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Short Communication

Click Chemistry and Bioorthogonal Chemistry Accoladed by Nobel Prize - 2022

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Modern chemistry is driven not only by important discoveries and improvements, but also by the formulation of notions that catalyse and accelerate new development. Despite being closely linked to significant discoveries, conceptualization plays a significant role in this year's nobel prize in chemistry. The azide-alkyne cycloaddition, also referred to as the "click" reaction was first developed by sharpless. It is an adaptable and modular method for joining two reactive partners wherein two reagents click together, like a seat belt in a simple, fast, selective, dependable, and high yield reaction under benign condition rapidly to form a single product without cumbersome purification steps. In the presence of a copper catalyst, K.Barry Sharpless and Morten Meldal separately found that the high energy molecule azide, with three nitrogen bonds, and alkyne, with two triple-bonded carbons, are excellent click partners. They discovered that the copper catalyst can bring the two pieces together in an optimal arrangement that snaps them together.

Further, Carolyn R. Bertozzi introduced the concept of bioorthogonal chemistry which refers to chemical reactions that happen in cells without disrupting their normal chemistry. She altered the original click reaction to make the copper free variant because copper is hazardous to living cells. This idea has greatly aided advancements in chemical biology, materials chemistry, medication transport, sensing, and diagnosis. In this article we honour Carolyn R. Bertozzi, K. Barry Sharpless, and Morten P. Meldal, the recipients of the 2022 Nobel Prize in Chemistry, by outlining the rich history of click and bioorthogonal chemistry.

The idea of click chemistry has a revolutionary impact on the various fields of chemistry, material science including medicine. It was first developed by Barry Sharpless an American Chemist 20 years ago with assistance from his colleagues V. Fokin and M.G. Finn [1]. They defined it as a theory for conducting organic reactions that was predicated on the idea that organic synthesis should concentrate attention on highly selective, straightforward orthogonal reactions that produce heteroatom-linked molecular systems with high efficiency under more tolerant conditions.

What precisely is click chemistry then? The snappy, cleverly alliterated phrase approaches chemistry from a fundamentalist standpoint. It's a theory where molecules are simply, rapidly, consistently, and frequently bonded

together, much like how a seatbelt clips into its buckle as illustrated in Figure 1. While everyone else was making furniture from scratch, the concept was the flat-pack wardrobe of the chemical world. It is quick and effective because it assembles molecules into building blocks through simple chemical interactions. The simple snap -together nature of Lego construction pieces has been used to compare the mechanics of click chemistry [2]. Azides and alkynes were subjected to chemical reactions in presence of copper catalyst. This serendipitously offered molecular synthesis new fascinating options, notably in the area of stem cell research. In order to hasten the discovery of compounds with valuable qualities, Sharpless and his colleagues suggested reviving up tried and true processes. A single trajectory should effectively be "spring loaded" by the reactions, and they shouldn't produce any undesired by-products.

Carolyn R Bertozzi

K. Barry Sharpless

Morten P Meldal

Specific, stringent requirements must be met in order to qualify as appropriate click-type reactions.

- They ought to function under simple and effective reaction conditions and provide extremely high yields.
- They should be expected to perform with no solvent or one that can be easily removed.
- They must only produce harmless by-products that can be eliminated using nonchromatographic techniques.
- They should be highly selective for a single product and stereospecific (but not necessarily enantio selective).
- They should move quickly towards completion and have a high thermodynamic driving force, often greater than 20 kcal/mol.
- Water and oxygen should have no effect on the process. Furthermore, the result must be stable under physiological settings and the starting materials and reagents must be easily accessible.
- By using techniques other than chromatography, including crystallisation or distillation, the resultant compounds should be simple to separate [3].

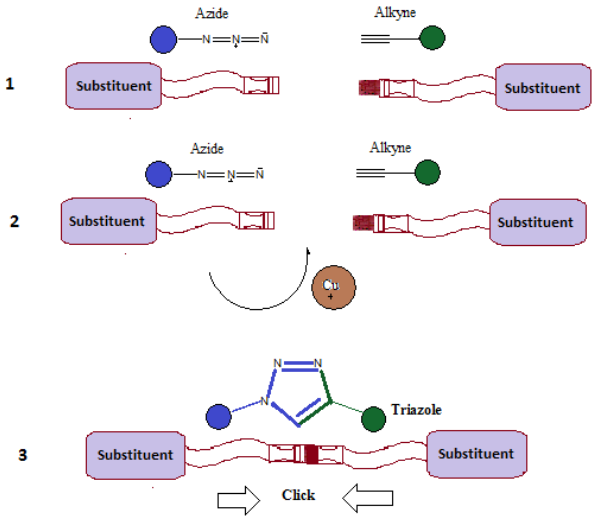

Figure 1: An easy illustration of click chemistry similar to seat and buckle

The Huisgen 1, 3-dipolar cycloaddition of azides and alkynes to generate 1, 2, 3-triazoles is undoubtedly the most well-known instance of a click reaction among all those that reach "click status". Sharpless and Meldal independently identified the classic click reaction, the Cu (I)-catalyzed azide-alkyne cycloaddition (CuAAC), which is a copper-catalyzed variant of the original Huisgen reaction [4]. A fascinating story and a prime illustration of Pasteur's adage that "In the field of observation chance only favours the prepared mind" is the "accidental" discovery of the CuAAC reaction in Meldal's laboratory. CuAAC produces only 1, 4-disubstituted 1, 2, 3-triazoles, in contrast to the uncatalyzed alkyne-azide reaction, and operates under benign circumstances [5]. The idea of connecting molecules in a very efficient and selective way is novel and is sometimes referred to as "molecular lego."

The separate discovery of azide-alkyne cycloaddition (CuAAC) by Sharpless and Meldal within the realm of click chemistry has attracted enormous attention towards the use of various copper(I) salts as very active catalysts for this crucial chemical transformation. Due to its dependability, specificity, and biocompatibility, CuAAC has been used

more frequently for the quick synthesis of agrochemicals, medicines, polymers, and numerous other useful compounds. For azide-alkyne cycloaddition (AAC), some of the well-known Cu(I) systems include the $CuSO_4$-ascorbate system, ligands supported Cu(I)/(II) and Cu-coordination complex, polymer-supported Cu(I), Cu(I)-zeolite, copper nanoparticles, metallic copper turning, magnetic copper-iron nanoparticles, magnetic nano-Fe_3O_4@- TiO_2/Cu_2O, graphene supported Cu_2O nanoparticles, charcoal supported Cu_2O nanoparticles, and Cu_2O micro/nanoparticles. Copper has drawn a lot of interest as a potential replacement for more conventional rare and pricey precious metal catalysts due to its high natural abundance and comparatively low cost.

The groundbreaking work of Carolyn Bertozzi has led to the development of novel click reactions known as "bioorthogonal click chemistry," which do not require copper catalytic [6]. This idea can be applied in instances where the CuAAC reaction and concomitant metal ion catalysed processes are unfeasible because of the metals' toxicity. The SPAAC reaction (strain-promoted azide-alkyne cycloaddition) as illustrated in Figure 3, which involves the reaction of an azide with a strained cyclooctyne, is an example of bio-orthogonal click chemistry. Under mild circumstances in acetonitrile or combinations of acetonitrile and phosphate-buffered saline, Bertozzi and her team were able to demonstrate that the SPAAC reaction involving a biotinylated cyclooctyne structure and different aliphatic azides proceeded as expected. In the absence of Cu (I), this azide-cyclooctyne (3 + 2) cycloaddition performed reasonably well [7]. By inducing reactions inside living things, Carolyn Bertozzi expanded upon the idea of "click chemistry."

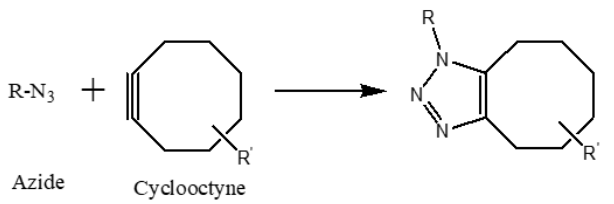

Figure 2: Strain promoted alkyne-azide cycloaddition

Although copper catalysts work well, living things may be poisoned by the metallic chemical element and hence, Bertozzi designed a copper-free variant of click chemistry [8]. The role of copper catalyst in conventional click chemistry is to force molecules to align in a straight path. In order to stabilise the reaction and make it suitable for usage with living things, Bertozzi eliminated the copper catalyst. As a result, the straight-line pattern was altered and the molecules were compelled to make right-angle bends. Bertozzi was able to snap molecules together without disrupting the cellular environment's normal metabolic processes by generating chemical reactions that are "parallel" to it. In reference to the shape of the molecular bonds formed during the procedure, she called this protocol as "bioorthogonal chemistry." She applied the method to map important macromolecules, referred to as glycans (Figures 3 and 4) that are present on the surface of cells [9]. The bioorthogonal processes could proceed due to click chemistry without altering cellular chemistry. Bertozzi and her team were also able to demonstrate that biotinylated cyclooctyne could be conjugated with human Jurkat cells that had undergone metabolic engineering to express azide derivatized glycoproteins. Thus, a dose-dependent rise in fluorescence was seen when probing the biotin conjugate that had been integrated with fluorescently-labelled avidin [10]. With the use of the bioorthogonal chemical reporter approach, biomolecules can be marked without the need for direct genetic encoding. The target biomolecule is modified using the metabolic machinery of the cell or a protein by virtue of its enzymatic activity, delivering a functional group (the chemical reporter) that does not interfere with any biological functioning (i.e., bioorthogonal) [11]. Today, researchers from all around the world analyse cellular activity and keep tabs on biological processes using the bioorthogonal reactions pioneered by Carolyn Bertozzi. The advantages have been particularly significant in the realm of cancer research, where researchers are utilising bioorthogonal processes to boost the effectiveness of cancer drugs and create focused treatments.

The field of bioorthogonal chemistry offers many lessons. For example,

1. The chemical reactions can be designed to perform in the environs as demanding, and also as intriguing, on living systems.
2. Biologists are eager to embrace the tools from chemistry, but they must be made accessible and straightforward to execute.
3. Interestingly, several commercial suppliers are providing azide and alkynes labelled sugars, amino acids, lipids and other biomolecular substrates. Such 'kits' enable the use of bioorthogonal chemistry by non-experts which is essential for widespread adoption of the protocol outside of chemistry circles. An ideal bioorthogonal chemical reaction should translate seamlessly from flask to fish.

A final lesson pertains to the importance of reaction discovery as the foundation of bioorthogonal chemistry. Very few reactions out of which current bioorthogonal chemistry transformations are based were discovered long before the chemistry/ biology/ was a fashionable venue for research. Staudinger, Huisgen and Wittig could not foresee that their discoveries would someday lead to methods for *in-vivo* biomolecule imaging. Likewise, contemporary

studies of fundamental chemical reactants can have an unforeseen impact in biology and beyond. Such explorations are expected to be encouraged even if they do not have specific applications on the horizon [12].

Olof Ramstrom, Member of Royal Swedish & Member of Nobel Committee for Chemistry Academy of Sciences rightly states that the discoveries of Bertozzi, Meldal and Sharpless have enormous influence on our society. Through the development of inspirational new concepts and highly efficient methods, the laureates have enhanced our capabilities and considerably deepened and widened our knowledge and understanding. Their remarkable accomplishments have increased our means to improve our world and better our lives, truly to the benefit of humankind.

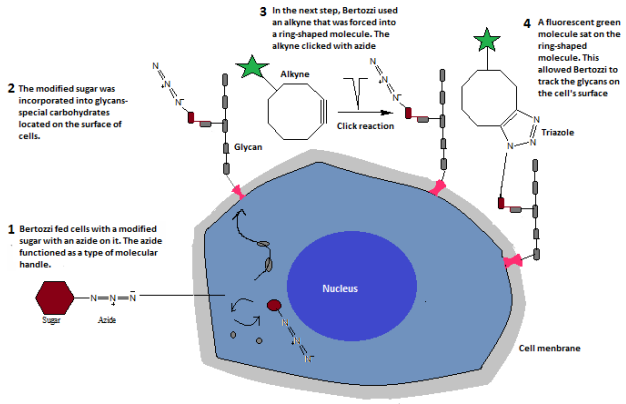

Figure 3: Schematic representation of bioorthogonal chemistry illuminating the cell

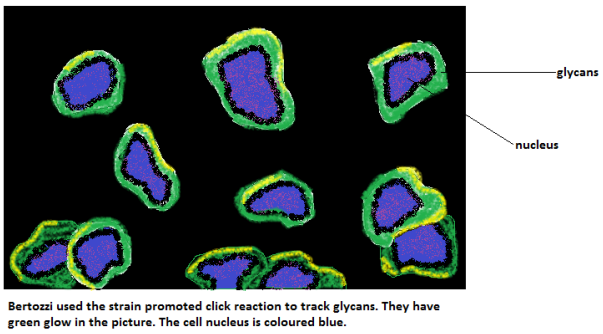

Figure 4: Illustration of fluorescently-labelled cells to track glycans

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