

The Use of Click Chemistry in Polymer Synthesis and Modifications

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Abstract. Click chemistry refers to the type of chemical reactions that occur between specific pairs of reagents, taking place under mild conditions with high stereoselectivity. These characteristics help chemists to construct very complex molecules in a relatively easy, quick, and precise manner. Polymers are widely used in daily life which are composed of repeating monomers. They can be designed and synthesized to meet certain characteristics to apply in real life. Click chemistry plays an essential role in creating new polymers, including modifying them afterwards. This paper introduces three typical click chemistry reactions in polymer synthesis and modifications, which include Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC), thiol-ene reaction, and Diels-Alder reaction. They all have positive impact in synthesizing and modifying polymer. CuAAC reaction is applied to make desired polymer with crosslinking structure or other desired protein structure and modify the product by introducing new functional groups. Thiol-ene reaction makes good use in producing adhesives, including light-curing adhesive and bio-based adhesive, as well as surface modification. Diels-Alder reaction provides new insights in the synthesized polymers. At last, double click chemistry, which is still at the stage of preliminary exploration, contributes to creating complex polymers. The use of click chemistry in polymers is powerful and useful, leading the development of advanced materials and upgrading synthesizing skills.

Keywords: Click chemistry, polymer, CuAAC reaction, Thiol-ene reaction, Diels-Alder reaction.

1. Introduction

Click chemistry refers to a set of chemical reactions that generate molecules in high efficiency, under mild conditions, and have selectivity by joining small molecules together as building blocks. The term “click” was explained by K. Barry Sharpless in 2001. Click also emphasizes how easily the building blocks join together just like a buckle [1]. Any chemical reactions can count as click chemistry such as cycloaddition reaction, carbonyl condensation, and addition reaction [2]. They all have click chemistry characteristics which make them versatile. The fields of organic synthesis and biomolecular synthesis are where click chemistry is most frequently applied. Biomolecules like nucleic acids, peptides, and carbohydrates can be linked together covalently to form specific drugs or proteins which has great use in drug development and bioconjugation [2]. Other than biomolecules, nanomaterials can also be made using click chemistry while its ability to small molecule building blocks provide an easy path for making materials with specific properties. Overall, click chemistry has numerous applications in real life. Since click chemistry works as an efficient tool in chemistry synthesis and molecule modification, polymer chemistry is also strongly influenced by click chemistry. Polymers are large, high molecular weight compounds made up of repeating units called monomers. It was first proposed by a German chemist, Hermann Staudinger [3]. It is divided into two types: natural polymers like cellulose and rubber, and synthetic polymers like polyethylene, polypropylene, polystyrene, and so on. Different from small molecules, polymers tend to have long chains or crosslinking as network structures which make them have unique properties such as being more flexible, rigid, or thermosetting. They are synthesized by various polymerization techniques while the monomers are joined together. Polymers are widely used in people’s daily life, and it covers many different areas such as packaging, medicine and healthcare, and adhesives. However, with the development of technology and higher requirements for materials, basic polymers are not suitable for daily uses anymore. For example, polyethylene used as plastic is not recommended anymore while

people use bio-degradable plastic instead. That is why polymer synthesis and modification play an important role in real life applications. Natural polymers are another example for use of polymers, they are good for the environment as they are biodegradable. Some environmental-friendly polymers can be synthesized out of those natural polymers, such as some new adhesives which contribute to the long-term development of materials [4]. As a result, polymers are important to us due to their wide application.

Both click chemistry and polymer chemistry are important to real-life applications. They are closely related. In the process of synthesis, functionalization, and modification of polymers, click chemistry has a significant influence. With the help of click chemistry, the polymerization processes can be accelerated and well-controlled in mild conditions. Due to the stereoselectivity click chemistry has it can produce specific polymers with the correct structure. Since there are many reactions considered as click chemistry, the discussion of how each reaction responds to polymer chemistry is meaningful and essential for a better understanding of the application of click chemistry in polymers. Click chemistry has many advantages that traditional synthesis methods do not have. Other methods require longer reaction time and more complex conditions or have bad selectivity. Compared with click chemistry, they are not ideal choices for synthesizing and modifying polymers. As a result, according to different reactions in click chemistry, which are copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), thiol-ene reaction, Diels-Alder reaction, and double click reaction, their use in polymers will be discussed in the following sections.

2. Use of click chemistry in polymers

In click chemistry, several reactions have been applied in polymer chemistry commonly and successfully. Each of these has specific use in polymer synthesis which brings high efficiency, more applications, and more varieties in polymer chemistry.

2.1. CuAAC reaction

CuAAC stands for copper(I)-catalyzed azide-alkyne cycloaddition and it is one of the most commonly used reactions in click chemistry. The organic azides and alkynes react together with copper(I) as a catalyst to form 1,2,3-triazoles, as shown in Figure 1. Its advantages are producing desired products with high efficiency and only requiring mild conditions. So, it works well under room temperature, with no specific high or low temperature is required [5]. It can be extensively employed in synthesizing biopolymers, polymer crosslinking, and post-polymerization modification.

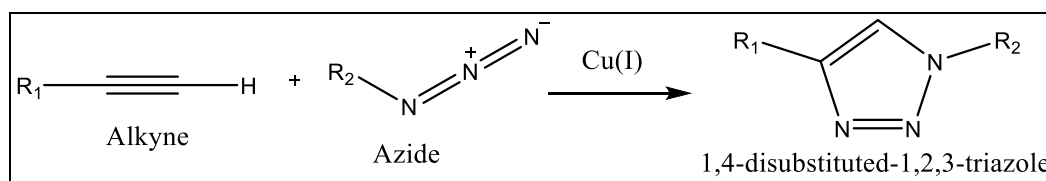


Figure 1. CuAAC reaction

Guan et al. synthesized hierarchical nanofibrils using peptide monomers through CuAAC reaction. Hierarchical nanofibril is a biopolymer that has a β -sheets structure (shown in Figure 2).

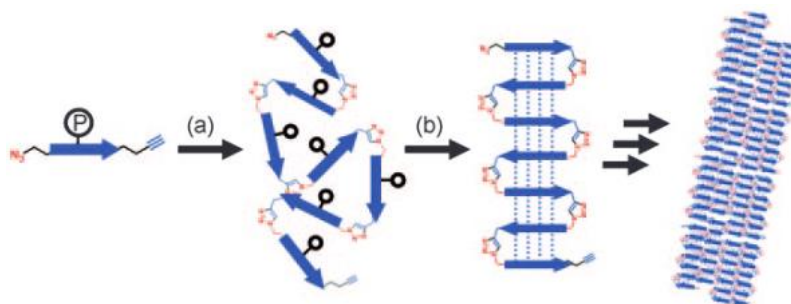


Figure 2. β -sheets structure of a biopolymer [6]

They were able to establish cycloaddition between peptide bonds ended with azide and alkyne groups, resulting in the production of a triazole ring and, later, β -turn formation, using CuAAC. This is because CuAAC reaction has great functional-group tolerance and it can be applied to a variety of substrates, overall becoming a great mechanism for synthesizing biopolymers like hierarchical nanofibrils. Moreover, with the versatility of CuAAC reaction, they could continue turning the β -sheets structure into hierarchical nanostructures through intermolecular organization [6]. For polymer crosslinking, a hydrogel is a good example of a crosslinking product. Crosslinking has provided it with a unique network structure to make it a good material for smart adhesion and applications in medicinal chemistry. Crescenzi et al. synthesized hyaluronic acid(HA)-sodium salt using water-soluble polysaccharides which contain alkyne and azide as their side chains respectively. Its mechanism is shown in Figure 3. This is an example of combing two polymers together to make a polysaccharide-bearing nanogel through a CuAAC reaction. It is used in drug delivery where they act like scaffolds to program cells and control drug release into the cells [7].

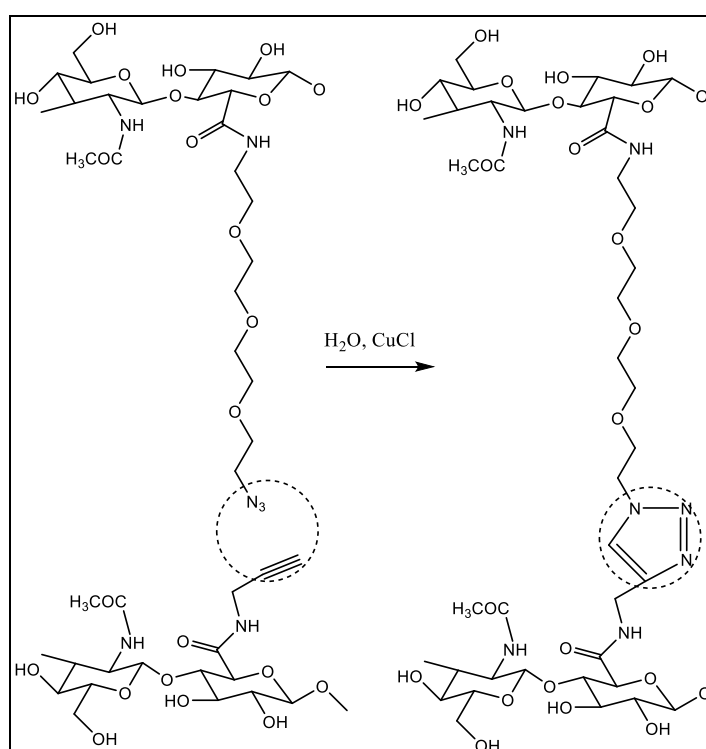


Figure 3. Mechanism of polymer modification with water and CuCl

In addition to using CuAAC reaction to make polymers, it can also be applied to post-polymerization modification to make more use of the existing polymers. Zengwen Li et al. successfully synthesized poly (propargyl 2-ylidene-acetate) and through CuAAC reaction completed its side chain attached by a pentafluorophenyl azide shown in Figure 4. The C1 polymerization is carried out first to avoid the self-polymerization of the reactant itself to proceed into post-polymerization. After going through the reaction of CuAAC, it provides a general route for other side chain reactions such as replacing one fluorine with a thiol group followed by para-fluoro-thiol (PFTR) reaction [8]. This application provides wider routes for molecules like this to be changed and go through more reactions by introducing new functional groups to the original molecule which helps to change its chemical properties. As a result, the CuAAC reaction can also be used as PPM methods as they provide high efficiency and compatibility with various functional groups.

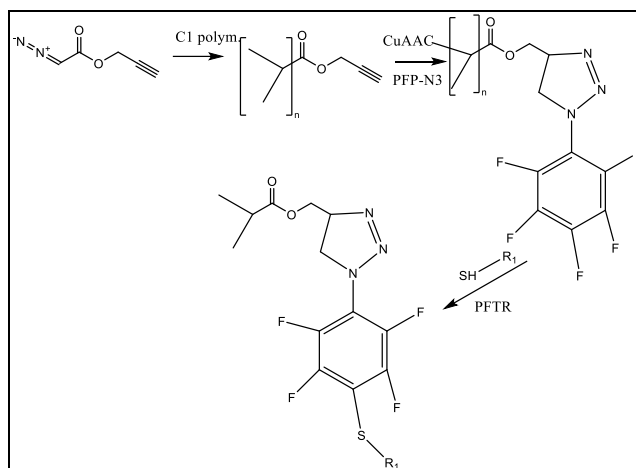


Figure 4. Mechanism of synthesizing poly (propargyl 2-ylidene-acetate)

2.2. Thiol-ene reaction

The thiol-ene reaction is an organic addition process in which a thiol group is added to an alkene group to generate a thioether, shown in Figure 5. It is widely used in click chemistry due to several advantages which are producing high-yield products, high reaction rate, mild reaction conditions required, and specific stereoselectivity as it is an anti-Markovnikov addition. Its first mechanism proceeds as free-radical addition which contains initiation, propagation, and termination. According to Scheme, after the radicals are generated, either chain growth or step growth will proceed. The second mechanism works as a Michael addition where the same product is produced [9]. Thiol-ene reaction has a wide application in polymer chemistry in surface modification and adhesives.

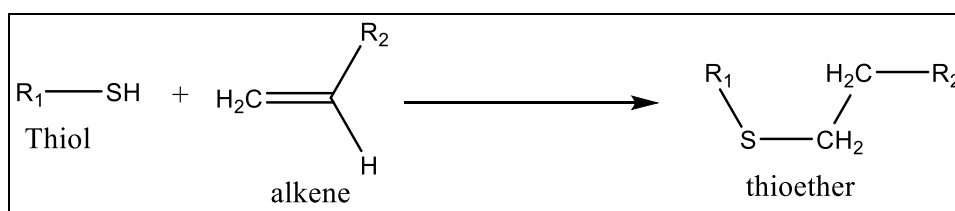


Figure 5. Thiol-ene reaction

Thiol-ene reaction is useful for polymer coating, which is a process of adding a thin layer of polymer material onto a surface to achieve specific purposes such as protection or aesthetic. In the area of UV-curing, the thiol reacts with different types of unsaturated compounds such as TTT or TEGDVE shown in Figure 6, and it leads to a thiol-ene polymer with a high Tg value in network structure. With the added thiol group, the molecule's functionality and rigidity can be controlled. Being insensitive to oxygen is another advantage of adding a thiol group because thiols with higher functionality lead to higher viscosity that is used to reduce oxygen diffusion through polymer layers. Reducing the diffusion of oxygen in polymer coating would enhance the stability of the material as most of these materials would be oxidatively degraded when exposed to oxygen. As a result, it also helps to prevent corrosion by acting as a barrier between the material and the environment [10]. Overall, this reaction provides a practical use in polymer materials, extending their durability.

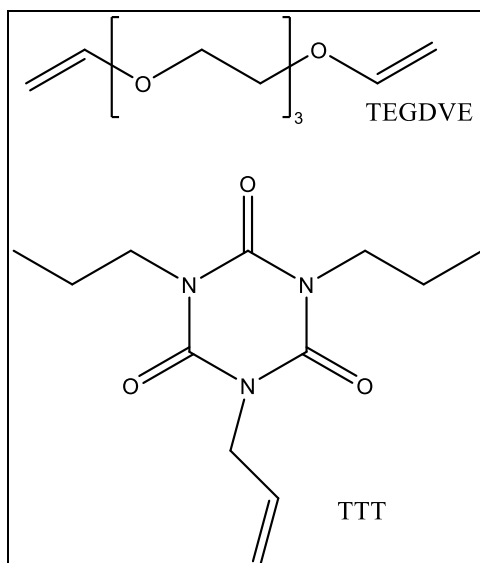


Figure 6. Structures of TEGDVE and TTT

Considering more about sustainability, the bio-based thiol-ene coating emerged which is more environmental-friendly. Johan et al. completed the reaction between thiol and methyl oleate and methyl linoleate, respectively, which are two common fatty acids. They discovered that it was a viable method for obtaining required unsaturated fatty acids from vegetable oils. It operated by unsaturated fatty acid double bonds interacting with the thiol group, producing a new type of oil called multifunctional thiol attached by the thiol group. Moreover, with this characteristic, they carried out UV-cured coating that provided high energy efficiency. It also created a hard and durable surface for abrasion resistance [11]. With the thiol group, the effect of thiol functionality shows a great advantage in pressure-sensitive adhesion compared to conventional photopolymerized acrylic pressure-sensitive adhesives. After this comparison, Oihane et al. concluded that polymers with a high gel content (66%), moderate crosslinking (swelling degree 391%), and a low T_g value can undergo polymerization quickly and operate effectively as a pressure-sensitive adhesive [11]. Overall, the thiol-ene reaction contributes to making better-adapted polymers in real-life applications such as surface modification and adhesives, providing a better structure of polymers, and making more useable materials with high efficiency.

2.3. Diels-Alder reaction

The Diels-Alder reaction is a chemical reaction between a conjugated diene (a molecule with two double bonds) and a dienophile (a molecule with one double bond) to create cyclohexene. It is also a one-step coordinated procedure that converts two pi bonds into two sigma bonds. Because diene is an electron-rich species and dienophile is an electron-poor species, the mechanism is depicted in Figure 7, where the ring is created by the interaction of four pi electrons from the diene and two pi electrons from the dienophile. As diene is an electron-rich species while dienophile is an electron-poor species, its mechanism is shown in Figure 7, where the ring is formed by the interaction of four pi electrons of the diene with two pi electrons of the dienophile. This reaction has recently been considered as click chemistry because it has selectivity, and versatility, and produces high efficiency although it may require high-temperature conditions and catalysts [12]. Its use in polymer chemistry is wide, including in different types of polymer synthesis, adding more useable features to the polymers synthesized and used in dynamic-covalent structures.

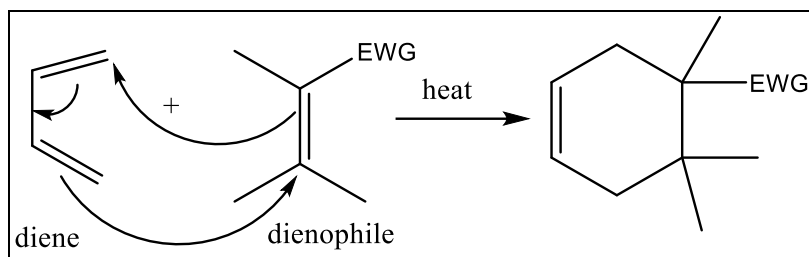


Figure 7. Diels-Alder reaction

The Diels-Alder reaction can be used to synthesize macromolecules such as homopolymers, telechelic polymers, and block copolymers. Taking homopolymers as an example shown in Figure 8, the Diels-Alder reaction starts by using either A-B monomer or A-A, B-B monomer to turn them into a cycloalkene. Then common polymerization reactions like polycondensation link these molecules to a long polymer chain. The use of Diels-Alder reaction in this case is creating a DA linkage on the polymer chain which can be used to adjust the chain length and control the viscosity [13].

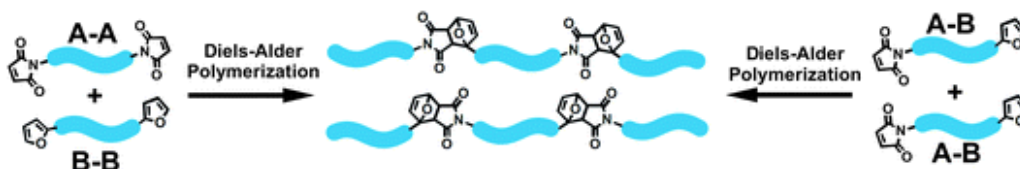


Figure 8. Synthesis of homopolymers [13]

As this reaction provides Diels-Alder linkages to the polymer chain which can contribute to making dynamic-covalent bonds in the structure of macromolecular stars. These bonds are used in reversible reactions, making highly branched macromolecules. By the reconfiguration of bonds, the structure of a molecule can be altered which makes the material adaptable for all kinds of uses. Abhijeet et al. carried out an experiment in synthesizing the block copolymer of maleic anhydride and styrene [poly(styrene-*alt*-MAN)-*b*-polystyrene (P(S-*alt*-MAN)-*b*-PS)] by reversible addition fragmentation chain transfer (RAFT) polymerization. To achieve the star-like structure shown in Figure 9, block copolymers are pre-assembled into polymeric micelles. Following that, a Diels-Alder reaction was performed at 50°C, resulting in core-crosslinked micelles and adding Diels-Alder connections to the polymer chains. They concluded that the linkage was a great way to make dynamic-covalent nanostructures for more adaptations [14]. To sum up, Diels-Alder reaction provides a way to create desired polymers by adding more features to those polymers. These modifications influence the development of polymer materials.

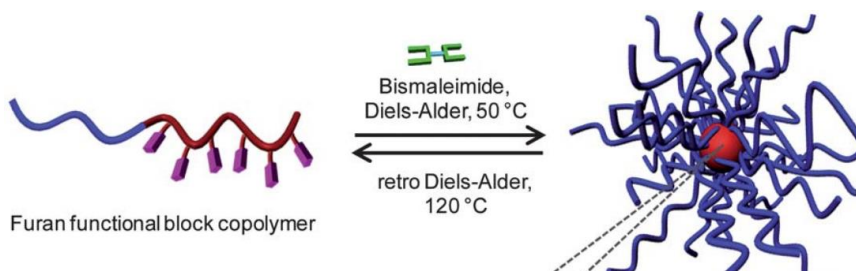


Figure 9. Cross-linked stars [14]

2.4. Double click reaction

Besides the individual reactions above, double click reaction has been developed more and more to design more complex molecules. Double click reaction provides new synthetic pathways or polymerization processes which can be applied to get more precise molecular weight and control the distribution of functional groups. Hizal et al. employed both the CuAAC and Diels-Alder processes to create linear ABC triblock copolymers. They used the orthogonal reactivity of azide-alkyne and anthracene-maleimide cycloadditions to their advantage. The intermediate block was a hetero-telechelic polystyrene with anthracene and azide functional groups at the chain ends (anthracene-PS-

N3). Triblock copolymers, PMMA-b-PS-b-PEG, and PMMA-b-PS-b-PCL were successfully produced in a modular manner by treating this polymer with furan-protected maleimide-terminated poly (methyl methacrylate) and either alkyne-terminated poly (ethylene glycol) or poly (ϵ -caprolactone). Overall, they successfully combined the CuAAC reaction and Diels-Alder reaction together to synthesize an ABC type block copolymer [15]. As a result, double click reaction can do stepwise functionalization in polymer synthesis which introduces different functional groups onto the polymer chain sequentially. This also allows more precise control of the reaction to make the desired composition of chemicals. In addition to linear polymers, double click reaction can also be used in synthesizing non-linear polymers, and branched polymers. Tunca et al. synthesized a three-arm star block polymer also using the combination of CuAAC and Diels-Alder reactions [15]. Although double click reactions can be used in many situations, only certain reactions can be combined and there are still many more reactions that need to be discovered.

3. Conclusion

Overall, click chemistry has a great impact on polymers. With its special advantages of high efficiency, only requiring mild reaction conditions, and specific stereoselectivity, desired polymers can be synthesized through click chemistry reactions. Since all click chemistry reactions have the advantages mentioned above, by analyzing each reaction separately, their own use is concluded in this paper. CuAAC reaction is good for making desired materials like hierarchical nanofibrils by changing the polymer structures. It can also be used for modifications of polymers after synthesizing to get better adapted material. Thiol-ene reaction mainly works in polymer coating which is another method in polymer modification. After polymer coating, the original polymer can be exposed to air for a longer time, with a better air resistance. It also helps to adjust adhesives, including UV-curing adhesive and pressure-sensitive adhesive using biodegradable materials. Diels-Alder reactions can help adjust the polymer chain length and control the viscosity, also making dynamic-covalent bonds in star-shape polymers. Double click chemistry is used to synthesize more complex polymers, both linear and non-linear polymers. With the description and conclusion of how each click chemistry reaction contributes to polymers, more precious and easier choices can be made when coming across with the application and modification of click chemistry in polymers. There are still many double click reactions combinations and adaptation to be discovered. One of the current challenges in click chemistry applied in polymer science is about scale-up and manufacturing. Some experiments went well in the lab but its transition from lab-scale to manufacturing-scale requires more innovative methods to keep the quality the same. As there are still many difficulties in polymer chemistry right now, in the future, with more study and discovery in this area, more advantages would give to polymer chemistry with its help.

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