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Perspective

Click chemistry in polymer science

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SUMMARY

The concept of click chemistry has revolutionized chemical sciences. For polymer science these high efficiency coupling reactions are of great importance as they enable coupling of large macromolecules and cyclic polymers, as well as quantitative end-group and side-chain modification. Hence, click chemistry has become an indispensable tool for polymer chemists for the development of functional materials. In this perspective, I will discuss my personal view on the key developments of click chemistry in polymer science focusing on the copper(I) catalyzed azide-alkyne cycloaddition reaction.

Polymer synthesis; polymer architecture; polymer modification; azide-alkyne cycloaddition

INTRODUCTION

The synthesis of functional polymers is an important research area that provides a strong basis for the development of advanced functional materials.[1] Functional polymers span a broad range of chemical functionalities in the side chain, main chain or end-groups as well as polymer architectures and monomer compositions, which all influence the final polymer properties and application potential. The development of living and controlled polymerization methods has provided enormous potential for the design and preparation of defined polymer structures, making it possible to prepare block copolymers and polymers with high end-group fidelity, for example.[2] However, not all monomer combinations or functional groups are compatible with the same polymerization method. Hence, certain block copolymers or functional polymers are prepared through post-polymerization modification methods to couple polymer building blocks or to functionalize a polymer precursor. Within the realm of such post-polymerization modification methods, the development of click chemistry has made a major contribution over the past twenty years.

The concept of click chemistry was introduced in 2001 by Sharpless to identify spring-loaded reactions that are modular, wide in scope, high-yielding, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and stereospecific (but not necessarily enantioselective).[3] In particular, the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) was identified to fulfill all these requirements and over the years has become the most popular 'click reaction' (Figure 1a).[4,5] This work also inspired further development in bioorthogonal chemistry based on non-catalyzed click reactions involving strained alkynes and strained alkenes as well as tetrazines.[6] These combined efforts were recognized with the 2022 Nobel Prize in chemistry that was awarded to Carolyn R. Bertozzi, Morten Meldal and K. Barry Sharpless for their development of click chemistry and bioorthogonal chemistry.[7]

The popularity of click chemistry in polymer science is related to the difficulty in purification of polymers. Coupling reactions involving multiple polymeric building blocks to obtain a larger polymer structure are associated with challenging removal of unreacted or partially reacted polymer precursors, as this requires separation of multiple macromolecules that may have similar solubility properties and similar hydrodynamic radius. For end-group modification, it becomes even more challenging (often impossible) to separate polymer chains that have different end-groups, as the end-group only has a minor effect on the

properties of the final polymer. These separation challenges become even more pronounced when working with higher molar mass polymers. To avoid these challenges, efficient post-polymerization protocols and methods are of utmost importance, which explains the popularity of click chemistry in polymer science as it allows near-quantitative post-polymerization modification. In 2011, a team of synthetic polymer scientists extended the original definition of click chemistry for polymer modification reactions to also include that polymer click reactions should be fast and proceed with high yields under equimolar conditions, to avoid purification problems.[8]

Within this perspective article, the important milestones of using click chemistry in polymer science will be discussed, from the author's perspective, highlighting how click chemistry has become an enabling tool in polymer science. The first section will focus on the use of click chemistry as an enabling tool for polymer synthesis, while the second section will highlight emerging applications of polymers prepared using click chemistry. This perspective will focus on the developments using the most important CuAAC click reaction, and the reader is referred to other reviews for a discussion on the use of other click reactions in polymer science.[9-14] At the end of this perspective article, a brief conclusion of the current status and future of CuAAC click chemistry in polymer science will be provided.

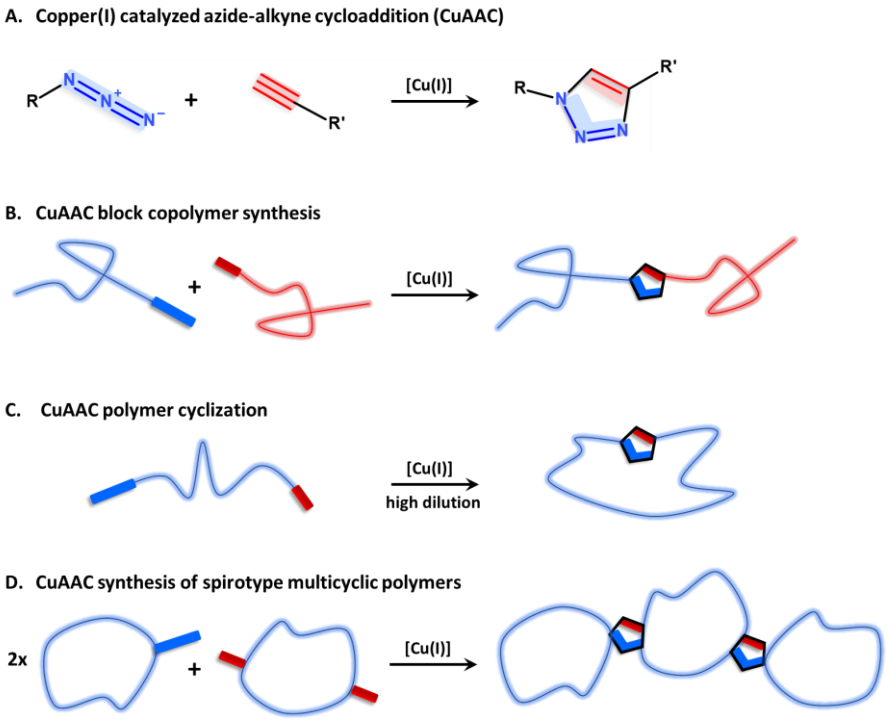

Figure 1. Overview of the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) click reaction and examples of its use in polymer science.

(A) The most common click reaction based on the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) resulting in the formation of a 1,2,3-triazole. Representative examples of the use of the CuAAC click reaction in polymer science for the formation of different polymer architectures, including the formation of block copolymers based on CuAAC of near-equimolar amounts of polymer precursors (B), cyclic polymers under high dilution CuAAC of α-alkyne-ω-azide-functional polymer precursors (C), and spirotype multicyclic copolymers using near-equimolar amounts of cyclic polymer precursors (D).

CLICK CHEMISTRY AS TOOL FOR POLYMER SYNTHESIS

The potential of the CuAAC click reaction for polymers science was quickly recognized after its introduction, and the first publications on 'clicking polymers' soon appeared around 2004. This perspective article does not intend to comprehensively describe all developments in this area, but rather highlights some key areas and key publications. For a comprehensive review of the early works on CuAAC click chemistry in polymer science, the reader is referred to previous review articles.[11,15,16]

In one of the first reports on using CuAAC click chemistry for macromolecules, Hawker, Sharpless and Fokin described the preparation of triazole-dendrimers using the CuAAC reaction to connect the azide-functionalized dendrons in a convergent approach to a multifunctional alkyne-functionalized core.[17] In this work high purity dendrimers were obtained in near-quantitative yield, highlighting the power of click chemistry to couple macromolecular building blocks. In a similar fashion, Fréchet demonstrated that dendrons could be efficiently attached to poly(vinylacetylene), a multifunctional alkyne, leading to dendronized polymers.[18] Shortly after, Hawker and coworkers demonstrated modification of dendrimers with peripheral alkyne groups through CuAAC.[19] These early works on clicking dendrimers clearly demonstrated the potential of CuAAc for quantitative modification of larger macromolecules.

The first report on clicking polymers appeared in 2004, when Van Hest and coworkers reported the modular preparation of amphiphilic block copolymers through CuAAC of alkyne- and azide-functionalized polymers (Figure 1B).[20] Atom transfer radical polymerization (ATRP) was used for the preparation of alkyne- and azide-functionalized polymers, either by using a protected alkyne initiator or substitution of the bromide end-group by an azide-group. The direct conversion of the halide end-group of ATRP derived polymers into an azide-group has become a very popular strategy to prepare azide-functionalized polymers.[21] Matyjaszewski and coworkers used similar end-group modification strategies, albeit using an unprotected propargyl-containing initiatior, to make α-alkyne-ω-azide-polystyrene that was used for CuAAC step-growth polymerization, resulting in high molar mass polymers.[22] It was, however, noted that a fraction of the reactive polymer precursor was transformed into cyclic polystyrene. The preparation of star-polymers by CuAAC was reported by Schubert based on coupling of alkyne-functionalized poly(ε-caprolactone) to heptakis-azido-β-cyclodextrin.[23] Simultaneously, Matyjaszewski and coworkers, as well as Tunca and coworkers, reported the coupling of azide-functionalized polymers to a multi-alkyne core for the preparation of star-shaped polymers.[24,25]

In 2006, Grayson and coworkers reported that the CuAAC of α-alkyne-ω-azide-polystyrene under dilute conditions quantitatively yielded the cyclic polystyrene (Figure 1C).[26] Facilitated by the high reactivity and quantitative nature of CuAAC, it was possible to perform the cyclization by slowly adding a solution of the reactive polymer precursor to a large volume of solvent containing the copper(I) catalyst. This procedure led to near-instantaneous cyclic polymer formation, which was the first reported scalable method for producing cyclic polymers. Within the area of topological polymer chemistry, Tezuka and coworkers have used CuAAC click chemistry to design and prepare multicyclic polymer structures, both by bridging of cyclic polymers with polymer linkers to make multicyclic polymers and by coupling of cyclic polymers to make spiro-type structures (Figure 1D).[27] The latter strategy was also used for making a quadruply fused pentacyclic polymer topology based on CuAAC preparation of a spirotype tetracyclic poly(tetrahydrofuran) that was fused and folded through olefin metathesis.[28] These early reports clearly demonstrate the power of click chemistry for coupling of polymer building blocks, providing access to complex polymer structures and topologies.

Besides the use of CuAAC for the coupling of polymer building blocks as described in the previous part, CuAAC has also been developed as tool for post-polymerization modification of polymer end-groups and polymer side chains. Matyjaszewski and coworkers were amongst the first to report the end-group modification of polymers via CuAAC.[29] α,ω-Diazido-polystyrene was obtained via ATRP followed by CuAAC end-group modification with propargyl alcohol to prepare α,ω-dihydroxy-polystyrene. Ever since, a wide variety of

functional telechelic polymers have been reported by the combination of living/controlled polymerization techniques and CuAAC click reactions.[30-33] For polymer side-chain modification it is required to introduce either the alkyne or the azide in the polymer side chain, followed by the CuAAC reaction, which has been demonstrated for poly(methacrylate)s with azide[34] and (protected) alkyne[35] side chains, aliphatic polyesters with azide[36] and alkyne[37] side chains, as well as poly(2-oxazoline)s with azide[38] and alkyne[39] side chains, amongst others. Finally, 1,2,3-triazole monomers have been developed with polymerizable vinyl groups as a new class of monomers for (controlled) free radical polymerization.[40,41] Over the years, the use of click chemistry has been recognized as one of the most efficient tools for quantitative end-group and side-chain modification of polymers.

CLICK CHEMISTRY AS TOOL FOR POLYMER APPLICATIONS

In the previous section, it has been illustrated how the introduction of CuAAC click chemistry has revolutionized the synthesis of defined polymer architectures and functional polymers. In this section, some key examples of the use of CuAAC click chemistry for the development of functional polymers for specific applications will be discussed to illustrate the potential of CuAAC to control polymer properties by providing straightforward access to functional polymer structures.

An application area where click chemistry has made a significant impact is covalent polymer hydrogels. Covalent polymer hydrogels are synthesized by either polymerization of water-soluble monomers in the presence of a cross-linker or by coupling of reactive polymer precursors. In this latter approach, Hedrick, Hawker and coworkers reported the preparation of well-defined hydrogels by CuAAC crosslinking of tetra-azide four-arm star poly(ethylene glycol) (PEG) with α,ω-dialkyne PEG.[42] It was demonstrated that the use of CuAAC led to the formation of near-ideal network structures (with less than 0.2 % of unreacted azide and alkyne groups left) that led to improved mechanical properties compared to hydrogels prepared by photopolymerization of PEG-diacrylate. In addition, it was demonstrated that the orthogonality of the CuAAC click reaction rendered the hydrogel formation process tolerant to wide range of additives that would usually interfere with radical hydrogel formation processes, such as carbon black, nitroxide radicals, or titanium dioxide. After this initial report, a wide variety of click reactions have been employed for the preparation and functionalization of hydrogels, often for biomedical applcations.[43,44]

Since CuAAC has provided a route towards larger scale synthesis of cyclic polymers, it also opened up the way to further exploration of the properties and potential applications of cyclic polymers.[45-47] In 2015, Grayson and coworkers reported the synthesis of cyclic poly(ethylene imine) (c-PEI) by CuAAC cyclization of α-alkyne-ω-azide-functionalized poly(2-ethyl-2-oxazoline) (PEtOx) followed by hydrolysis of the amide side-chains (Figure 2A).[48] The successful cyclization was confirmed by a decrease in hydrodynamic radius compared to the linear analogue. The c-PEI was used as a cationic polymer for DNA transfection to cells, revealing that the c-PEI was significantly more efficient for gene transfection than linear poly(ethylene imine) and as good or better than branched poly(ethylene imine), but with significantly reduced toxicity compared to the latter. The improved gene transfection efficiency of c-PEI was ascribed to the enhanced charge-density of the more compact cyclic polymer.

A similar CuAAC strategy for the preparation of cyclic PEtOx was utilized by Benetti and coworkers to prepare cyclic polymers with a nitrodopamine functional handle, which allowed coupling of the cyclic PEtOx to surfaces (Figure 2B).[49] As such, the CuAAC method to prepare the cyclic PEtOx allowed an in-depth comparison of the properties of cyclic polymer brushes, revealing significantly lower protein adsorption (i.e. better antifouling properties) and lower friction (i.e. better lubrication) of the cyclic polymer coating compared to a linear PEtOx coating analogue. The improved properties of the cyclic polymer brushes were ascribed to the absence of interdigitation and the higher steric stabilization of cyclic polymer brushes. Cyclic polymer brush coatings were also demonstrated to lead to superior stabilization of inorganic nanoparticles.[50] Finally, the same group reported that adsorption of cyclic polymer graft copolymers onto damaged cartilage provided excellent biopassivation and lubrication to restore native cartilage properties and to slow down further degradation.[51]

More recently, Ng, Weil and coworkers reported that cyclic poly(hydroxyethyl methacrylate) (PHEMA), prepared by CuAAC, self-assembled into wormlike structures while the linear analogue led to insoluble gel-like aggregates.[52] The hierarchical self-assembly into worm-like structures was ascribed to the preorganization of the cyclic polymer with a hydrophobic collapsed polymer backbone core surrounded by hydrophilic side chains. The resulting disk-like individual amphiphilic cyclic polymers self-assemble into larger worm-like structures. Moreover, macrocyclic brush polymers containing amphiphilic polystyrene-poly(acrylic acid) block copolymer side chains were prepared by converting the cyclic PHEMA into a macroinitiator for ATRP. These cyclic brush polymers also self-assembled into wormlike structures and higher order network structures through hierarchical self-assembly of the amphiphilic cyclic polymers.

Besides the development of CuAAC for preparation of defined polymer architectures, it also has been established for the modification of polymer side-chains and end-groups, which has been especially used for the preparation of polymers for biomedical applications.[53] For example, the preparation of an injectable polymer-drug conjugate (SER-214) has been successfully developed and tested in a Phase 1A clinical trial by Serina Therapeutics.[54,55] This polymer-drug conjugate is based on a PEtOx copolymer with alkyne comonomer side-chains that were used to conjugate rotigotine, a dopamine antagonist for the treatment of Parkinson's disease patients, through CuAAC (Figure 2C).[56] The azide was coupled to rotigotine via an ester containing linker, thereby yielding a polymer-prodrug that slowly releases the drug through ester hydrolysis. This design enabled constant blood plasma levels of the drug in humans upon weekly subcutaneous administration, which could be highly beneficial for treatment of Parkinson's disease patients to avoid motor fluctuations, dyskinesias (involuntary muscle movements), and neuropsychiatric problems. Besides the biomedical field, CuAAC click chemistry approaches have also been demonstrated for the modification of bulk commodity polymers[57] and for making materials from biobased resources, such as vegetable oils[58] and polysaccharides.[59] However, it remains to be seen whether the added cost of CuAAC modification of such materials is justified in such low cost polymer applications.

Another application potential that will be highlighted is the development of 1,2,3-triazolium containing polymers, also referred to as poly(ionic liquids).[60] These constitute a new class of polyelectrolytes that is accessible through alkylation of the 1,2,3-triazole moiety that results from CuAAC. In 2013, Drockenmuller and coworkers reported the step-growth polymerization of an alkyne-azide functional monomer via CuAAC followed by alkylation with iodomethane.[61] Polymers with side-chain 1,2,3-triazolium groups were reported by Matyjaszewski, Nulwanai and coworkers based on synthesis and radical polymerization of the corresponding vinyl-triazolium monomers.[62] The application potential of such polymers containing 1,2,3-triazolium groups in the main chain with a bis(trifluoromethylsulfonyl)imide counteranion was demonstrated by Drockenmuller and coworkers, who demonstrated the high ion conductivity of these polymers around 10^{-5} S cm^{-1} at 30 °C (Figure 2D).[63]

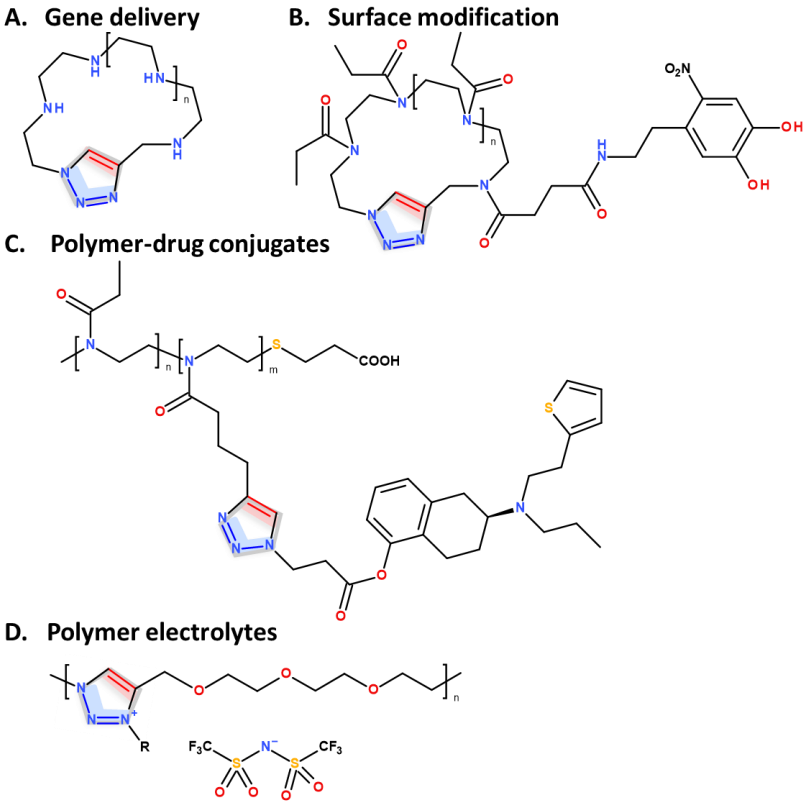

Figure 2. Overview of CuAAC derived functional polymers for different applications.

(A) Cyclic poly(ethylene imine) that was shown to be more efficient for transfection of DNA than linear analogues;[48] (B) Cyclic poly(2-ethyl-2-oxazoline) having lower protein adsorption and friction when coated to surfaces compared to the linear polymer coating;[49] (C) Polymer-drug conjugate that successfully completed phase 1A clinical trials prepared by CuAAC[55] and (D) poly(1,2,3-triazolium) bis(trifluorosulfonyl)imide with high ion conductivity.[63]

CONCLUSION AND OUTLOOK

After its introduction, the concept of click chemistry, the CuAAC reaction in particular, was quickly adopted by the polymer science community. It was recognized that such high yielding reactions aided the development of improved protocols for complex and functional polymers, without the need for tedious purification protocols. Hence, CuAAC has led to major improvements in the synthesis of topologically complex polymers and has enabled larger scale production of cyclic polymers. As such, CuAAC has been at the basis of fundamental breakthroughs in understanding of cyclic polymer properties as well as unveiling the application potential of cyclic polymers. Furthermore, CuAAC has become a major tool for the preparation of functional polymers and polymer-drug conjugates for biomedical applications. Finally, the CuAAC reaction has added new 1,2,3-triazole and 1,2,3-triazolium monomers and CuAAC-based polymerization methods using azide and alkyne monomers to the polymer science toolbox. It should, however, be mentioned that the removal of the copper(I) catalyst is sometimes tedious as it can coordinate to the formed triazole rings, in particular when multiple triazole rings are present in the polymer chains. Furthermore, care should be taken when working with azides as this can lead to explosive materials, posing limitations for large-scale production.

Nowadays, if a polymer scientist wants to couple two polymer building blocks or develop a functional polymer, click chemistry has become one of the first options to consider. Hence, click chemistry has evolved from a niche research subject into a common, indispensable tool

for designing advanced functional polymer materials. For the future, it is therefore to be expected that more click-based polymer materials will be developed for real-life applications, especially for biomedical applications where the function and reproducible synthesis of a polymer material is often more important than its cost. For lower added-value applications, the removal of the copper(I) catalyst and the additional safety precautions for working with azides might lead to too expensive products. Hence, despite the advantages of the CuAAC reaction, its commercial use for production of polymer products may be limited to higher added-value niche applications. Nonetheless, in a relatively short time period, CuAAC has become a standard tool for polymer chemists.

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AUTHOR CONTRIBUTIONS

R.H.is responsible for conceptualization, funding acquisition, visualization and writing.

DECLARATION OF INTERESTS

The author declares no competing interests.

Scheme 1. Title without panel labels and reference or footnote citations

Scheme legend.

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