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248th ACS National Meeting & Exposition, San Francisco

Cysteine side-chain functionalized poly(2-oxazoline) as versatile building blocks for biomaterials

Poly(2-oxazolines) are an interesting and upcoming class of polymers as potential alternative to poly(ethylene glycol). While poly(ethylene glycol) has to be prepared using highly reactive oxirane-monomers via anionic polymerization, the living cationic ring-opening polymerization is an easy and experimentally robust method to polymerize 2-substituted 2-oxazolines. It offers the advantage of controlled degree of polymerization and polymer architecture for polymers with low dispersity and broad variability in terms of the chemical functionalization of the polymer side chains. For example, different oxazoline monomers with acrylic or allyl side-chains combine oxazoline-based advantages like biocompatibility with the opportunity of metal salt free “thio-ene-click” reactions [1] that can be exploited for the preparation of cytocompatible hydrogels.[2]

The introduction of thiazolidines (protected cysteines) at the side-chain of polymers would provide water-soluble macromers with cysteine capacity.[3] Vicinal amino thiols offer versatile opportunities, for example using the amine for ionic interaction and the thiol for redox sensitive cross-linking. They especially permit chemo-selective coupling using native chemical ligation (NCL) which describes the selective conjugation of cysteine moieties with thioesters via a stable peptide bond. Thioesters rapidly exchange with α -aminothiols yielding thioesters with an adjacent amine. These amine-substituted thioester rearrange fast to the final stable amide.

Here we present an easy route to synthesize water-soluble cysteine functionalized poly(oxazolines) by living cationic ring opening polymerization of the thiazolidine-functionalized monomers 2-(methyl)-2-oxazoline and 2-(butenyl)-2-oxazoline respectively 2-(decenyl)-2-oxazoline and subsequent deprotection to cysteine-residues. The amount of cysteine side-chains were predetermined by the statistical copolymerization of the monomers and confirmed by NMR. We present examples of hydrogel formation using these polymers and show that the functionalization with deprotected thiazolidines enables simple attachment of proteins by NCL and leads to polymer-protein conjugates in a chemically orthogonal and highly selective manner.

[1] R. Luxenhofer and R. Jordan, *Macromolecules*, 2006, **39**, 3509-3516.

[2] B. L. Farrugia, K. Kempe, U. S. Schubert, R. Hoogenboom and T. R. Dargaville, *Biomacromolecules*, 2013, **14**, 2724-2732.

[3] C. P. R. Hackenberger and D. Schwarzer, *Angewandte Chemie International Edition*, 2008, **47**, 10030-10074.