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THE ROYAL SWEDISH ACADEMY OF SCIENCES

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Scientific Background on the Nobel Prize in Chemistry 2022

CLICK CHEMISTRY AND BIOORTHOGONAL CHEMISTRY

The Nobel Committee for Chemistry

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Click Chemistry and Bioorthogonal Chemistry

*The Royal Swedish Academy of Sciences has decided to award **Carolyn R. Bertozzi**, **Morten Meldal**, and **K. Barry Sharpless** the Nobel Prize in Chemistry 2022, for the development of click chemistry and bioorthogonal chemistry.*

Introduction

Modern chemistry is driven not only by important discoveries and improvements, but also by the formulation of concepts that catalyse and accelerate new development. Such concepts can foster innovative thought-processes that open up novel pathways to address different challenges. Both ideation and conceptualization are fundamentally important tenets of science and technology, essentially allowing the expansion of our perception of current knowledge and accentuate new perspectives. As humans, we all need occasional, sometimes surprising, eyeopeners to stimulate our minds, and concepts energize and expand our comprehension.

This year's Nobel Prize in Chemistry is to a large extent about conceptualization, albeit strongly coupled with important discoveries. In a sense, the two facets are linked through an entangled mechanism, whereby one fosters the other. Thus, new discoveries spur novel cerebrations and new concepts incite the uncovering of novel findings. Nonetheless, separately or in combination, both effects have had strong impact on chemistry and have opened up new doors that benefit humankind. The accomplishments behind this year's prize has thus led to very strong activity in a range of disciplines across the field of chemistry and related areas, with numerous important discoveries made along the pioneered paths.

Click Chemistry

The making of molecules and materials is a very challenging and complex process. Not only do we need to master how to put different parts of the compounds together, forming the actual linkages, but we also need to be able to control all the intricacies of linking atoms together in the right way to form the correct products. Over the years, highly creative chemists have devised a wealth of methods to efficiently build molecules of different types and worked out principles on how to control the outcomes. This development has enabled us to make astonishingly complex structures with high fidelity, and we are now at a point where we can make almost any structure we can imagine or anything we can find in nature.

However, all these developed methods require strict considerations as to how we put everything together, and we need to plan how we make the molecules in great detail to have every step of the process work appropriately to reach the final product. Furthermore, many complex processes

demand for linking methods that are difficult and cumbersome to perform and that require highly optimized conditions to proceed. Skilled and talented chemists can learn to master these methods to perfection, however a learning process that may take significant effort and time to realize.

In the 1990s, one of the most creative chemists, **K. Barry Sharpless**, who would be awarded with the Nobel Prize in 2001 for some of his earlier work, had been giving these challenges a lot of thought. At the time, the development of combinatorial chemistry methods had received a lot of interest, especially for drug development purposes, and large compound collections (a.k.a. "combinatorial libraries") were synthesized and the compounds tested for their pharmaceutical activities.

Sharpless realized that the efficient manufacture of such compound collections would strongly benefit from a more "streamlined" preparation process, where each compound could be made using a limited set of highly robust and efficient reactions. Rather than relying on a plethora of possible methods, all with their specific scopes and limitations, he envisaged that many sought-after structures should be possible to make with more general, robust and high-yielding reactions at hand. This would not only speed up the manufacturing process, but also lead to higher amounts of pure products for efficient testing.

By the turn of the millennium, **Sharpless** presented some of these thoughts at a conference,[1] and in 2001 he and his coworkers Hartmuth C. Kolb and M.G. Finn, summarized the concept in article form.[2] The article: 'Click chemistry: diverse chemical function from a few good reactions', described how complex and functional molecules could be efficiently synthesized using a modular approach that relied on a limited set of highly robust reactions. In a broader sense, the principle is somewhat akin to an IKEA 'flatpack' approach, in which all necessary components, the 'building blocks', along with a set of easy-to-use hardware, the 'reactions', were provided together with a reliable assembly instruction for almost anybody to follow.

> Click chemistry
>
> *A set of powerful, selective and modular "blocks" that work reliably in both small- and large-scale applications.*[2]

In contrast to such flatpacks, however, where the hardware is of more secondary importance, the reactions constituted the most important part of the click chemistry concept. As the article title implies, these reactions should essentially lead to the building blocks 'clicking' together as a belt is locked in by a belt buckle. Each reaction should be straightforward and lead efficiently to the desired connection. However, in contrast to a belt buckle that can be reopened, the reactions should have a strong thermodynamic driving force and not be reversible.

The concept was in part motivated by natural processes, aiming to generate substances by joining smaller units together with heteroatom linkages (C-X-C). To realize this, **Sharpless** and his coworkers proposed the reinvigoration of established, well-tested reactions, with the goal to accelerate the discovery of substances with useful properties. The reactions should essentially be 'spring-loaded' for a single trajectory and not lead to any undesirable by-products.

Suitable click-type reactions should abide by specific – and quite tough – criteria:

- The reactions should be modular and wide in scope
- They should operate under simple reaction conditions and give very high yields
- They should take place in no solvent or a solvent that is benign or easily removed
- They should only generate inoffensive by-products that can be removed by non-chromatographic methods
- They should be stereospecific (but not necessarily enantioselective) and be highly selective for a single product
- They should have a high thermodynamic driving force, usually greater than 20 kcal/mol and proceed rapidly to completion

Ideally, the process should be insensitive to oxygen and water. Furthermore, the starting materials and reagents should be readily available, and the product should be stable under physiological conditions. The resulting compounds should also be easy to isolate by non-chromatographic methods, such as crystallization or distillation.

Kolb, Finn, and **Sharpless** also listed a range of different reactions that could be envisaged to fulfil many of these criteria:

- Nucleophilic ring opening of strained heterocycles, such as epoxides and aziridines
- Non-aldol carbonyl chemistry, such as formation of ureas and amides
- Addition to alkenes/alkynes, such as epoxidation and dihydroxylation
- Cycloadditions involving unsaturated structures, such as hetero–Diels-Alder reactions and **1,3-dipolar cycloadditions**

Of these, the 1,3-dipolar cycloaddition reaction between azides and alkynes was to become almost synonymous with the concept.

1,3-Dipolar Cycloadditions

Although the 1,3-dipolar cycloaddition reaction type was defined, and its mechanism delineated, by Rolf Huisgen around the year 1960,[3,4] it has a long history with early examples reported in the 19th century. The azide functionality, in part owing to its reactivity and stability, has played a central in this development. Already in 1864, Peter Grieß described the synthesis of phenyl azide (azidobenzene), a compound he called diazobenzolimide, from phenyldiazonium tribromide and ammonia.[5] A few decades later, in 1893, Arthur Michael used phenyl azide in a reaction with the

alkyne dimethylbutyndioate and obtained the 1,2,3-triazole, the cycloaddition product.[6] Further understanding of the azide reactivity was gained in the 1930s, when Lawrence Brockway and Linus Pauling (Nobel Prize in Chemistry 1954; Nobel Peace Prize 1962) noted the dipolar nature of alkyl azides,[7] describing reasonable resonance structures of such compounds (Figure 1).

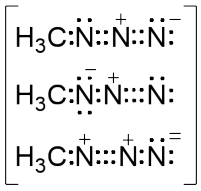

Figure 1: Methyl azide resonances, showing the dipolar nature of the compound, according to Pauling.[7]

At the same time, Kurt Alder (Nobel Prize in Chemistry 1950) and coworkers noted the reaction between phenyl azide and norbornene derivatives,[8,9], and in 1954, as part of a series of studies involving multicyclic compounds, Karl Ziegler (Nobel Prize in Chemistry 1963) and coworkers presented additional studies on the high reactivity of such structures (Figure 2).[10]

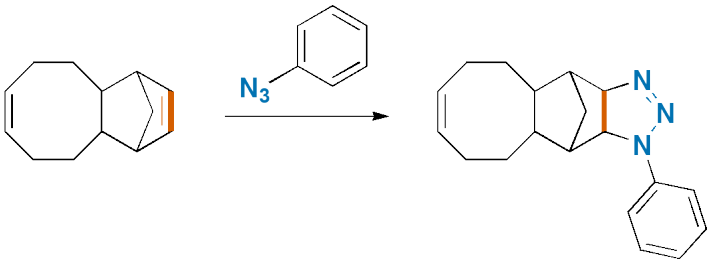

Figure 2: Formation of 1,2,3-triazole from phenyl azide and strained alkene.[10]

The fast reaction kinetics observed with these strained norbornene derivatives was intriguing, representing a feature that prompted Huisgen to study these systems in more detail. By the end of the 1950s, he carried out a series of studies with such compounds, and came to the conclusion that the reactions were concerted cycloadditions between compounds carrying a 1,3-dipole and a matching dipolarophile, *i.e.* the alkene (Figure 3).

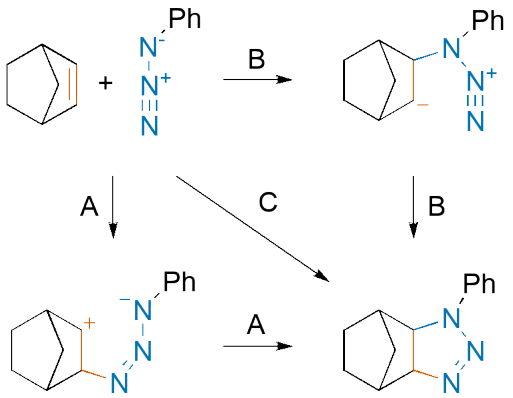

Figure 3: Alternative reaction mechanisms between phenyl azide and norbornene. From results obtained using different solvents, Huisgen proposed concerted pathway "C".[4]

Huisgen proposed that certain compounds, such as azides, contain dipoles with a 1,3-relationship, especially visible in the sextet resonances, that can undergo (3 + 2) (or [4 + 2]) cycloaddition reactions with alkenes (and alkynes), thereby forming 5-membered rings (Figure 4). Apart from azides, Huisgen also identified a range of other 1,3-dipolar compounds, such as nitrile oxides, diazoalkanes, azomethine ylides, nitrones, and ozone, and demonstrated their various addition products.[3]

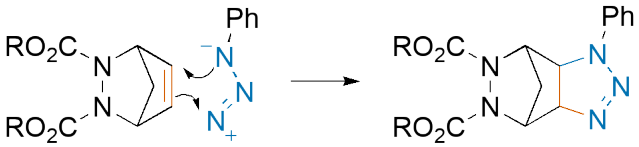

Figure 4: Cycloaddition mechanism of the reaction between phenyl azide and strained alkene leading to 1,2,3-triazole structure.[4].

The work of Huisgen and others had thus laid a foundation for 1,3-dipolar cycloadditions, which prompted **Sharpless** to identify these reactions as candidates for the click chemistry concept. However, azides and the associated cycloadditions were at the time not extensively used, and several challenges with the reaction remained. Thus, in these earlier studies of the 1,3-dipolar cycloaddition reaction between azides and alkenes/alkynes, the dipolarophile was generally substituted at both ends (internal alkenes/alkynes), most often carrying the same substituent group at the ends. One reason for this was to avoid the formation of more or less complex mixtures during the reaction, owing to the low reaction regioselectivity. When terminal alkynes are used in the reaction, mixtures of the 1,4-disubstituted triazole and the 1,5-disubstituted triazole are typically produced, sometimes in a near 1:1 ratio (Figure 5).[11]

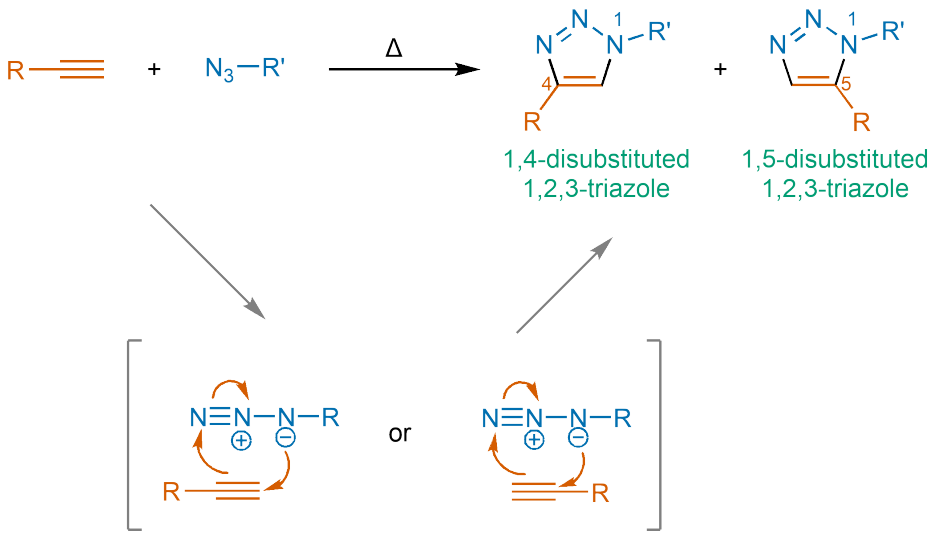

Figure 5: Thermally induced 1,3-dipolar cycloaddition between azides and terminal alkynes typically lead to mixtures of 1,4- and 1,5-disubstituted 1,2,3-triazoles.

Furthermore, unless the alkyne is activated by electron-withdrawing groups or subject to ring strain, the reaction rates are typically low at ambient temperature,[12] and the reaction requires heating to proceed to high conversions within a reasonable time frame. An alternative solution in this context, apart from heating, is to confine the two reactants in space, thereby substantially accelerating the process, an approach used to, for example, identify inhibitors of acetylcholinesterase.[13]

From a more practical standpoint, the potential hazards of synthesizing energetic azides at large scale led to diminished interest in using this reaction.[14] Although azides are relatively unreactive towards many functionalities, including oxygen and water, thereby making them ideal for click chemistry, they are often explosive in nature and must be handled with care.

Catalysed Azide-Alkyne Cycloaddition

The situation changed dramatically when the catalysed reaction was discovered. In 2001, while working on the identification of efficient and mild methods to introduce the 1,2,3-triazole pharmacophore in peptides, **Morten Meldal** and Christian W. Tornøe discovered that Cu^{I} substantially catalyses the cycloaddition reaction between azides and terminal alkynes (Figure 6a).[15] A first study of this copper-catalysed azide-alkyne cycloaddition (CuAAC) was presented at a conference, where they described that high yields (80–95%) could be obtained by allowing a terminal alkyne (attached to a solid support) to react with different alkyl and aryl azides in the presence of a Cu^{I} salt at room temperature, producing the 1,4-disubstituted 1,2,3-triazoles. They could also show that the chemistry was compatible with standard Fmoc

(fluorenylmethyloxycarbonyl) chemistry and solid phase peptide synthesis. A more detailed account was published a few months later,[16] in which the copper-catalysis process was described in more detail.

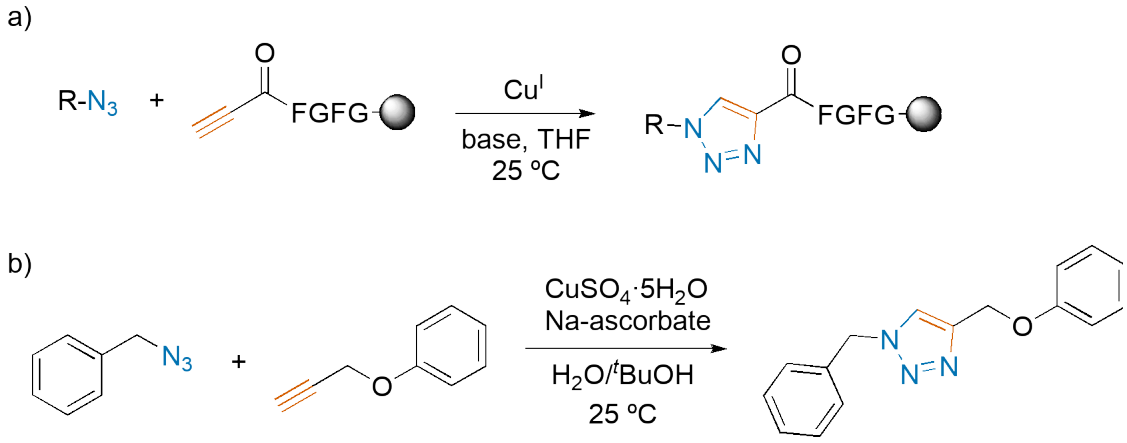

Figure 6: Copper-catalysed reactions from a) **Meldal** and coworkers,[15,16] and b) **Sharpless** and coworkers;[17] F: phenylalanine, G: glycine, filled circle: solid support, THF: tetrahydrofuran, ^{t}BuOH: *tert*-butanol.

Independent of, and in parallel with, the work of **Meldal** and Tornøe, **Sharpless**, together with Valery V. Fokin and coworkers, could also identify Cu^{I} as a catalyst for the 1,3-cycloaddition reaction.[17] In this case, it was found that Cu^{II} salts could be used in combination with a reducing agent, such as ascorbate, to yield Cu^{I} *in situ*, an approach that improved the reaction with respect to cost and catalyst purity. Again, the copper-catalysed reaction proceeded in high yields with a variety of starting materials, essentially only producing the 1,4-disubstituted 1,2,3-triazole product (Figure 6b).

The active copper-species (Cu^{I}) turned out to be a remarkable catalyst that accelerates the cycloaddition reaction up to 10^{7} times while primarily producing the 1,4-disubstituted isomer.[18] The catalysed process is also very robust and exhibits a broad scope with respect to starting materials. Thus, the triazole formation is nearly independent of the substituents of both reaction partners, and the outcome of the CuAAC reaction is relatively insensitive to steric or electronic effects of the substituents. Moreover, the functional group interference is low, and various substituted primary, secondary, tertiary, and aromatic azides readily participate in the transformation. The tolerance for variations in the acetylene component is also excellent. The process is experimentally straightforward and the triazoles can often be obtained in a procedure which generally involves little more than stirring the reagents and filtering off the pure products. Typically, the reaction proceeds to completion within hours at ambient temperature in a variety of solvents, including alcohols and water without any organic co-solvent. Although most

experiments are performed at close to neutral pH, the catalysis seems to proceed well at a wide range of pH-values.

Very soon, this copper-catalysed reaction was to enjoy a dramatic upsurge in interest across a range of disciplines. The efficiency with which this reaction operates, combined with the robustness and ease of operation, rapidly made it a standard go-to transformation when one structural entity needed to be connected to another. With a few simple transformations, possible to carry out even in less well-equipped laboratories, the two cycloaddition partners could be prepared, and addition of a copper source could essentially produce the 1,4-disubstituted triazole in high yield in reasonable time. Due to the remarkably high interest, manufacturers of chemical compounds swiftly added a wealth of starting materials to their catalogues, making the process even smoother. Seldom has the community seen such an immense and immediate impact of a single chemical reaction. Because of this, the CuAAC reaction became the very epitome of click chemistry, essentially becoming synonymous with the concept. Regardless, the reaction was very much within the framework of the overall concept, and its discovery paved the way for other click-type reactions in the field.

One reason for the immediate success of CuAAC is the selective formation of 1,4-disubstituted triazoles. Importantly, the triazole species is essentially inert to many reactive conditions, *e.g.* oxidation, reduction, and hydrolysis. It is a stable compound with high functional group-tolerance. It is a compound of intermediate polarity with a dipole moment of ~5 D, so it is compatible with a range of different solvents. It also resembles an amide bond, and can be used to replace these in certain situations.[19]

Biological Applications - Copper-Free Click Chemistry

The immense success of the CuAAC reaction rapidly triggered the interest in using this transformation in biological systems. However, the toxicity of copper ions to cells and living organisms was found to limit the use of CuAAC chemistry for such applications. Therefore, the identification of conditions that avoided copper became an immediate challenge. Fortunately, very soon a viable alternative was introduced.

One of the conspicuous findings that prompted Huisgen to study the reactions that led to the concept of 1,3-dipolar cycloadditions was the unexpectedly rapid reactions between phenyl azide and norbornene derivatives.[8–10] Similarly, Georg Wittig (Nobel Prize in Chemistry 1979) and Adolf Krebs reported that certain cyclic alkynes acted as efficient dipolarophiles with azides.[20] One reason for the high reactivity was the strained nature of such dipolarophiles,[21] which results in the release of ring strain upon cycloaddition and facilitation of the reaction progress.

In 2004, **Carolyn R. Bertozzi** and coworkers used this feature of cycloalkynes, especially the highly strained cyclooctynes,[22] as a solution to replace CuAAC in biological systems (Figure 7).[23]. Again based on azides, this type of 1,3-dipolar cycloaddition was named strain-promoted azide-alkyne cycloaddition (SPAAC). **Bertozzi** and her group could show that the SPAAC reaction involving a biotinylated cyclooctyne structure and various aliphatic azides proceeded as expected under mild conditions in acetonitrile or mixtures of acetonitrile and phosphate-buffered saline (PBS), albeit at a low rate at the concentrations used. This azide-cyclooctyne (3 + 2) cycloaddition worked fairly well in the absence of Cu^{I}, although potentially giving a mixture of isomeric compounds.

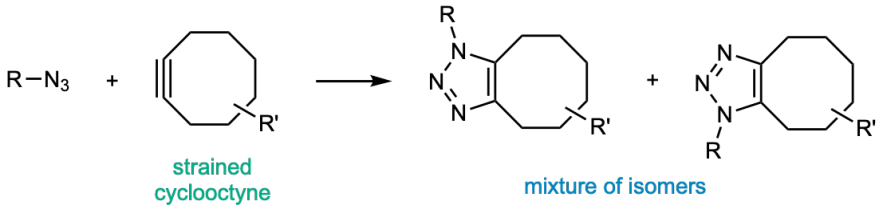

Figure 7: Strain-promoted azide-alkyne cycloaddition (SPAAC).

Building on their previous work on cell surface engineering,[24,25] **Bertozzi** and her group could also show that human Jurkat cells that had been metabolically engineered to express azide-derivatized glycoproteins, could undergo conjugation with the biotinylated cyclooctyne. Thus, probing the incorporated biotin conjugate with fluorescently-labelled avidin revealed a dose-dependent fluorescence increase.

To achieve this metabolic engineering, **Bertozzi** had noted that the normal sialic acid biosynthesis *in vivo* can be tricked to accommodate unnatural substrates, as shown by the group of Werner Reutter,[26,27] leading to the presence of derivatized sialic acid groups as part of the cell-surface glycans. By feeding cells with *N*-levulinoyl mannosamine (ManLev),[25] or peracetylated *N*-azidoacetylmannosamine (Ac_4ManNAz),[24] both of which analogues of the natural carbohydrate *N*-acetylmannosamine, **Bertozzi** could introduce either ketone groups or azides in the glycan structures produced by the cell machinery. These groups could subsequently be targeted for ligation with matching functionalities (Figure 8).

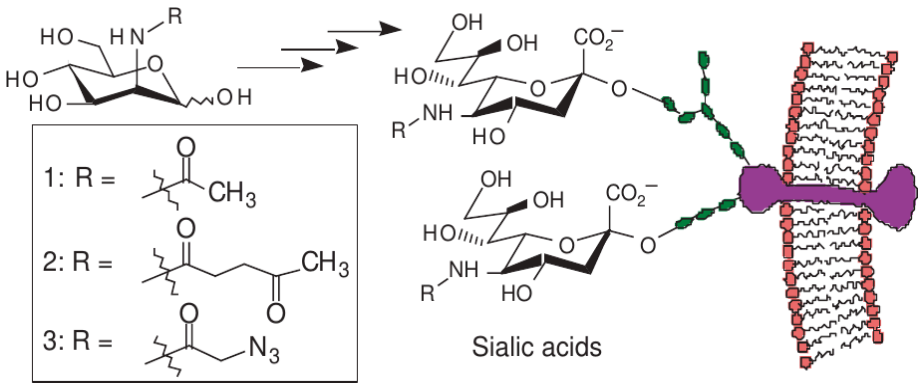

Figure 8: Cell labelling using metabolic engineering. *N*-levulinoyl mannosamine or *N*-azidoacetylmannosamine is fed to cells, converted into functionalized sialic acids, and expressed in glycans at the cell surface.[24]

Bioorthogonal Chemistry

This development of applying SPAAC directly in human cells accentuates another concept: that of bioorthogonal chemistry. Even before she identified SPAAC, **Bertozzi** had been attempting to perform conjugation chemistry directly in living systems. Having explored the formation of oximes, acyl hydrazones, and thiosemicarbazones,[25,28] her group turned to the Staudinger reaction, discovered by Herman Staudinger (Nobel Prize in Chemistry 1953) and Jules Meyer in 1919.[29] This reaction takes place between an azide and a phosphine, forming an iminophosphorane that can be trapped by a variety of reagents. For example, studies by the group of Fèlix Urpí and Jaume Vilarrasa had demonstrated the utility of this reaction in peptide synthesis and intramolecular amide coupling.[30,31]

Bertozzi used this amidation sequence, named 'Staudinger ligation', by designing a biotinylated, phosphine-containing ester structure. She and her coworkers could show how this can react with the azide-containing carbohydrate structures metabolically expressed at the cell surfaces.[24] Jurkat cells were first incubated with $Ac_4ManNAz$ and then allowed to react with the phosphine structure. The presence of biotin at the cell surfaces could subsequently be demonstrated through staining with fluorescently-labelled avidin. In this case, the phosphine oxide formed as a consequence of the Staudinger reaction remained in the final conjugate, potentially disturbing ensuing processes. However, shortly afterwards, the groups of **Bertozzi** and Ronald T. Raines devised methods to circumvent the presence of a phosphine oxide in the product; so-called 'traceless' Staudinger ligation.[32,33]

Furthermore, the **Bertozzi** group could show that the cell surface engineering method and the Staudinger ligation could be applied directly in living animals.[34] When mice were fed with

Ac4ManNAz, harvested mice splenocytes presented azide groups at their surfaces. This was demonstrated by labelling the cells *ex vivo* with a phosphine-derivatized tag using the Staudinger ligation reaction, and analyzing the cells with anti-tag antibodies. Moreover, the reaction could be achieved directly in the living mouse by administering the tag after a series of daily injections of Ac4ManNAz.[34]

In the early 2000s, **Bertozzi** introduced the term 'bioorthogonal' in the context of chemoselective reactions for use in biological systems,[35–37] (also highlighted in the PhD Thesis of George A. Lemieux, a graduate student in the **Bertozzi** group)[38]. The concept of bioorthogonal chemistry could then be more explicitly described by Danielle H. Dube and **Bertozzi**,[39] as an emphasis of the previously introduced concepts of chemoselective ligation, orthogonal coupling, and native chemical ligation,[40–43] with a specific focus on biology. Essentially, bioorthogonal reactions should be able to occur under physiological conditions without interfering with, or being affected by, any surrounding biological processes.

> Bioorthogonal reactions
>
> "…reactions of functional groups that are so selective for each other that they can be ligated in a richly functionalized biological milieu.[39]"

In this context, the term 'orthogonal' stems from studies on protecting group chemistry in peptide synthesis, distinguishing the mutually exclusive reactivity of different protecting groups under specific deprotection conditions. Thus, in 1977, George Barany and R.B. Merrifield (Nobel Prize in Chemistry 1984) defined an 'orthogonal system' as 'a set of completely independent classes of protecting groups … [where] each class of groups can be removed in any order and in the presence of all other classes.'[44]

This orthogonality concept was later adopted also for mutually exclusive synthetic reactions. Applied to peptide synthesis, orthogonal coupling reactions should be specific and allow for 'only a single specific coupling reaction between the C^{α} moiety of one peptide segment and the N^{α}-amine of another peptide segment, in the presence of other reactive amino moieties'.[42]

In part, these developments in peptide synthesis, and likely also the related studies on 'self-assembling drugs',[45] served as an inspiration for both click chemistry and bioorthogonal chemistry. In the early 1990s, methods were developed with the aim to produce polypeptides and proteins through selective coupling of longer, unprotected peptide chains.[42,43,46,47] For example, selective peptide coupling could be achieved using either aldehyde- or thioacid-functionalized peptides and matching peptides carrying a cysteine group at the *N*-terminal.[43,46]

While the Staudinger ligation reaction proved less optimal for living systems, the **Bertozzi** group continued to develop SPAAC for *in vivo* applications. The original reaction involving the basic cyclooctyne motif displaying relatively slow kinetics, room for improvement could be found in the use of activated cyclooctyne groups. Thus, a range of structures was developed by the **Bertozzi** group and others, leading to higher cycloaddition rates with the matching azides.[48–54] For example, the metabolic incorporation of a galactose analogue of Ac_4ManNAz (Ac_4GalNAz) in the glycans of zebrafish embryos could be followed using an improved SPAAC reaction with a difluorinated cyclooctyne.[55] Similarly, the reaction could be used directly in the murine environment, as shown in a study where living mice were first exposed to Ac_4ManNAz, again resulting in azide-presenting cells, followed by different cyclooctyne structures carrying recognition tags.[56]

Alternative Bioorthogonal Reactions

Following the emergence and rapid burgeoning of bioorthogonal chemistry, in parallel to the growth of the click chemistry field, a variety of alternative reactions have been applied and developed for use in living systems. Among these, the inverse-electron-demand Diels-Alder (IEDDA) reaction between a strained alkene and a tetrazine, developed independently by the groups of Joseph M. Fox and Scott A. Hilderbrand, have gained special interest.[57,58] This reaction displays unusually fast kinetics in the absence of catalysts, is compatible with a wide range of conditions, and produces a stable dihydropyrazine product upon release of nitrogen. Due to the high rates, the reaction can be used at low concentrations, which is often required in biological systems. The potential of using this IEDDA reaction in living animals could be shown shortly after its discovery.[59] Thus, tumours could be targeted in mice through a two-step, pre-targeting approach, where *trans*-cyclooctene-labelled antibodies were first allowed to interact with the tumour cells, followed by reaction with a tetrazine-derivatized radio-labelled probe.

Since these seminal accounts, several studies have been reported that involve the application of SPAAC, IEDDA, or related reactions directly in living animals.[60,61] These have not only demonstrated the feasibility of carrying out selective reactions in the highly complex biological environments of living organisms, but they have also highlighted the many challenges associated with such processes. Nevertheless, the potential for applications in the delineation of complex biological processes, metabolic tracing, sensing and diagnostics, targeted therapies, drug delivery, etc., has been clearly shown, and the scope is likely to become significantly wider in the future.

Summary and Outlook

The two concepts of click chemistry and bioorthogonal chemistry have had a tremendous impact on Chemistry and its neighbouring sciences. The discoveries of CuAAC, SPAAC, and other related reactions addressed a significant unmet need, and spurred intense activity across many different

areas. This has resulted in the identification and development of a wide range of reactions that make up the click chemistry palette or can be applied to bioorthogonal chemistry.[62] Coupled with the eyeopening power of conceptualization, the discoveries essentially opened a research floodgate that rapidly resulted in a wealth of new, highly important results. Thus, researchers around the world have demonstrated a wealth of applications - especially involving azide-alkyne cycloadditions. In a transferred sense, the use of the spring-loaded and selective nature of these transformations also acted to release the tension that had arisen from a lack of suitable chemistry tools, thereby harnessing potential ideas and actively promoting a plethora of new developments. For example, click chemistry and bioorthogonal chemistry has been used in the development of enzyme inhibitors and receptor ligands, pharmaceuticals (anticancer agents, antimicrobials, etc.), herbicides, photostabilizers, diagnostics and sensing elements, corrosion retardants, brightening agents, biomacromolecule conjugates, tissue regeneration matrices, and various macromolecular materials (gels, polymers, etc.), as well as in the mapping of complex biological processes.

The achievements and discoveries of **Carolyn R. Bertozzi**, **Morten Meldal**, and **K. Barry Sharpless** have had 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.

Olof Ramström
Professor of Chemistry
Member of the Royal Swedish Academy of Sciences
Member of the Nobel Committee for Chemistry

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