Poly(2-oxazoline)s and click chemistry: a versatile toolbox towards multi-functional polymers

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Abstract: Poly(2-alkyl/aryl-2-oxazoline)s (PAOx) have been gaining increasing attention because they combine biocompatibility with so-called stealth behavior, making them ideal candidates for use in a wide variety of biomedical applications. Especially, the possibility of side-chain modification makes them a valuable alternative to poly(ethylene glycol), currently the gold standard amongst biocompatible polymers. Nevertheless, the cationic ring opening polymerization of 2-oxazolines is not compatible with nucleophilic entities, for example hydroxyl and amine moieties. Therefore, the modular approach of 'click chemistry' offers an elegant strategy towards functional PAOx by post-polymerization modification of PAOx that contain clickable groups. This feature describes the synthesis of PAOx with such clickable entities at the chain-end or in the side-chain, as well as their potential (bio)materials applications.

Keywords: poly(2-oxazoline), click chemistry, post-polymerization functionalization, biomaterials

Kathleen Lava (born 1985) graduated in 2007 as a M.Sc. in Chemistry at the University of Leuven. In 2012, she successfully completed her Ph.D. thesis entitled 'Ionic liquid crystals based on novel heterocyclic cores' under the supervision of Prof. Binnemans at KULeuven, as fellow of the 'Agency for Innovation by Science and Technology' (IWT). She presently performs postdoctoral research in the team of Prof. Richard Hoogenboom at Ghent University, focusing on functional poly(2-oxazoline)s for (bio)materials applications.

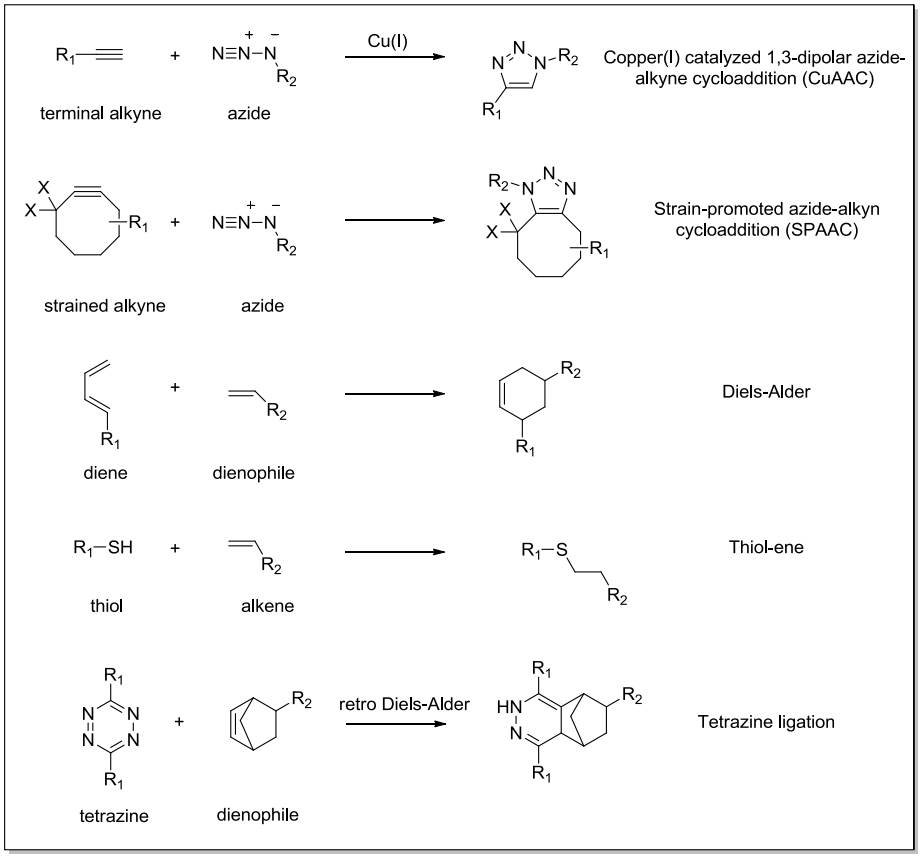
Bart Verbraeken was born in Hasselt, Belgium, in 1988. He earned his master's degree with honors in the field of organic synthesis on (4+3) cycloaddition with a furfuryl cation to natural products under the supervision of Prof. Johan Winne at the Department of Organic and Macromolecular Chemistry, Faculty of Natural Sciences, Ghent University in Ghent. While remaining in the same department, he switched to the Supramolecular Chemistry Group of Prof. Richard Hoogenboom for his Ph.D. research, as IWT fellow, in the field of cationic ring opening polymerization of 2-oxazolines leading to stimuli-responsive materials.

Richard Hoogenboom was born in 1978 in Rotterdam (the Netherlands) and studied chemical engineering at the Eindhoven University of Technology (the Netherlands). In 2005, he obtained his Ph.D. under the supervision of Ulrich S. Schubert and continued working as a project leader for the Dutch Polymer Institute. After postdoctoral training at the RWTH Aachen with Prof. Martin Moeller and at the Radboud University Nijmegen with Prof. Roeland Nolte, he was appointed as associate professor at Ghent University in 2010 and in October 2014 he was promoted to full professor. His research interests include stimuli-responsive polymers, supramolecular polymers, and poly(2-oxazoline)s. He has published more than 250 refereed scientific articles and is currently associate editor for European Polymer Journal and Australian Journal of Chemistry.

1 Introduction

Environmental, economical and social considerations have directed scientific research towards the development of sustainable materials and technologies. In organic chemistry, this has progressed to a general mindset of reducing the complexity of synthesis routes and minimizing the use of harmful reactants and solvents. Especially research in chemistry for biomedical applications is bound to extreme reduction of toxic chemicals, which is strictly regulated by different agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In this context, Kolb, Sharpless *et al*. introduced the concept of click chemistry in 2001, which embodies a selective set of reactions that are wide in scope, modular, tolerant to a broad range of functional groups, excel in terms of yield, purity, simplicity and ease of purification (use of non-chromatographic methods) and are conducted under mild conditions (*e.g.* low temperatures), producing only inoffensive or no byproducts.[1] Reactions that meet these criteria are usually highly energetically favorable, for example, by formation of σ-bonds from energetically less stable π-bonds (*f.e.* 1,3-dipolar azide-alkyne cycloadditions)[1-2] or by relaxation of ring strain energies (*f.e.* tetrazine ligation).[3]

Within the field of polymer science, click chemistry has proved to be extremely successful and has found application in the synthesis of biohybrids,[4] hydrogels,[5] nanocarriers for drug delivery,[6] functionalized surfaces,[7] and design of polymers with a variety of architectures.[7b, 8] It must be noted that true polymer click reactions must comply with some additional criteria, such as equimolarity, which is especially important for polymer-polymer coupling reactions, large scale purification and fast time scales.[9] The latter requirement is probably more relevant to biochemical reactions than to pure polymer chemistry. In Scheme 1, an overview of click reactions that have extensively been used in polymer chemistry is given.



Scheme 1. Illustrative click reactions that are frequently used in polymer chemistry.

The copper(I) catalyzed azide-alkyne (Huisgen) cycloaddition (CuAAC), as reported by Kolb, Sharpless *et al*., has been the most popular click reaction to date. Nevertheless, the presence of residual copper poses toxicity issues for further use in biomedical applications, stimulating the development and use of metal-free click reactions.[10] As such, strain promoted azide-alkyne cycloadditions (SPAAC) have been emerging as metal-free, bioorthogonal alternative to the CuAAC reaction.[11] Furthermore, thiol-ene coupling has proven to be an extremely efficient and non-invasive method for post-polymerization modifications and for the formation of polymeric networks.[12] However, it is important to distinguish between the base-catalyzed thiol Michael addition and the radical-mediated thiol-ene reaction. For the latter, the real 'click' nature can be debated as large excesses of the thiol-containing compound is often needed in order to reach full conversion and the radicals present in the reaction mixture can induce side reactions. This argument is particularly true for polymer-polymer coupling, for which purification becomes complicated in the presence of side-

products and/or unreacted starting materials.[13] Nevertheless, thiol-ene coupling can be an efficient tool for ligation of smaller thiol-containing molecules that can easily be separated from the modified polymer by simple precipitation. The popularity of click chemistry has stimulated researchers to look for new modular reagents for efficient polymer conjugation. Hawker *et al*. recently reported the nitrosocarbonyl hetero-Diels-Alder cycloaddition for the synthesis of block copolymers.[14] Also, reversible linking was recently realized by Winne, Du Prez and coworkers, using 1,2,4-triazoline-3,5-dione (TAD) click chemistry.[15] At the same time, it should be emphasized that not all efficient reactions can be associated with the click concept and a critical evaluation of Sharpless' criteria and additional polymer click requirements is essential before labeling new procedures 'click reactions'.

In polymer chemistry, clickable entities can be introduced on polymer chains by end-functionalization, using functional initiating and terminating species and/or by side-chain functionalization, making use of functional monomer(s) or by post-polymerization modification. Ideally, a universal polymer backbone could serve as scaffold to which different functionalities can be attached in an orthogonal fashion, as was previously applied for, *e.g.*, supramolecular side-chain functionalized polynorbonenes.[16] Such a multi-functional design strategy requires synthesis of highly versatile polymers with well-defined microstructures. In this view, poly(2-oxazoline)s (PAOx) seem to be perfect candidates (Figure 1).[17]

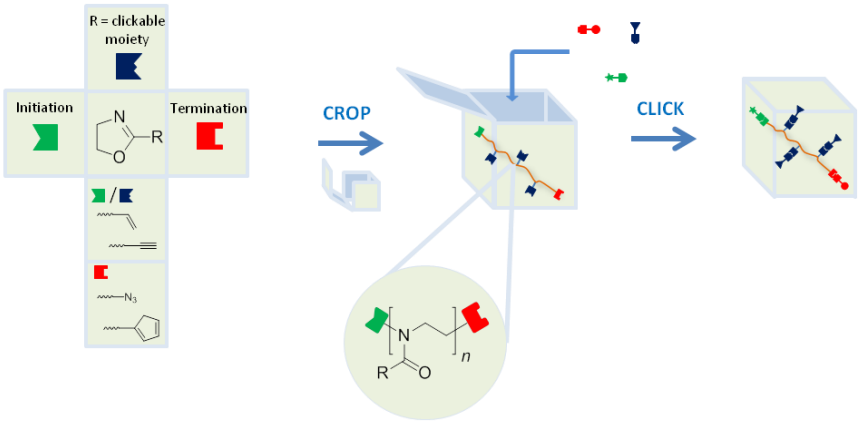
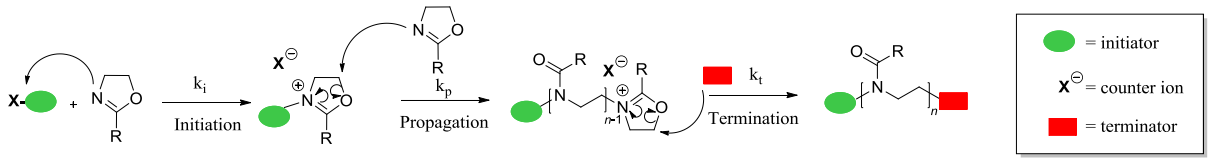


Figure 1. Representative functionalization possibilities of poly(2-oxazoline)s using click chemistry.

PAOx are prepared by living cationic ring-opening polymerization (CROP) of 2-oxazolines (Scheme 2).[18] The living nature of CROP can lead to narrow molar mass distributions (Đ < 1.2) and allows for controlled introduction of chain-end (initiation/termination) and side-chain functionalities.[19] However, the CROP of 2-oxazolines is associated with limitations in terms of monomer and initiator choice as well as purity of the reaction mixture, since undesired nucleophilic groups/species, including water, induce termination or chain transfer and coupling side reactions leading to less defined polymers.[20] Nevertheless, a variety of 2-oxazoline monomers suitable for CROP are readily available or can easily be synthesized, which allows for tuning of physico-chemical properties such as solubility (*e.g.* lower-critical solution temperature (LCST)),[21] and crystallinity.[18c, 22]



Scheme 2. Schematic representation of the cationic ring opening polymerization (CROP) of 2-oxazolines.

In the past decade, PAOx – that can be regarded as pseudo-peptides based on structural analogy – have become of particular interest as versatile biomaterials and potential alternatives to poly(ethylene glycol) (PEG), which is currently the gold standard in polymer-based biomaterials.[23] The biocompatibility and non-cytotoxicity of PAOx, mostly documented for poly(2-methyl-2-oxazoline) (PMeOx) and poly(2-ethyl-2-oxazoline) (PEtOx), have been demonstrated in several *in vitro* and *in vivo* studies.[24] The structural adaptability, biocompatibility and so-called 'stealth' behavior of PAOx makes them suitable for a variety of biomedical applications such as polymer therapeutics,[21a, 25] scaffolds for 3D cell culture,[26] surface modification,[27] tissue adhesives,[28] matrix excipient for solid dispersions,[26c, 29] and antimicrobial agents.[30]

As the living CROP of 2-oxazolines is susceptible to chain-transfer reactions, conjugation of biological functionalities such as targeting groups, labeling moieties, *etc.* to the polymer backbone is preferably performed *via* post-polymerization modification reactions.[31] In order to retain the highly defined structure in the final (co)polymer, the number of post-polymerization reaction steps should be

minimized and highly selective reactions with quantitative conversion are of utmost importance. The concept of click chemistry, therefore, perfectly matches this need for straightforward, efficient post-polymerization modification of PAOx (co)polymers that are intended for biomedical use. The aim of this feature article is to show that PAOx can serve as a universal clickable polymer platform and that click chemistry presents a versatile toolbox towards multi-functional PAOx as biocompatible polymers. Therefore, the synthesis of PAOx with clickable chain-end and side-chain functionalities will be discussed in detail as well as their potential applications, especially in the biomedical area.

2 Poly(2-oxazoline)s with clickable chain-end functionalities

End-group functionalization of PAOx is fairly straightforward in the sense that functional initiators and/or terminating agents can be utilized during CROP to introduce α- and/or ω-chain-end functionalities, which has widely been reported in the past.[19] While many end-functionalities suitable for post-polymerization modification using click chemistry can be introduced, only a limited number have been used as such (Figure 2). Thus far, most research has focused on material properties and applications of CuAAC 'end'-coupled PAOx, rather than exploring new synthetic click strategies and reports are mostly limited to PMeOx and PEtOx.

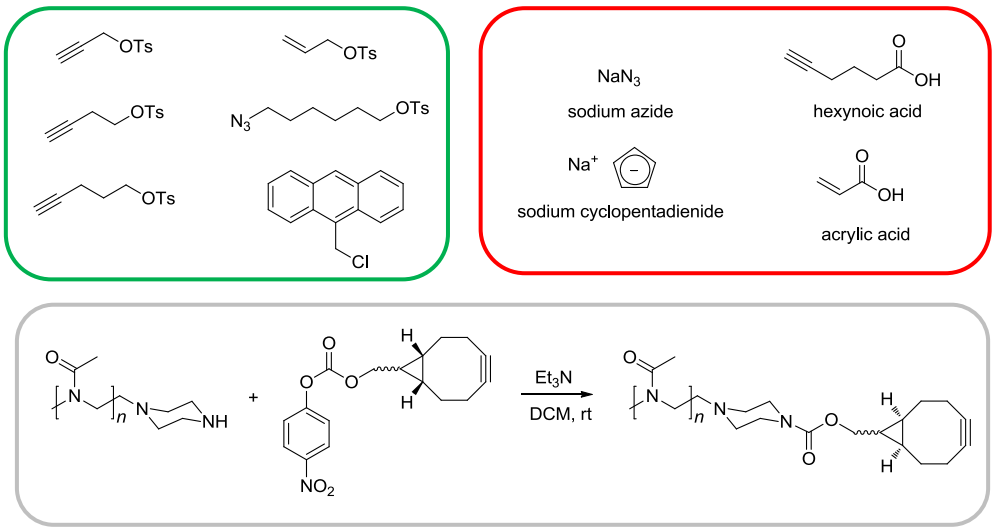


Figure 2. Overview of end-functionalities used for click chemistry introduced by initiation (top left), termination (top right) and post-polymerization modification (bottom).

2.1 Synthesis of chain-end clickable poly(2-oxazoline)s

As discussed above, the living CROP of 2-oxazolines offers good control over molar mass distribution as well as high end-group fidelity of the resulting PAOx. In terms of initiation, this requires fast initiation and compatibility of functional groups in the initiator with CROP. Currently, alkylating agents such as halides, triflates and tosylates are predominantly used to achieve the required fast initiation, with tosylates being mostly preferred based on their higher stability and ionic character of the propagating species. It should however be noted that less reactive aliphatic tosylates, such as butynyl and pentynyl tosylates lead to slow initiation and nosylates might be used instead as faster intiating, yet stable, alternatives.[32] In a first report on clickable end-functionalized PAOx by Hoogenboom and Schubert, propargyl tosylate was used as initiator.[33] As a proof of concept, acetylene-functionalized PEtOx was subsequently clicked to aromatic, UV-active moieties bearing an azide group as well as heptakis-azido-*β*-cyclodextrin by means of CuAAC "click" chemistry. However, conjugation of heptakis-azido-*β*-cylcodextrin had to be performed at high temperature (100 °C) under microwave irradiation, so that the click nature of this reaction is questionable. It must be noted that the acetylene group is susceptible to deprotonation and side reactions can occur upon termination with methanolic potassium hydroxide, which is a commonly used terminating agent for the CROP of 2-oxazolines.[34] The commercial availability of propargyl tosylate and the efficiency of the CuAAC click conjugation, made this route towards clickable PAOx very popular and many functionalities, including virus-like particles,[35] thermo-responsive dendrimers,[36] amino acids,[37] and cyclic peptides[38] have been coupled in a similar way (*cfr*. section 2.2). However, clicking of incompatible macromolecules, *e.g.* for the synthesis of polymer-polymer and polymer-dendrimer conjugates, does not always result in the expected high yields, because of solubility issues.[34, 39] Schubert *et al.* prepared star-shaped poly(ε-caprolactone)-*block*-PEtOx copolymers by an arm-first approach using CuAAC.[40] As pointed out by the authors, these reactions technically do not qualify as true click reactions because quantitative conversion requires a large excess (> 24-fold) of polymer arms. Additionally, the polyamide backbone of PAOx strongly interacts with residual copper, making its removal rather cumbersome, especially for difficult to solubilize amphiphilic multiblock

conjugates. Theogarajan *et al*. showed effective removal of the copper catalyst using sodium sulfide, but this led to the introduction of trace amounts of sulfur.[34] A transition-metal free alternative to the CuAAC click reaction is thiol-ene coupling. Therefore, allyl *p*-toluene sulfonate was employed by Robin and coworkers to initiate the CROP of 2-oxazolines PAOx yielding allyl end-functionalized PAOx. Subsequent radical thiol-ene modification was optimized for radical initiator content and concentration of the reaction mixture.[41]

While the introduction of clickable triple bonds is mostly accomplished by propargyl tosylate initiation, it has also been reported using hexynoic acid as terminating agent leading to PAOX with a pentynyl group that is connected via a degradable ester linkage.[42] Similarly, azide functionalities can be easily incorporated during termination by addition of an excess of sodium azide,[40, 43] or can be incorporated during CROP by initiation with 6-azido-1-hexane tosylate.[44] These azide end-capped PAOx can be used in CuAAC coupling, as well as for the metal-free SPAAC reaction. However, cyclooctyne precursors are more expensive and have a low shelf stability compared to terminal alkynes and copper catalysts.

Theogarajan *et al.* synthesized cyclooctyne functionalized PAOx that can be used in SPAAC coupling, by post-polymerization modification of piperazine end-capped PMeOx (Figure 2).[45] The *in vitro* biocompatibility of polymersomes prepared *via* SPAAC, proved to be superior compared to their copper-clicked counterparts, emphasizing the importance of the Cu-free synthesis routes.

Another bioorthogonal approach, reported by Hoogenboom, Barner-Kowollik *et al.*, is the endcapping of living PAOx with clickable sodium cyclopentadiene yielding PAOx with cyclopentadiene at the ω-terminus that can be conjugated to *N*-substituted maleimides at ambient temperatures using Diels-Alder chemistry.[46]

Recently, acrylic acid was used as terminating agent, which was used in a metal-free nitrile oxide 1,3-dipolar cycloaddition by *in situ* nitrile oxide generation.[47] A one-pot double ‘click’ post-polymerization modification of PAOx was achieved by Hoogenboom and Schubert based on an anthracene-based initiator and sodium azide as terminating agent for Diels-Alder and CuAAC

clicking, respectively, presenting a prime example of the versatility of the PAOx-click synthetic platform.[36b]

2.2 Applications of chain-end clickable poly(2-oxazoline)s

Whereas (defined) block copolymers of PAOx are easily synthesized by sequential polymerization, linking of structurally different polymers is not achievable during the polymerization process. In this respect, chain-end modification using click chemistry is an elegant route towards the modular synthesis of block copolymers by coupling of well-defined macromolecular structures. Such block copolymers have the ability to self-assemble into supramolecular nanomaterials (*f.e.* micelles or nano-phase separation in bulk), depending on the polymer design. PAOx polymer-polymer coupling using copper-mediated and copper-free click chemistry has been reported with hydrophilic PEG blocks.[43b, 46] In this way, PAOx-PEG star-shaped architectures could be obtained in an arm-first approach by CuAAC clicking of propargyl PAOx arms to an azido-functionalized star-shaped PEG core.[48] In a similar approach, star polymers have been prepared starting from azido-functionalized *β*-cyclodextrin.[33] However, conjugation of hydrophilic PAOx (PMeOx or PEtOx) with hydrophobic polymer blocks offers even more possibilities towards complex architectures due to microphase segregation of immiscible polymer segments. Well-defined micellar assemblies consisting of a hydrophobic core and a hydrophilic outer shell have received a great amount of attention as drug delivery vehicles to prevent fast blood clearance of small drug molecules or enhance dissolution of poorly water-soluble drugs.[49] It was shown that star-shaped poly(ε-caprolactone)-*block*-PEtOx copolymers with good loading capacities (19 $mol_{dye}/mol_{polymer}$) of the hydrophobic dye fat brown RR could be obtained through CuAAC click chemistry.[40] Moreover, high blood compatibilities were observed for these micellar assemblies, proving their potential in biomedical applications. Other PAOx-based polymeric architectures that were synthesized using the CuAAC click concept and are able to form self-assembled vesicles include amphiphilic poly(ε-caprolactone)–PEtOx graft copolymers,[50] linear PMeOx-poly(*tert*-butyl acrylate) copolymers,[39] and ABA triblock copolymers of PMeOx (block A) and poly(siloxane) (block B).[34] The latter could also be obtained *via* metal-free SPAAC coupling.[45] Besides block copolymers, self-assembling polymer-dendrimer conjugates have

also been prepared based on the click concept. Acid-labile polyester dendron-PEtOx aggregates were prepared by Sanyal, Hoogenboom *et al.* in a one-pot cascade reaction using 9-(azidomethyl)anthracene, a difunctional linker that can be reacted using Diels-Alder cycloaddition and contains an alkyne moiety for CuAAC click chemistry.[36b] Dual-responsive poly(benzyl ether)-poly(2-*iso*propyl-2-oxazoline) (P*i*PropOx) assemblies could be obtained using CuAAC click chemistry. Interestingly, these copolymers combine dendron pH-responsiveness and P*i*PropOx LCST behavior resulting in reversible morphology changes upon variation of both pH and temperature (Figure 3).[36a] Under basic conditions the acidic groups on the dendron are deprotonated, so that both blocks are hydrophilic and the dendritic-linear block copolymers are fully water-soluble. On the other hand, at low pH and high temperature, these dendritic-linear block copolymers were insoluble in aqueous solution. At low temperatures, fibrous assemblies could be obtained by increasing the pH, due to aggregation of the hydrophobic dendritic wedges, whereas increasing the temperature at high pH resulted in the formation of lamellar structures with a hydrophilic carboxylate periphery and a hydrophobic (collapsed) P*i*PropOx interior. Similar temperature-induced alterations of the morphology were observed for CuAAC clicked PEtOx-peptide bioconjugates that self-assembled into nanotubes below the LCST and hydrophobic microspheres above the LCST.[38] Conjugates of P*i*PropOx and fluorenylmethoxycarbonyl-amino acids, prepared using CuAAC click chemistry, formed colloidal particles depending on the type of amino acid attached, as shown by Caponi *et al.*[37] Moreover, two component mixtures of these colloidal systems and a phosphate functionalized *i*PropOx-amino acid, showed additional enzyme responsive behavior upon addition of phosphatase, which alters the amino acid charge and functionality by transforming the phosphate moiety to a hydroxyl group.

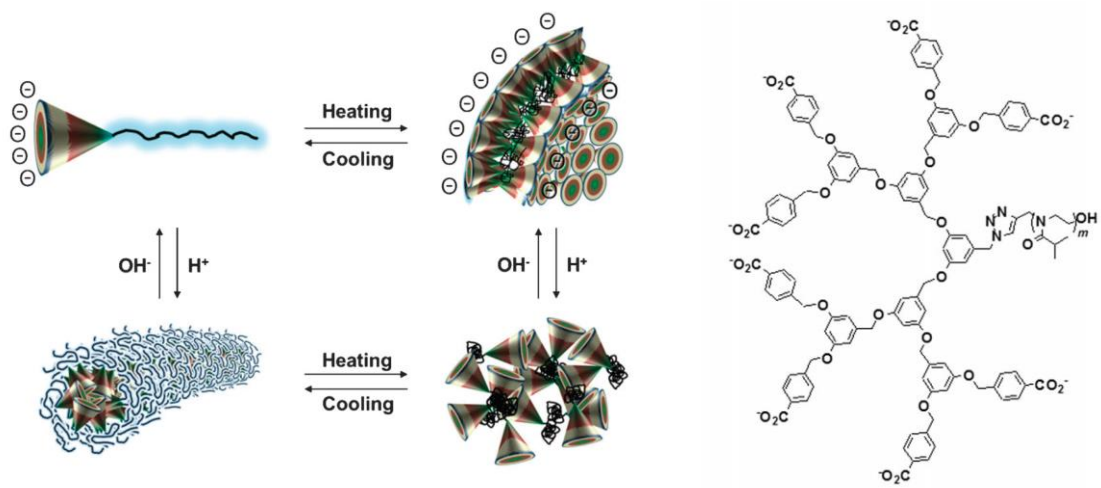


Figure 3. Morphology changes upon variation of pH and temperature, by dendron (de)protonation and reversible LCST behavior of P*i*PropOx, respectively. *Reproduced with permission from Kataoka, K.; Jang, W.-D. et al. Chem. Commun.* ***2012****, 48, 3662-3664.*

In an interesting study of Xia *et al*., liposome morphology alteration was used to release the anti-cancer drug doxorubicin encapsulated in the hydrophobic core.[44] Therefore, an alkyne-modified pH-sensitive distearoyl phosphatidyl ethanolamine (DSPE) moiety was clicked to azide-functionalized PEtOx. Additionally, a tumor targeting folate unit could be attached to the ammonium terminated PEtOx-DSPE block polymer through a *N*-hydroxysuccinimide/amine coupling. This study nicely exemplifies that click chemistry can be used to selectively attach certain functionalities and, as such, obtain multifunctional PAOx in a straightforward manner. Other drug delivery vehicles, characterized by a hydrophobic core and a hydrophilic PAOx shell, that have been synthesized through CuAAC click chemistry, are deep-cavity cavitands, *i.e.* rigid hydrophobic cage-like macrocycles for which the attachment of peripheral PAOx is essential for water-solubility.[43a]

Other, non-spherical nanostructures, were reported by Schacher *et al.* for self-assembling oligophenyleneethynylenes (OPE)-PEtOx bolaamphiphiles.[51] In order to avoid side reactions of the azido-functionalized PEtOx with the internal alkyne bonds present in OPE, a template assisted CuAAC coupling was performed. Therefore, sheet-like aggregates of OPE, in which the internal alkyne bonds are situated at the interior and the terminal alkyne bonds are located at the exterior, were prepared prior to CuAAC with azido-PEtOx. Depending on the ratio of the hydrophilic/hydrophobic parts, the resulting bolamphiphiles showed a cooperative two-step (nucleation-elongation) supramolecular organization in aqueous solution into anisotropic platelets. Furthermore, the self-assembly of block copolymers consisting of incompatible blocks has been investigated for use in nanolithography.[42] Microphase-segregation of such block copolymers is controlled by the size and chemical composition of the individual blocks and a modular synthetic approach allows optimization of both characteristics in a straightforward manner. In this respect, a family of polystyrene-PEtOx block copolymers with varying PEtOx volume fraction, have been prepared by means of CuAAC click chemistry. Thin films of the resulting block copolymers on a silicon substrate showed, after annealing, the formation of hexagonally packed cylinders with sub-20 nm feature sizes perpendicular to the surface (Figure 4).

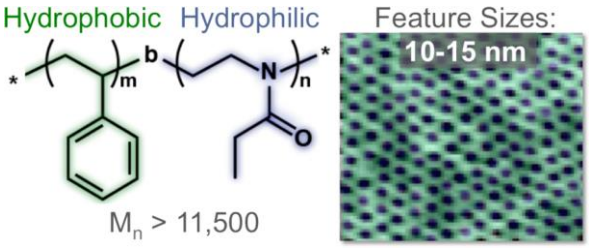


Figure 4. AFM height image of hexagonally packed cylinders formed in annealed thin films of phase-segregated polystyrene-PEtOx block copolymers. *Reproduced with permission from Schubert, U.S.; Campos, .L.M. et al. ACS Macro Lett.* ***2013****, 2, 677-682.*

Click chemistry-based surface modification of icosahedral virus-like particles (VLP) was demonstrated by Jordan, Finn *et al.*[35] Ligation of polymers on the VLP surface not only leads to enhanced bioavailability, but also allows for biological labeling. In this study, the thermal stability of the capsids was demonstrated to significantly increase by CuAAC coupling with chain-end and side-chain alkyne-functionalized PAOx, of which the latter showed the best results. Surface modification of inorganic substrates has proven to be extremely successful making use of click chemistry, because of its high reactivity in heterogeneous media.[7a] PAOx functionalization of silicon surfaces was demonstrated using microwave-assisted CuAAC modification.[52] Furthermore, thin polymer films bearing azido groups could be coated with propargyl tosylate initiated PMeOx, resulting in antifouling surfaces.[53] Contrary to PEG, these PMeOx coatings proved to be suitable for micropatterning using RGD-functionalized poly(3,4-ethylenedioxythiophene) (PEDOT), resulting in nanoarrays with specific cell binding sites. In a different approach, crack-free PMeOx films on different polymeric substrates were prepared from α,ω-alkoxysilane PMeOx that was cross-linked in a sol-gel process through condensation with tetraethoxysilane and (3-glycidoxypropyl)trimethoxysilane.[41] To this end, the α,ω-telechelic alkene-functionalized PMeOx precursor, synthesized using allylic tosylate as initiator and allylamine as terminating agent, was silylated at both the α- and ω-end using thiol-ene coupling.

3 Poly(2-oxazoline)s with clickable side chains

One of the main features and advantages of PAOx, *f.e.* compared to the widely utilized PEG, is the possibility of straightforward side-chain modification. Side-chain functionalities can be introduced making use of functional 2-oxazoline monomers. Similar to initiating species, compatibility of the functional group on the 2-oxazoline moiety with CROP is of prime importance. Therefore, many interesting functionalities are not directly accessible *via* CROP and protected monomers with additional post-polymerization functional group deprotection is often required, complicating the synthetic procedure. Quantitative post-polymerization modifications using click chemistry has been successfully reported for PAOx with side-chain alkenes, alkynes and azides (Figure 5).

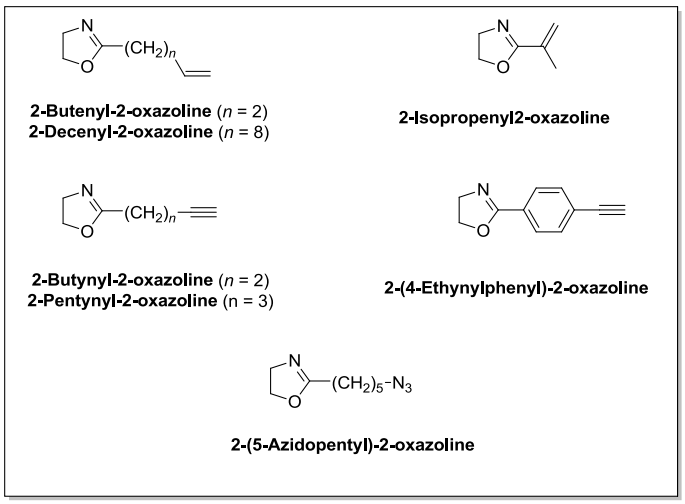


Figure 5. Overview of reported 2-oxazoline monomers with clickable side chains.

In addition, polymer properties such as hydrophilicity can be further fine-tuned by copolymerization of two monomers. Especially copolymerization of functional monomers with hydrophilic MeOx and EtOx has proven to be very popular in order to obtain water-soluble, biocompatible copolymers with clickable side chains. In a typical (co)polymerization a solution of the initiator and monomer(s) in a dry solvent, typically acetonitrile, is reacted at high temperatures by means of conventional heating or microwave irradiation.[54]

3.1 Synthesis of poly(2-oxazoline)s with clickable side chains

Since the first synthesis of a 2-oxazoline structure in 1889, a variety of strategies have been developed for the preparation of 2-oxazoline monomers.[17b, 55] Especially the Wenker method (starting from activated carboxylic acids) and the Witte-Seeliger reaction (starting from nitriles) are widely applied synthesis routes, both of which have been applied for the synthesis of 2-oxazolines with clickable side chains (Figure 6). In a first report on side-chain clickable PAOx by Jordan *et al.*, the Wenker method was used for the synthesis of an alkyne 2-substituted-2-oxazoline.[56] Therefore, hexynoic acid acid (**1a**) was activated to the acid chloride (**1b**) which was subsequently reacted with 2-chloro-2-ethylamine, resulting in a secondary amide (**1c**). Ring-closure of the secondary amide under basic conditions yielded the corresponding 2-pentynyl-2-oxazoline. A variation of the Wenker method was reported for the synthesis of 2-butynyl-2-oxazoline (ButynOx), where a carbodiimide / *N*-hydroxysuccinimide system was used to activate the carboxylic acid.[57] Although this butynyl moiety was used for post-polymerization functionalization and cross-linking of P(EtOx-ButynOx) copolymer micelles through a thiol-yne click reaction, it can also be used in CuAAC or SPAAC click reactions.[58] The Witte-Seeliger reaction is used to a much lesser extent for the synthesis of clickable 2-oxazoline monomers, due to the high cost of their nitrile precursors and possible side-reactions of the unsaturated bonds at the required elevated reaction temperatures. Also, the release of ammonia during this reaction is a major drawback as it acts as a chain transfer agent in CROP. 2-(4-Bromophenyl)-2-oxazoline was prepared *via* the Witte-Seeliger procedure and was further reacted in a Sonogashira coupling to obtain trimethylsilyl-protected 2-(4-ethynylphenyl)-2-oxazoline.[59]

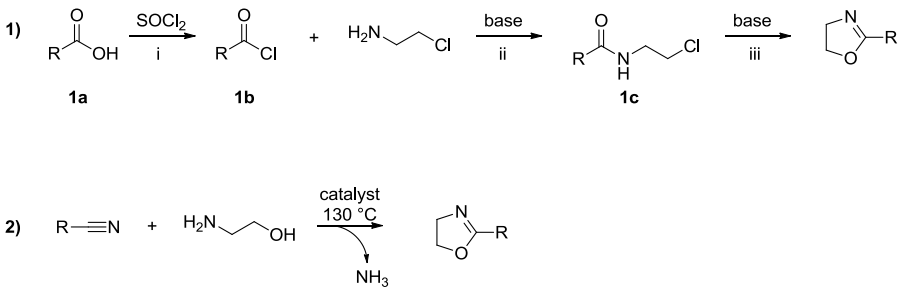


Figure 6. Commonly used synthesis routes towards 2-substituted-2-oxazolines: 1) Wenker method using an activated carboxylic acid. 2) Witte-Seeliger reaction.

The carbodiimide / *N*-hydroxysuccinimide variation on the Wenker method, similar to that for the synthesis of ButynOx, was also used to prepare 2-butenyl-2-oxazoline (ButenOx) by Schlaad *et al.*[60] In contrast to 2-isopropenyl-2-oxazoline, in which the double bond interferes with CROP,[61] the double bond of ButenOx is preserved during the polymerization as it is electronically decoupled from the oxazoline ring. Hoogenboom, Schubert *et al.* reported on a green approach for the synthesis of 2-decenyl-2-oxazoline (DecenOx) based on naturally derived undecenoic acid, in which traditionally used organic solvents such as dichloromethane and methanol were replaced by 2-methyl-tetrahydrofuran (mTHF), a solvent obtained from waste biomass.[62] As the (co)polymerization of DecenOx was performed in bulk and the subsequent UV-initiated thiol-ene click reaction proceeded in mTHF or methyl laurate, this represents a green alternative towards functional PAOx. Furthermore, the carbodiimide / *N*-hydroxysuccinimide system was applied for the synthesis of an azido-functionalized 2-oxazoline monomer, using 6-azidohexanoic acid as starting material by Udet and coworkers.[63]

The use of thiol-ene click reactions at the monomer stage has been explored for 2-isopropenyl-2-oxazoline, resulting in PAOx with aryl, ester, (protected) amine and (protected) carboxylic acid side chains.[64] However, CROP of these functional monomers gave low yields and no high molecular weight PAOx could be obtained because of incompatibility of the thio-ether bond with the CROP of 2-oxazolines.[65] A modular approach, using PAOx as a universal backbone, is also amenable since the number of synthesis steps is reduced to a minimum and a variety of functional PAOx can be produced. Up to now, post-polymerization modification of PAOx by means of click chemistry is mainly focused on CuAAC and thermal or UV-initiated free radical thiol-ene reactions.[56, 60]

3.2 Applications of poly(2-oxazoline)s with clickable side chains

Side-chain functionalization offers new perspectives in the sense that different architectures are achievable and higher degrees of functionality can be obtained compared to end-group functionalization. Polymer-polymer coupling, as described in section 2.2, has been performed on

PAOx with clickable side chains to obtain amphiphilic graft copolymers that self-assemble into nanoparticles. The grafting-onto approach as reported by Monge *et al.* (*cfr*. section 2.2),[50] has been applied for grafting of poly(D,L-lactide) onto side-chain functionalized azido-PAOx.[63] A frequently adopted approach to stabilize self-assembled micelles is covalent cross-linking of the micellar core. Such cross-linked micelles show better pharmaco-kinetic profiles, *i.e.* longer retention times, because fast disintegration is prevented. PAOx-based micelles have been cross-linked using thiol-yne click chemistry, with poly[2-(heptyl/pentynyl)-2-oxazoline] serving as hydrophobic blocks (Figure 7).[66] Moreover, amine end-functionalization of the hydrophilic PMeOx block, allowed surface modification of the obtained nanoparticles by alkylation of the amine functionality with different aromatic molecules.

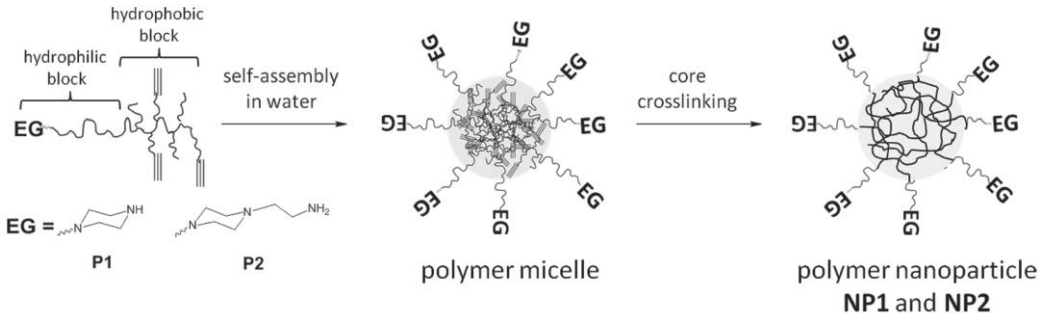


Figure 7. Self-assembly of amphiphilic PAOx and subsequent core cross-linking using CuAAC chemistry. *Reproduced with permission from Weberskirch, R. et al. Macromol. Chem. Phys.* ***2013****, 214, 2783-3791.*

Other PAOx-based microparticles, for which click chemistry has been applied to cross-link side-chain functionalized linear PAOx, are hollow capsules that can be used in drug delivery applications.[67] These capsules were synthesized by layer-by-layer assembly of PAOx/poly(methacrylic acid) brush copolymers onto silica particle templates, which were etched away with HF. Investigation of the protein adsorption showed low fouling behavior, although the best results were obtained for brush-like capsules based on a oligo(2-ethyl-2-oxazoline)methacrylate macromonomer with cross-linkable oligoethyleneglycol moieties.

Multifunctional nanoparticles based on P(EtOx-DecenOx) were synthesized by fully exploiting the versatility of PAOx and the modular approach of click chemistry, as reported by Hoogenboom,

Schubert *et al.* (Figure 8).[68] Here, three different clickable groups were incorporated into the PAOx structure, namely anthracene (initiation), alkene (side-chain) and azide (termination). Three Cu-free reactions, namely the Diels-Alder, thiol-ene and SPAAC reaction with maleimide, a thiol-functionalized sugar and cyclootyne, respectively, could be performed in a one-pot synthesis, emphasizing the orthogonality of the different reactions. Nanoparticles were obtained by labeling the cyclooctynol hydroxyl group with hydrophobic fluorescein 5(6)-isothiocyanate, which is a well-known biomarker.

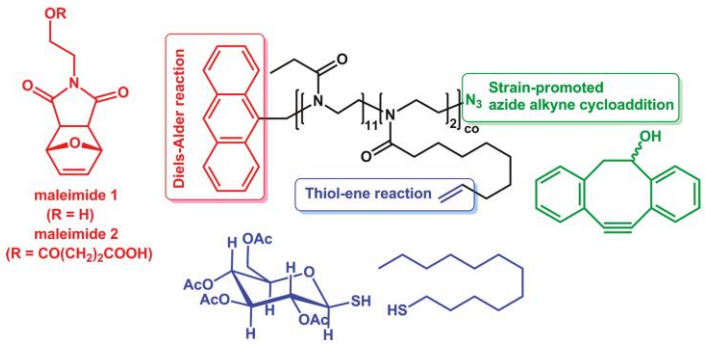


Figure 8. Schematic representation of multi-functional PAOx, synthesized using multiple bioorthogonal click reactions. *Reproduced with permission from Hoogenboom, R.; Schubert, U.S. et al. Macromolecules, **2011**, 44, 6424-6432.*

Cross-linking of polymeric chains has also been widely applied for the formation of hydrogels. Such swollen polymeric networks are emerging as biomaterials for controlled drug delivery and as three dimensional cell (3D) culture scaffolds.[69] Hydrolytically degradable PAOx hydrogels, based on MeOx/EtOx and DecenOx and an ester containing dithiol crosslinker, were synthesized by mild, cytocompatible radical thiol-ene cross-linking under low-intensity UV irradiation as reported by Dargaville and Hoogenboom.[70] Peptide adhesive sites (arginine-glycine-aspartic acid = RGD) were incorporated in protease degradable PAOx hydrogels, using the same mild thiol-ene photochemistry.[71] A live/dead assay showed that fibroblasts were largely unaffected by the curing process and were viable within the 3D hydrogel. In a related study, cross-linked networks of P(EtOx/2-nonyl-2-oxazoline-co-DecenOx) copolymers were obtained making use of a bis-2-oxazoline initiator.[72] Attachment of RGD motifs, using thiol-ene click chemistry, resulted in the formation of microparticles that show preferential binding to cancer cells.

Besides the use of cross-linking for hydrogel fabrication or stabilization of micro/nanoparticles, cross-linked hydrophobic PAOx have been proposed to produce alternative polyurethane thermosets.[73] Hard-rigid to soft-elastic materials could be obtained by control over the polymer microstructure during CROP, which determines the position and degree of functionalization. Solid-state UV-mediated cross-linking of alkene-functionalized PAOx copolymers was reported by Wiesbrock *et al*. for the fabrication of negative photoresists.[74]

Furthermore, physicochemical properties of PAOx are largely determined by the side-chain structure and can be tuned by changing the substituent in the 2-position of the monomer. In particular, tailoring of the LCST behavior of PAOx by side-chain variation has been widely investigated, because stimuli-responsive polymers hold great potential for biological applications.[75] The use of click chemistry for tuning of the cloud point was shown for P(*i*PropOx-ButenOx) copolymers using thiol-ene chemistry with different ω-functional thiols (Figure 9).[76] A series of glycosylated PAOx exhibited cloud points over the entire aqueous temperature range (10-85 °C) depending on the fraction of functional units and presence of hydrophilic hydroxyl groups. Similar glycopolymers based on P(EtOx-DecenOx) copolymers showed LCST behavior with cloud point temperatures increasing with increasing (hydrophobic) protected sugar content.[77] This counterintuitive effect was attributed to the formation of aggregates by hydrogen bonding between the sugar moieties, which is facilitated by the flexible decyl spacer. As such, the hydrophobic chain is shielded from the aqueous environment, resulting in an overall decrease of the hydrophobicity. In a related, but more advanced, system two sugar units were attached to the polymer backbone using CuAAC monomer modification and post-polymerization thiol-ene functionalization.[59] These thermo- and pH-responsive glycopolymers showed lectin (Concanavalin A) binding which renders them useful for cell targeting in diagnostic or therapeutic applications.[78] Lectin binding microspheres have been fabricated based on the irreversible LCST behavior of P*i*PropOx. P*i*PropOx undergoes irreversible crystallization upon long-term annealing above 60 °C, resulting in the formation of coagulate particles.[79] Surface modification of such microparticles was enabled *via* copolymerization of P*i*PropOx and ButenOx and subsequent thiol-ene reaction with thiol-functionalized sugars. A thermal stability study of thiol-ene glycosylated PButenOx

showed that C-S bond cleavage already occurs around 275 °C, while its unmodified analogue was stable up to ~ 405 °C.[80] This indicates that click functionalization can result in thermally less stable materials.

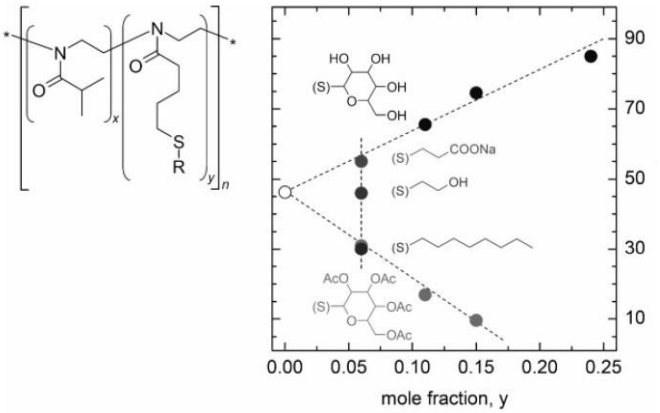


Figure 9. Tuning of the LCST behavior of thiol-ene modified PAOx. *Reproduced with permission from Schlaad, H. et al. Macromol. Biosci.* ***2009****, 9, 157-161.*

Interestingly, the homopolymer of ButenOx displays an upper critical solution temperature (UCST) at around 44 °C in ethanol/water mixtures (55/45 w/w).[81] Crystalline PButenOx microspheres, obtained by cooling down from solution, could be functionalized with hydrophilic short single-stranded nucleic acids using thiol-ene chemistry. No morphology change was observed after post-polymerization modification, and the nucleic acid grafts present on the surface of the microspheres were still active towards hybridization with complementary sequences. The specifity of the hybridization makes such systems attractive for sensing applications.

Zwitterionic PAOx could be synthesized starting from statistical P($EtOx_{30}$-$ButenOx_{10}$) copolymers by thiol-ene reaction with 2-dimethylaminoethanethiol and subsequent quaternization of the amino-functionality with 1,3-propansultone and β-propiolactone (Figure 10).[82] The resulting poly(sulfobetaine)s and poly(carboxybetaine)s were characterized with good cell and blood compatibility as well as anti-coagulant activity. Moreover, given the 'stealth' behavior of these zwiterionic PAOx, they are excellent candidates for use in anti-fouling coatings, *f.e.* for medical devices. The same P($EtOx_{30}$-$ButenOx_{10}$) precursor was used for the preparation of Pt(II)-containing

PAOx with tumor targeting saccharides to produce an alternative for the commercial anticancer drug, cisplatin (Figure 10).[83] Both the sugar and Pt(II) coordinating ligand, terpyridine, were attached to the polymer chain through thiol-ene click chemistry with the PAOx alkenyl side-chain. The *in vitro* cytotoxicity of these platinum containing glycopolymers showed similar results to cisplatin.

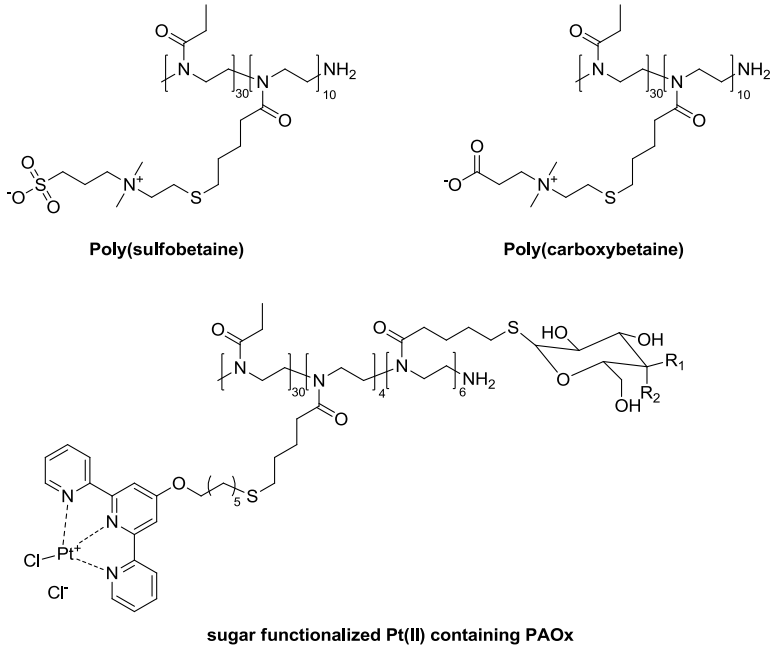


Figure 10. Structure of zwitterionic PAOx and Pt(II) containing PAOx, synthesized using thiol-ene chemistry.

Very recently, Traeger, Schubert and coworkers reported the synthesis of a library of cationic PAOx by thiol-ene functionalization of P(MeOx-ButenOx/DecenOx) copolymers with *t*-butyl carbamate (boc) protected 2-aminoethanethiol or dimethylaminoethanethiol.[84] These PAOx, with pendant primary and tertiary amino groups in the side-chain, were screened for non-viral gene delivery. It was shown that the transfection efficiency, DNA condensation as well as cytotoxicity and polyplex stability strongly depends on the hydrophobicity of the PAOx copolymer and the type and amount of amino groups.

Furthermore, CuAAC click chemistry was used to conjugate the antiparkinsonian drug rotigotine to P(PentynOx$_{10}$-EtOx$_{190}$).[85] The use of a hydrolytically cleavable ester linker between the PAOx chain and the drug allowed for control over drug release rate. As such, sustained release of rotigotine was

observed in male rats, leading to long-term anti-parkinsonian effects as well as a reduction of motor complications, which is commonly observed in therapies that cause large dopamine fluctuations.

4 Conclusions and outlook

In the past few decades, click chemistry has become very popular in polymer science as click reactions are characterized by quantitative yields, high functional group tolerance and can be performed in heterogeneous reaction media. This review describes the use of click chemistry for post-polymerization modification of poly(2-oxazoline)s (PAOx) towards a variety of functional materials ranging from new polymeric architectures *via* supramolecular assemblies for drug delivery applications to bioconjugates and organic-inorganic hybrids. Especially for biomedical applications, PAOx have been gaining increasing interest because they combine biocompatibility with so-called stealth behavior leading to a wide variety of PAOx-based drug delivery systems that are already described. We have shown that the living nature of the cationic ring opening polymerization, followed by post-polymerization modification using click chemistry, allows for the synthesis of highly defined structures with specific (stimuli-responsive) properties. To this end, well-defined PAOx with a variety of 'clickable' groups including unsaturated bonds and azide functionalities have been synthesized, making use of functional initiating species, monomers and/or terminating agents.

Nevertheless, to the best of our knowledge, a number of click chemistries has not been investigated in combination with PAOx so far, leaving a myriad of possibilities to be explored. For example, aldehyde-functionalized PAOx, that have been used in amine and hydrazine ligation reactions were recently reported,[86] and could be further utilized in aldehyde-aminooxy click type reactions.[87]

More advanced, multi-functional PAOx materials can be obtained using multiple orthogonal click reactions. The use of various orthogonal click reactions offers an elegant route towards complex polymer structures with specific functionalities and properties, as was recently reviewed by Tunca.[88] We believe that further advances within this relatively new research area will help to develop PAOx-based platforms that fully exploit the versatility of this interesting class of polymers.

5 Acknowledgements

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