which bears a soy-bean fatty acid side chain.[141,142] The unsaturated bonds in the fatty acid side chain allow oxidative cross-linking with UV light,[143] which was used for the preparation of core-cross-linked micelles.[141] These core-cross-linked micelles underwent a reversible transition from spherical micelles in water to short rod "rice-grain"-like micelles in the nonselective solvent acetone because of the swelling of the core (Figure 11).

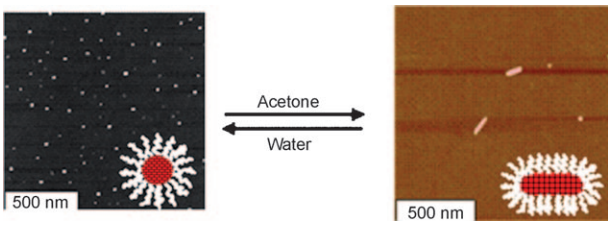
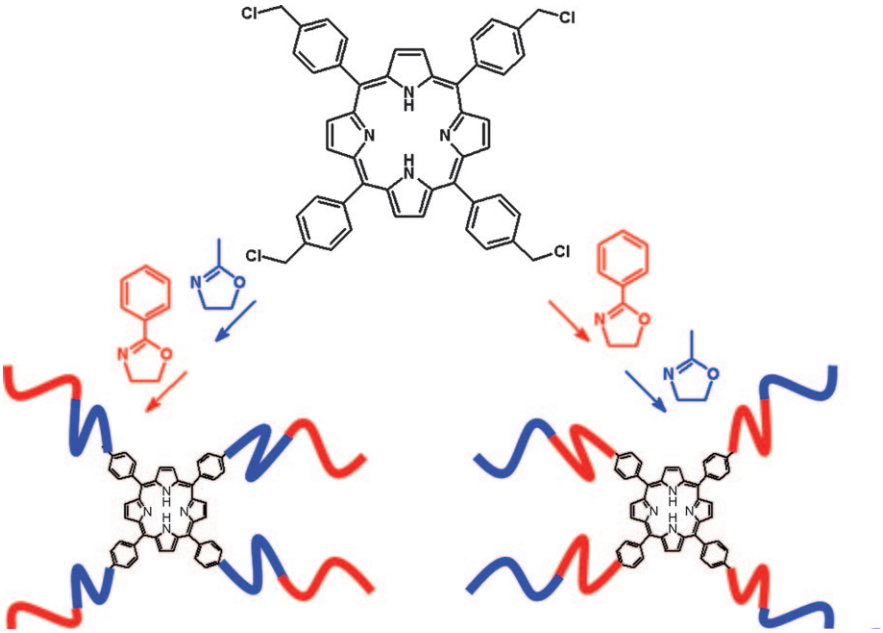


Figure 11. TEM images of core-cross-linked poly(2-ethyl-2-oxazoline)-*block*-poly(2-"soy-alkyl"-2-oxazoline) diblock copolymer micelles in water (left) and acetone (right). Reprinted from Ref. [141].

Besides the self-assembly of linear diblock copolymers, Schubert and co-workers reported the synthesis and micellization of triblock and tetrablock copoly(2-oxazoline)s based on 2-methyl-, 2-ethyl-, 2-nonyl-, and 2-phenyl-2-oxazoline.[144,145] It was demonstrated that triblock copolymers consisting of two hydrophilic blocks and PhOx or NonOx as the outer block formed larger micelles than similar polymers with the hydrophobic polymer as the middle block. Furthermore, polymers with PhOx as the outer block formed larger micelles than polymers with the flexible NonOx as the outer block.



Scheme 4. Synthesis of porphyrin-centered star-shaped block copolymers.[151]

4.3.2. *Self-Assembly of Gradient Copolymers in Solution*

Linear gradient copolymers consist of a gradient in the monomer composition along the polymer chain rather than a sharp transition, as observed in block copolymers.[146] The effect of such a gradient in the monomer distribution on the self-assembly of copoly(2-oxazoline)s was demonstrated by Jordan and co-workers by using fluorescence correlation spectroscopy.[147] The copolymerization of NonOx with the more reactive MeOx results in the formation of a gradient copolymer with a broad shallow monomer gradient.[148] Fluorescence correlation spectroscopy revealed a distinct CMC for these gradient copolymers, which was similar to the CMC of the corresponding block copolymer. Nonetheless, the hydrodynamic radius of the micelles formed was smaller than those of both diblock and triblock copolymers with similar composition.[147] Hoogenboom et al. studied the self-assembly of block and gradient copolymers consisting of MeOx and PhOx in water/ethanol mixtures.[149] The statistical copolymerization of these two monomers results in a sharper and steeper monomer gradient than the statistical copolymers of MeOx and NonOx.[150] The PMeOx-*b*-PPhOx formed cylindrical micelles in water which transformed into spherical micelles upon addition of ethanol. Up to 20 wt% ethanol, the micelle size decreased as a result of the better solvation of the PMeOx block, followed by a plateau in the micelle diameter.[149] In contrast, the corresponding gradient copolymer was insoluble in water and only formed stable micelles with 10 wt% ethanol in water. The micelle diameter decreased linearly with the addition of ethanol up to 40 wt% ethanol, which was ascribed to partial dissolution of the monomer gradient leading to a smaller solvophobic content.

4.3.3. *Self-Assembly of Star-Shaped Block Copolymers in Solution*

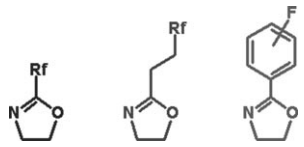
The synthesis of star-shaped block copolymers further expands the range of accessible structures and the positioning of the blocks. Jin has developed a synthetic strategy for the preparation of amphiphilic porphyrin-centered star-shaped block copoly(2-oxazoline)s based on a tetra[meso-(4-chloromethylphenyl)]porphyrin initiator (Scheme 4).[151]

By controlling the block order, the location of the porphyrin in the corresponding self-assembled aqueous micelles could be controlled either in the core or the corona of the micelles, as demonstrated by the pH responsiveness of the different architectures: no pH response was observed when the porphyrin was attached to the hydrophobic PPhOx, thereby leading to "normal" micelles, while pH-responsive flowerlike micelles were formed when the porphyrin was attached to the hydrophilic PMeOx. The self-assembly of the porphyrin-centered star-block copolymer with PPhOx connected to the porphyrin was also investigated in water/*N*,*N*-dimethylformamide (DMF) mixtures.[152] The star-shaped block copolymer formed spherical micelles in DMF-poor solutions, while vesicles and hollow tubes were observed in DMF-rich solvent mixtures. HCl titrations revealed pH-responsiveness in the DMF-rich solutions, thus indicating that the PPhOx forms a mobile, swollen vesicular membrane. Jin also reported that porphyrin-centered PMeOx is preferentially dissolved in water in a water/chloroform mixture, while PEtOx is preferentially dissolved in chloroform.[24] This difference in solvation was explored with a porphyrin-centered star-shaped block copolymer consisting of a PEtOx inner block and a PMeOx outer block. This star-block copolymer behaved as an amphiphilic surfactant and could stabilize water/chloroform emulsions for several weeks. In addition, the emulsion droplets were used to template the formation of silica–polymer hybrid spheres.

4.3.4. *Fluorinated Copolymers and Multicompartment Micelles*

In recent years, interest in triblock copolymers containing both lyophilic and fluorophilic hydrophobic blocks has increased tremendously because of the promise of multi-

compartment micelles from such materials.[153–155] The synthesis and living cationic ring-opening polymerization of three different classes of fluorinated 2-oxazoline monomers, namely 2-perfluoroalkyl-2-oxazolines,[156,157] 2-perfluoroalkylethyl-2-oxazolines,[158,159] and fluorinated 2-phenyl-2-oxazolines,[160,161] have been reported (Scheme 5). In addition, a number of block copolymers and poly(2-oxazoline)s with fluorinated end groups were reported without detailed investigations on their self-assembly behavior.[159,162–164]



Scheme 5. Classes of fluorinated monomers that have been used for living cationic ring-opening polymerization. Left: 2-perfluoroalkyl-2-oxazolines; middle: 2-perfluoroalkylethyl-2-oxazolines; right: fluorinated 2-phenyl-2-oxazolines (Rf = perfluorinated group).

Spiess and co-workers reported the synthesis and self-assembly of PMeOx with a fluorocarbon chain at one end and a hydrocarbon chain at the other.[165] Detailed investigations revealed the formation of a pure hydrocarbon micellar core together with segregated, collapsed fluorocarbon domains at high concentration, that is, the formation of multicompartment micelles. In addition, Thünemann and co-workers reported that these copolymers form cylindrical micelles at lower concentration (Figure 12).[166] The core of the micelles is phase segregated into hydrocarbon and fluorocarbon domains and could be loaded with a fluorocarbon dopant.

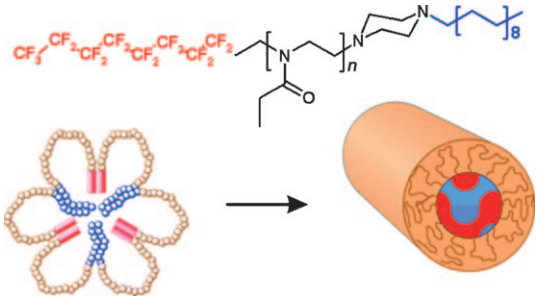


Figure 12. Structure of PMeOx with a fluorocarbon chain at one end and a hydrocarbon chain at the other (top) together with its proposed self-assembly into cylindrical micelles with a segregated core. Reprinted from Ref. [166].

In addition, Weberskirch and Nuyken reported the synthesis of naphthalene-labeled block copolymers of MeOx with 2-pentafluoroethyl-2-oxazoline and 2-heptafluoropropyl-2-oxazoline.[167] Steady-state fluorescence spectroscopy of the micelles formed revealed formation of the naphthalene excimer, thus indicating the presence of a flexible micellar core because of the relatively short fluorinated hydrophobic blocks. However, the very low reactivity of 2-perfluoroalkyl-2-oxazolines complicates the preparation of such block copolymers. Jordan and co-workers reported the synthesis of fluorinated block copolymers based on 2-fluoroalkylethyl-2-oxazoline in which the strong electron-withdrawing perfluoroalkyl chain was decoupled from the 2-oxazoline ring.[168] Block copolymers of this fluorinated monomer with MeOx were prepared and small-angle neutron scattering revealed that aqueous micelles of this block copolymer have an elongated core–shell structure, presumably as a consequence of the high stiffness of the perfluorinated chain and the strong segregation from the water phase. Mixing the fluorinated block copolymer with a nonfluorinated block copolymer resulted in the coexistence of lyophilic and fluorophilic micelles rather than the formation of mixed micelles.

The synthesis and micellization of gradient copolymers based on EtOx and 2-(3,5-difluorophenyl)-2-oxazoline were reported by Schubert and co-workers.[169] This statistical copolymerization resulted in a steeper monomer gradient than the copolymerization of EtOx and PhOx because of the lower reactivity of the fluorinated aromatic monomer. In addition, larger micelles were obtained from fluorinated block copolymers, which was ascribed to the stronger demixing of the fluorinated blocks from the aqueous phase compared to analogues nonfluorinated block copolymers.

4.3.3. Self-Assembly of Amphiphilic Copolymers in Thin Films

In contrast to the large number of studies on the self-assembly of poly(2-oxazoline)s in solution, only a few reports have appeared on their organization in thin films. This is most likely because all the poly(2-oxazoline)s have the same backbone structure, which results in only weak repulsion between the different poly(2-oxazoline)s. Nonetheless, Schubert and co-workers reported some surface features for PNonOx-containing diblock and triblock copoly(2-oxazoline)s.[170,171] The main origin of the formation of a definite structure seems to be crystallization of the PNonOx chains rather than phase segregation between the different blocks.

Thomas and co-workers reported the phase separation of the iron(II)-centered metallosupramolecular star-shaped poly(2-ethyl-2-oxazoline)-*block*-poly(2-undecyl-2-oxazoline).[172] Transmission electron micrography with staining revealed the formation of cylindrical PEtOx domains and a liquid-crystalline ordering of the poly(2-undecyl-2-oxazoline). Furthermore, the iron(II) ions diffused out of the core on annealing and formed iron-rich clusters in the PEtOx domains.

Another approach towards structured poly(2-oxazoline) films was developed by Gohy and co-workers.[173–175] During spin-coating of a solution of amphiphilic poly(2-oxazoline) copolymers with molecularly dissolved polymer chains in ethanol, the concentration of the block copolymer increases, which causes collapse of the hydrophobic block, thereby resulting in evaporation-induced aggregation of the polymer chains. As a result, this straightforward spin-coating procedure results in an array of micelles on the surface (Figure 13), whereby the structure is governed by the hydrophilic/hydrophobic ratio in the copolymers.

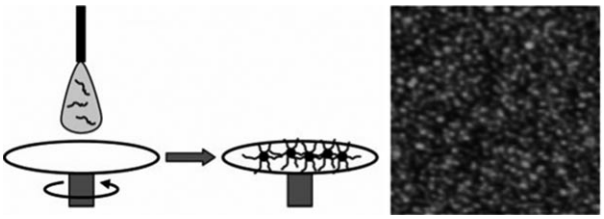


Figure 13. Left: Evaporation-induced micellization of amphiphilic poly(2-oxazoline) copolymers; right: a representative example of the resulting array of micelles on a surface (0.5×0.5 μm). Reprinted from Ref. [174].

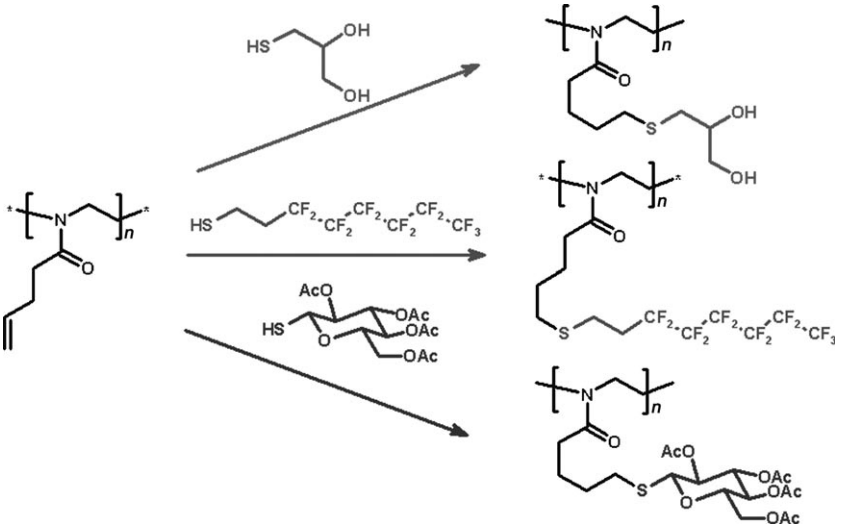
5. Click Chemistry and Poly(2-oxazoline)s

In recent years, the combination of click chemistry and polymers rapidly evolved into a common synthetic strategy for the preparation of well-defined functional macromolecular architectures.[176–178] The simplicity and high efficiency of click reactions[179] appears to be ideal for the coupling and postfunctionalization of polymers. As such, the combination of poly(2-oxazoline)s with click chemistry might be an important stimulus for the broader application of poly(2-oxazoline)s.

The first report on poly(2-oxazoline)s and click chemistry was published by Luxenhofer and Jordan.[180] A 2-(pent-4-ynyl)-2-oxazoline) monomer was prepared, homopolymerized, and copolymerized with MeOx and EtOx to give well-defined alkyne-functionalized polymers; this result indicates that the alkyne is compatible with the cationic ring-opening polymerization. Various azides were subsequently coupled quantitatively to the polymer by copper(I)-catalyzed azide–alkyne cycloaddition. The same approach was used for the side-chain conjugation of PEtOx, as discussed in Section 2.2 (Scheme 2).[30] In addition, Binder et al. reported the synthesis of poly(2-oxazoline)s with azide groups in the side chain by (co)polymerization of 2-(4-azidophenyl)-2-oxazoline without further click reactions.[123] Poly(2-oxazoline)s end-functionalized with alkyne[181] and azide groups[182–184] and subsequent click functionalization was reported by Hoogenboom and co-workers, Cortez and Grayson, as well as Cheradame and co-workers, respectively. These end-functionalized polymers were used for the formation of star-shaped poly(2-oxazoline)s,[181] block copolymers,[183,184] and terpyridine-functionalized metal-coordinating polymers,[185] as well as for surface grafting of PEtOx[186] by click reactions.

Thio-click modification, that is, thiol-ene radical addition, of poly[2-(but-3-enyl)-2-oxazoline] (co)polymers was reported by Schlaad and co-workers.[187] The alkene side-chain-functionalized polymers were functionalized with a variety of thiol compounds, including hydroxy-functionalized compounds, fluorinated chains, and sugars (Scheme 6).[66,88,187] Poly(2-oxazoline)s with thiol functionalities in the side chain were also reported by Nuyken and co-workers, although the thiol-ene click functionalization has not yet been demonstrated with these polymers.[188] The preparation of alkene end-functionalized polymers was demonstrated by Chujo et al., by using allyl tosylate as the initiator, which might be a promising building block for thiol-ene click chemistry.[189,190]

Finally, the preparation of anthracene end-functionalized poly(2-oxazoline)s was performed by Müllen and co-workers, who used 9-bromomethylanthracene as an initiator.[191] The resulting polymers might be suitable candidates for Diels–Alder click reactions.[192,193]



Scheme 6. Thiol-ene click functionalization of alkene-functionalized poly(2-oxazoline).[187]

6. Concluding Remarks

The synthesis and living cationic ring-opening polymerization of 2-oxazolines was already established several decades ago. Nonetheless, widespread application of poly(2-oxazoline)s has been limited by their relatively high cost. In recent years, a strongly renewed interest in poly(2-oxazoline)s has been observed because of their biocompatibility, which in combination with their "stealth" behavior led to the development of POXylation as an alternative to PEGylation. The main advantage of poly(2-oxazoline)s over poly(ethylene oxide) is the easy variation of the monomer composition as well as the introduction of side-chain functionalities. However, much more knowledge has to be generated on the stealth behavior, in vivo fate, as well as degradation pathways of poly(2-oxazoline)s before they might compete with poly(ethylene oxide).

A variety of thermoresponsive copoly(2-oxazoline)s were reported in recent years, which suggests that the tunable LCST in combination with the absence of hysteresis in the transition make these polymers superior to the golden standard, namely poly(*N*-isopropylacrylamide), for applications. Nonetheless, the easier availability of poly(*N*-isopropylacrylamide) by radical polymerization, compared to the living cationic ring-opening polymerization of 2-oxazolines, represents a major advantage for poly(*N*-isopropylacrylamide).

Nonetheless, it is expected that thermoresponsive poly(2-oxazoline)s will be further developed for a variety of applications, especially in the biomedical area.

The easy access to hydrophilic, lyophilic, and fluorophilic poly(2-oxazoline)s makes this class of polymers ideally suited for self-assembly studies in aqueous solution. In fact, poly(2-oxazoline)s were already applied to address a range of fundamental self-assembly questions, such as the effect of monomer distribution, fluorination of the hydrophobic block, as well as the formation of multicompartment micelles.

The development of click chemistry for poly(2-oxazoline)s will be important for further expanding the scope and applicability of this class of polymers, by making them readily available to a larger community of polymer chemists.

Taken together, these recent developments clearly demonstrate that the field of poly(2-oxazoline)s is flourishing, which is also indicated by the increasing number of research groups working on them. I am confident that future investigations will further stimulate the development of poly(2-oxazoline)s for these exciting new areas of application, and will eventually lead to commercial applications.

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