Rolf Huisgen (1920–2020)

Rolf Huisgen left us on 26 March 2020, just three months shy of his 100th birthday. His work has had an enormous influence on chemical biology, ranging from new methods for the synthesis of chemical probes to “click chemistry” and its application to in vivo bioconjugation.

Rolf Huisgen grew up in the Eifel region of western Germany, studied chemistry in Bonn and Munich, and received his PhD from work with Heinrich Wieland in 1943. Shortly after the launch of his independent career at the University of Tübingen, he became Wieland's successor in 1952 and was charged with rebuilding the University of Munich's famous chemistry department, which had been all but destroyed in World War II. Frustrated by his graduate work on the arduous structure elucidation of a *Strychnos* alkaloid, he decided to dedicate himself to careful kinetic measurements for the elucidation of reaction mechanisms, a theme that continued throughout his life. His most productive period coincided with a time when organic chemistry was making enormous, revolutionary advances and when the rational planning of reactivity based on physical principles became possible.

Huisgen's most famous contribution to chemistry is the recognition and classification of 1,3-dipolar cycloadditions, a name he coined in an influential 1960 review article. Such reactions had been observed before, mostly with azides and diazo compounds, but their kinship had not yet been realized and their prominent place in the conceptual framework of organic chemistry had not been recognized. Based on a thorough electronic analysis, Huisgen predicted and studied new 1,3-dipoles such as azomethine ylides and thiocarbonyl ylides and showed that most, but not all, of them react in a concerted fashion. 1,3-Dipolar cycloadditions (“Huisgen reactions”) have since proven to be among the most powerful methods for the synthesis of ubiquitous five-membered heterocycles. They have been used to great effect in the functionalization of fullerenes (Prato reaction), in the synthesis of numerous natural products (cocaine, histrionicotoxin, phorbol, etc.), approved drugs (such as rufinamide), and a wide range of drug candidates and molecular probes. In addition to (3+2) cycloadditions, Huisgen also carried out seminal studies on (2+2) cycloadditions, including those involving ketenes and tetracyanoethylene, as well as classic investigations on arynes.

The significance of Huisgen's work became even more apparent after

his retirement in the 1990s with the introduction of click chemistry by Barry Sharpless and Morten Meldal. Chemical biologists began to realize the usefulness of ‘biorthogonal’ reactions, such as azide/alkyne cycloadditions, for forming specific bonds in a sea of nucleophiles and electrophiles. The ability to catalyze these reactions, or promote them with strained dipolarophiles, made them truly useful for applications to biomolecules and living systems with their aqueous environment and narrow temperature tolerance.

1,3-Dipoles and their addition products have also been identified in a range of natural products, raising interesting biosynthetic questions. In addition, 1,3-dipolar cycloadditions and cycloreversions have been implied in an enzymatic reaction mechanism. An artificial enzyme, aptly named a “Huisgenase”, was engineered that can catalyze the reaction between azomethine ylides and nitroalkenes. Huisgen's impact on biosynthesis, however, goes beyond the chemistry with which his name is mostly associated. In an effort to demonstrate the predictive power of the Woodward–Hoffmann rules, he studied 8π – 6π electrocyclization cascades, which were subsequently found to occur in the formation of several natural product families, such as the endiandric acids, kingianins, and elysiapyrones.

In another aspect of Huisgen's scientific impact, a large number of his graduate students and postdocs, and their own scientific progeny, have assumed chairs all

over the world. His famous experimental lectures, delivered during his introductory course on organic chemistry, drew numerous students into the field who subsequently had successful careers in the industry and in academia. All of them were deeply influenced by his intellectual rigor, occasionally intimidated by his high standards and pointed remarks, impressed by his discipline, and euphoric when they received rare but honest praise from him. Few had the privilege of getting to know him well personally. Those who did, saw him as both an avid skier and a very dedicated and knowledgeable collector of German expressionist art. His guided tours through Munich's magnificent collections were as legendary and as well-prepared as his lectures. His own apartment was filled with prints by Ernst Ludwig Kirchner and Franz Marc, whose emotional distortions provided an interesting contrast to Huisgen's precise manner of speaking and dispassionate intellect, perhaps hinting at a more complex character behind the professorial façade.

While some scattered 1,3-dipolar cycloadditions had been reported before, Huisgen put these reactions into context, in a classic case of “seeing what everybody else had seen but thinking what nobody else had thought” (Szent-Györgyi). Arguably, this is one of the greatest rewards that a scientist could hope for, and Huisgen was content with having climbed such intellectual heights. He was exhilarated to witness the ‘second act’ of 1,3-dipolar cycloadditions in click chemistry and enjoyed interacting with chemical biologists, such as Carolyn Bertozzi, who received the 2012 Wieland Prize in his presence. Huisgen was already 92 years old at this time and in full command of his mental powers, and he continued to publish until the year 2018. As such, his active career extended over 74 years. It is hard to imagine a more fulfilled scientific life. □

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