

ABSTRACT

Since the discovery of the copper catalyzed cycloaddition reaction between azide and alkyne (CuAAC), the scientific community has been motivated to explore additional highly orthogonal and efficient reactions, which can be conducted under mild reaction conditions. Some of the chemistries, which are widely explored are thiol-ene/yne reactions, nucleophilic ring opening reactions, as well as Diels-Alder/hetero Diels-Alder ligations. Thiol-ene reactions can proceed by either a radical mechanism or in a base catalysed fashion (Michael addition). The well-known radical-mediated thiol-ene reaction can be initiated by UV-light in the presence of a photo initiator or by heat in the presence of a thermal initiator. Recently, new pathways for initiating/catalyzing the thiol-ene reaction have been explored such as ultrasound, transition metal polypyridyl photocatalyst, 1,8-diaza bicyclo(5.4.0) undec-7-ene (DBU), base generated *via* visible light, and photo-labile base/super base.

In this thesis, we have studied in detail, a new method for initiating the thiol-ene reaction *via* the use of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) under ambient conditions, which can be applied for the synthesis of functionalized polymeric microspheres, amphiphilic block copolymers, bioconjugate hybrids as well as for modification of solid substrates. TEMPO is a stable nitroxyl radical, whose stability is due to the steric hindrance of four methyl groups surrounding the nitroxyl functionality. TEMPO is commonly used in nitroxide mediated polymerization (NMP) at high temperatures. The governing mechanism of NMP is the reversible deactivation of the propagating polymer radical by combination with a nitroxide radical. Importantly, using TEMPO as an initiator for the thiol-ene reaction is beneficial as the reaction can be performed under ambient conditions without applying heat or UV light, and therefore opening an avenue for the conjugation of biological entities such as amino acids or peptides, which are heat-sensible.

The optimization of thiol-ene reaction initiated *via* TEMPO was performed by using variety of thiols, enes, solvents and TEMPO concentration. In order to explore application of TEMPO initiated thiol-ene reaction for the construction of amphiphilic block copolymers, bioconjugate hybrids, polymeric microspheres and functionalization of solid substrates, firstly well-defined and responsive thiol and ene functionalized polymers were synthesized using reversible addition-fragmentation chain transfer (RAFT) and high-temperature polymerization techniques. The thiol-terminated polymer (poly(*N*-isopropylacrylamide), poly(acrylic acid), polystyrene) were prepared by RAFT polymerization of *N*-isopropylacrylamide, acrylic acid and styrene in the presence of RAFT agent and its subsequent aminolysis. The high-temperature polymerization of isobornylacrylate (iBoA) resulted in poly(isobornylacrylate) functionalized with ene moiety (PiBoA-Ene).

In order to synthesize bioconjugates hybrid materials, on the conjugation of poly(*N*-isopropylacrylamide) (PNIPAM)/poly(acrylic acid) (PAA) with cysteine (Cys) (PNIPAM-Cys/PAA-Cys) was performed *via* TEMPO initiated thiol-ene reaction. In order to use cysteine for the preparation of these hybrids materials, firstly functionalization of cysteine with 1,4-bis(acryloyloxy)butane was carried out using TEMPO initiated thiol-ene reaction in an aqueous medium under ambient reaction conditions. The thiol terminated polymers were reacted with Cys-Ene monomer again using TEMPO initiated thiol-ene reaction in an aqueous medium under ambient reaction conditions to yield responsive hybrid bioconjugates. In addition, the antibacterial activity of hybrid materials based on cysteine was evaluated.

The well-defined and responsive amphiphilic block copolymers based on poly(*N*-isopropyl acrylamide)-*b*-poly(isobornyl acrylate) (PNIPAM-*b*-PiBoA), poly(styrene)-*b*-poly(acrylic acid) (PS-*b*-PAA) and poly(isobornyl acrylate)-*b*-poly(acrylic acid) (PiBoA-*b*-PAA) were also synthesized using TEMPO initiated thiol-ene reaction under ambient conditions.

Additionally, modification of silicon wafer was performed by grafting responsive polymer brushes using TEMPO initiated thiol-ene chemistry under mild reaction conditions. The antifouling property of silicon wafer conjugated with cysteine was studied using fluorescence microscopy.

Finally, a series of cross-linked microspheres were synthesized by TEMPO-initiated thiol-ene dispersion polymerization using combinations of a variety of thiols and enes. The surfactant polyvinylpyrrolidone (PVP) loading was varied in order to establish particle dispersion and morphology of cross-linked microspheres. We have synthesized microspheres possessing excess thiol functionalities as well as possessing excess ene functionality, as this will open the possibility to perform a second thiol-ene reaction using TEMPO as an initiator. Therefore, the ability of the microspheres for a second TEMPO-initiated thiol-ene reaction was demonstrated by the ligation of fluorescein-5-maleimide (an ene) to the microspheres' surface containing an excess of thiol functionality and by ligation of cysteine (containing a thiol group) to the microspheres' surface containing an excess of ene functionality.