

# “Clicking” Polymers or Just Efficient Linking: What Is the Difference?\*

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click reactions · polymer chemistry ·  
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The introduction of the click chemistry concept by Sharpless and colleagues in 2001<sup>[1]</sup> clearly marks a turning point in synthetic chemistry as its fundamental principles have been rapidly adopted and it has served as inspiration for chemists in almost all areas. The large number of reviews already published in this relatively young field demonstrates the increasing relevance of this concept, and the wide variety of applications serves as a testament to its impact.<sup>[2]</sup> The definition of click reactions entails numerous conditions including the ease in conducting a reaction, its broad applicability in modular approaches, and its ability to proceed without the lack of significant side products. Even though the specific chemistries that were proposed to represent click reactions are not new—in fact most of these reactions have been well known for years or decades—Sharpless’ concept has led to a significant change in design strategies and the overall approach to synthetic problems. The click philosophy is based on the concepts of modularity and orthogonality: building blocks for a final target are made individually and subsequently assembled by means of click reactions. Such a modular approach is often more efficient than a conventional synthesis strategy involving sequential reactions. Moreover, the orthogonality of click reactions also results in ready access to a large number of compounds as the individual building blocks can be combined in different ways.

In 2001 Sharpless defined in this journal a set of criteria that a process must meet in the context of click chemistry: “The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation. Purification—if required—must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions. [...] Click processes proceed rapidly to completion and also tend to be highly selective for a single product: we think of these reactions as being ‘spring-loaded’ for a single trajectory”.

While the main application of click chemistry was originally envisaged by Sharpless to be in the synthesis of biologically active molecules, the click concept has arguably had a greater influence on polymer chemistry.<sup>[3]</sup> It is in the area of polymer synthesis, where the standard design protocols and purification procedures of organic chemistry are significantly challenged, that the advantages of click chemistry come to the fore. For the design and synthesis of functionalized macromolecular architectures, the efficiency of click conjugations combined with the lack of side products and facile purification all lead to a strong practical value. The modular concept introduced by the click philosophy facilitates the synthesis of polymer materials that would not have been achievable otherwise, revealing a true paradigm shift in macromolecular design.<sup>[4]</sup> Not only do these efforts expand synthetic methodologies in a fundamental sense, but they also greatly increase the range of structures that can be prepared, while the simplified techniques allow a much wider spectrum of researchers access to these materials. Nevertheless, many chemists use the term “click” to describe their reactions. Over twenty reactions have been referred to as click reactions according to a detailed literature study, even though the reported reactions often do not proceed to high conversions or require tedious purification procedures.

We therefore believe it is necessary to defend the core ideas of click chemistry and point to a set of requirements that

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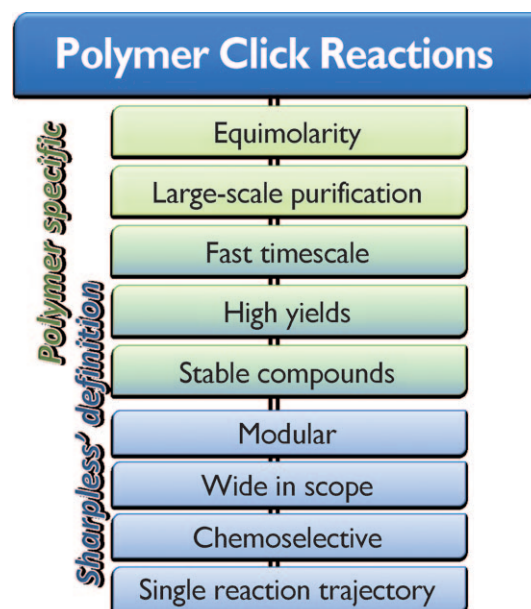
should be fulfilled in order for a reaction to be designated as “click” in the context of synthetic macromolecular chemistry. All proposed requirements are directly based on or derived from the original definition of click reactions by Sharpless et al. While a steadily increasing number of reports in polymer science use the term “click” in reference to their reactions, many of these infringe at least one of the originally outlined requirements. Indeed, we believe that “click” is often intended to mean “efficient” or “successful”. While click reactions are intrinsically highly efficient reactions, not necessarily all efficient reactions can be classified as click reactions. Without wanting to judge specific reactions, we feel that the label “click” may become entirely meaningless if it does not refer to a specific set of characteristics. It is also important to differentiate between actual click reactions and those that are inspired by click chemistry—a related but different topic that is also important since it underlines the awareness of what makes reactions truly useful in a practical sense.

In order to assess whether a reaction may be classified as a click reaction, an adapted definition in the context of polymer chemistry, a modified definition adapted to polymer chemistry is required. At the same time, we realize that a universal definition that covers all areas—from organic synthesis over polymer chemistry to biomedical applications—may not exist. Several criteria, as we will point out later, are important in all fields, while other criteria, may only apply to specific research areas. Examples may include the choice of solvents (e.g. restriction to aqueous solutions) and the question of molarity, that is, the use of excess amounts of reagents to drive the reaction to completion (vide infra).

The requirement for easy product separation in the original definition (“by nonchromatographic methods, such as crystallization or distillation”) has profound consequences for the polymer field. Indeed, when dealing with polymers, purification methods such as distillation are not feasible and thus one must rely on the (selective) precipitation of polymers or the removal of all volatile compounds. Advanced separation methods such as preparative size-exclusion chromatography clearly do not qualify as a simple reaction workup. For reactions involving polymers, these restrictions often imply that the reaction should proceed with strictly or at least close to equimolar amounts of starting materials in order to obtain a pure product. However, when selective precipitation can be easily applied to remove one compound from the product mixture, it is reasonable that one use an excess of one compound to shorten the reaction time. Nevertheless, whether selective precipitation (or other purification methods) can be used depends on the physical properties of the synthesized product, not of the reaction itself. Thus, even if an excess of one compound may be tolerable, it is highly desirable that click reactions be performed—at least in principle—under equimolar conditions. This also follows from the fact that any reaction leading to a significant amount of side products, that is, the result of an undesired side reaction, violates the definition of click chemistry. If a reaction requires an excess of one reagent to counter a side reaction, it is not “spring-loaded for a single trajectory”.<sup>[5]</sup>

Especially in polymer–polymer conjugation reactions, the equimolarity feature is of critical importance as mixtures of similar polymers are difficult to separate, definitely not on a large scale. As stated in the Sharpless’ definition, this also requires that the click reaction “gives very high yields” to avoid removal of unreacted species. Similar considerations apply to the modification of surfaces, colloids, and cross-linked polymer structures. Although purification may be relatively facile even when an excess of reagents has been employed, high yield is a required feature in these cases as well; nevertheless, we realize that quantification of the extent of the conjugation reaction may not be straightforward. We are well aware that these requirements limit the number of reactions that can be considered as click reactions in macromolecular synthesis. Nevertheless, from the requirements of simple purification, high selectivity, and high conversion, equimolarity results as a key criterion for a polymer click reaction. Without it, one of the most challenging reactions in macromolecular synthesis, that is, polymer–polymer ligation, is simply impossible, and at this point the largest distinction between simply efficient and click reactions may be made. Again, we do not pass a judgment on how useful a reaction is. Indeed, there are many reactions that do not fulfill all of the click criteria but are nevertheless highly useful and effective.

Figure 1 summarizes the most important criteria for a successful click reaction in macromolecular synthesis. As given at the bottom (in blue), a click reaction must be modular, wide in scope, and chemoselective/orthogonal, and the respective reaction must proceed by a single reaction trajectory. These requirements are taken without alteration from the Sharpless’ original definition and should not be put into question. Any reaction not fulfilling these basic criteria cannot be considered a click reaction in either classical



**Figure 1.** Requirements for click reactions involving one or more polymeric reagents (blue: originally defined by Sharpless; green and blue-green: adapted requirement related to synthetic polymer chemistry).

organic chemistry or in polymer chemistry. On top (in green) the specific requirements of click reactions in polymer chemistry are collated, and we explore these further below. A few requirements are given in blue–green, indicating that they are also part of the original definition but have major consequences in the polymer field. As discussed above, equimolarity is an important criterion. Easy purification of polymeric materials differs from Sharpless' definition, and one may stipulate that it must be achievable above the usual laboratory scale, thus excluding chromatographic methods (see discussion earlier). Next, a click reaction should “*proceed rapidly to completion*”. Sharpless et al. did not define a specific timescale for the reason that a high reaction rate—while desirable—is obviously a relative term. Thus, it may only be stated that a reasonable time frame should be adhered to. Furthermore, the product of a click reaction should be “*stable under physiological conditions*”. In our opinion, the obtained products must be stable under the influence of air and should, unless specifically designed to react on an external stimulus, not require any special conditions during storage. Similar considerations apply to the starting materials and reagents: they must be “*readily available*” or at least easily prepared using straightforward synthetic routes. Click reactions are performed under “*simple reaction conditions (ideally, insensitive to oxygen and water)*”. This excludes reactions that require unusual measures (such as the use of a glove box). An oxygen-free atmosphere may be tolerable as it is a standard condition in modern macromolecular synthesis. Finally, click reactions must be “*wide in scope*”, that is, applicable under a broad range of conditions with a multitude of starting substrates, ideally applicable to any polymeric backbone. In our opinion, a reaction that requires time-consuming refinement of reaction conditions for each particular system does not belong to the class of polymer click reactions.

Each entry in Figure 1 is a *sine qua non* condition. Sharpless' original definition includes more requirements, such as stereospecificity, which is often not of great concern for polymer conjugations. In some specific areas, especially in bio-related fields such as for the design of foldamers,<sup>[6]</sup> stereospecificity remains, of course, highly important. Furthermore, Sharpless specified that a click reaction should “*generate only inoffensive byproducts that can be removed by nonchromatographic methods*”. In material science, byproducts of any kind may be tolerable as long as product isolation is not compromised. However, click reactions in the biopolymer and biomedical fields may require more stringent criteria. Next, Sharpless' definition reads: “*use of no solvent or a solvent that is benign (such as water) or easily removed*”. In the polymer field, we may broaden this restriction to generally used organic solvents, which are preferably low boiling as polymeric materials are often solids or highly viscous liquids, and nonsoluble in water. However, the use of water as the solvent may be an absolute requirement in bio-related areas.

With the above reconsideration we aim to arrive at a set of criteria to judge whether a reaction that involves one or more polymeric reagents—be it a polymer modification or polymer–polymer conjugation—can be referred to as a click

reaction. Thus, in addition to the original definition by Sharpless, we believe that a true click reaction in macromolecular synthesis should allow a polymer chemist to use equimolar amounts of the building blocks. If not, one will often encounter complex purification techniques. For the same reason, a click reaction should reach a very high yield. However, if a simple large-scale purification process is feasible, one may still prefer to use an excess of one building block. Finally, a click reaction should proceed on a reasonable timescale and require no tedious fine-tuning of reaction conditions.

We hope that in future polymer chemists will consider the term “click” in a stricter fashion guided by the requirements given above. Otherwise significant danger exists that the term may become over time a synonym for “successful” and thus largely irrelevant and meaningless. As restrictive the requirements reported herein may be, they are very important. The true meaning of a click reaction—with its strict definition—is worth defending as it distinguishes truly universal reactions from the pool of efficient reactions that are applied for specific synthetic aims. At the same time it should be clear that the term click chemistry denotes a philosophy and is therefore somewhat fluid. In this spirit, scientists should not feel restricted by the definition but rather inspired, and research must continue to broaden the number of available click reactions. An increased awareness of the core criteria for click reactions will also enable synthetic polymer chemists to acquire a greater appreciation of truly practical approaches to the preparation of highly functionalized macromolecular architectures while at the same time facilitating a wider spectrum of researchers access to these materials and synthetic techniques.

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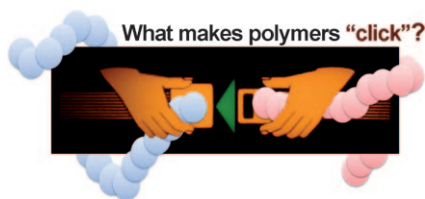
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## Essays

### Polymer Click Reactions

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Linking: What Is the Difference?



**The “click” trick:** Many reactions are classified as click reactions even though some are limited to certain applications. Thus, there is danger that the term “click” will become meaningless over time and simply a synonym for “successful”. To prevent this, the original click criteria are evaluated in this Essay specifically for the synthetic polymer field and a set of criteria are specified that distinguishes click from other efficient reactions.