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Albert Eschenmoser (1925–2023): A Giant of Organic Chemistry

Albert Eschenmoser (Figure 1), one of the greatest organic chemists of the past hundred years, died on July 14, 2023 at the age of 97. The extraordinary breadth of his scientific contributions ranged from synthetic methodology, structure elucidation, and synthesis of natural products to the chemical etiology of biomolecular structures.

Figure 1. Albert Eschenmoser.

Albert Eschenmoser was born in Switzerland on August 5, 1925, in Erstfeld in the canton Uri. He studied chemistry in the Department of Natural Sciences at the ETH from 1944 to 1949, obtaining his doctorate in 1951 from Nobel laureate Leopold Ružička working in the group of Hans Schinz on acid-catalyzed cyclizations in mono- and sesquiterpene compounds. Eschenmoser became a Privatdozent in organic chemistry in 1956, was promoted to associate professor in 1960, and received a full professorship in 1967. After retiring in 1992, propelled by ever-active curiosity, Eschenmoser continued his research with postdoctoral fellows at the ETH Zurich until 2000, at the Biozentrum of the University of Frankfurt am Main from 1993 to1996, and at the Scripps Research Institute in La Jolla, California from 1996 to 2009.

Eschenmoser's lifelong fascination with the reactivity of organic compounds was backed by unusually sensitive intuition, experimental ingenuity, and intellectual rigor. For example, his early studies of aliphatic polyenes, begun while still a graduate student, served as a mechanistic guide to the assignment of many terpene structures. With the subsequent elaboration of stereoelectronic and conformational rules, he worked out a mechanistic basis for the biogenetic isoprene rule and paved the way for later synthetic applications. Together with his colleague and friend Duilio Arigoni, Eschenmoser derived the constitution as well as the configuration of all tetra- and pentacyclic triterpenes known at the time.

Throughout his career, Eschenmoser demonstrated an almost uncanny ability to shed light on fundamental questions in organic chemistry. Examples of this versatility include an explanation for slow stereochemical inversions of amines; studies of the transition state geometries of nucleophilic substitutions at carbon centers, showing that endocyclic S_N2 reactions are forbidden if a linear transition state is geometrically impossible; and preparative application of novel fragmentation reactions. For instance, he established the so-called Eschenmoser fragmentation, a mild method for converting α,β-epoxyketones into acetylenic ketones and aldehydes with p-toluenesulfonyl-hydrazine or N-aminoaziridines.

These methodological achievements often originated in the context of challenging natural product syntheses. Eschenmoser's strategic and tactical skills, evident in the early total synthesis of the alkaloid colchicine, a natural painkiller for gout, culminated in the pioneering total synthesis of vitamin B12. The assembly of this complex natural product, spanning 12 years of intensive research, was a milestone in organic chemistry that impressively established the range and power of synthetic methods. Initially conducted in competition with R. B. Woodward, the ETH and Harvard groups ultimately opted for a "competitive collaboration" to tackle the enormous challenges posed by this demanding target. What followed is unique in the history of chemistry. One half of the corrin ring system was produced at Harvard University, the other at ETH, and the final stages were worked out jointly. Extensive model studies, in which new strategies and methods for building the corrin framework were developed, including the sulfide contraction, a C–C bond forming reaction that was used several times in the final synthesis, were an integral part of the B12 project at ETH. In parallel, Eschenmoser also produced an independent route that included an ingenious, light-induced cycloisomerization in

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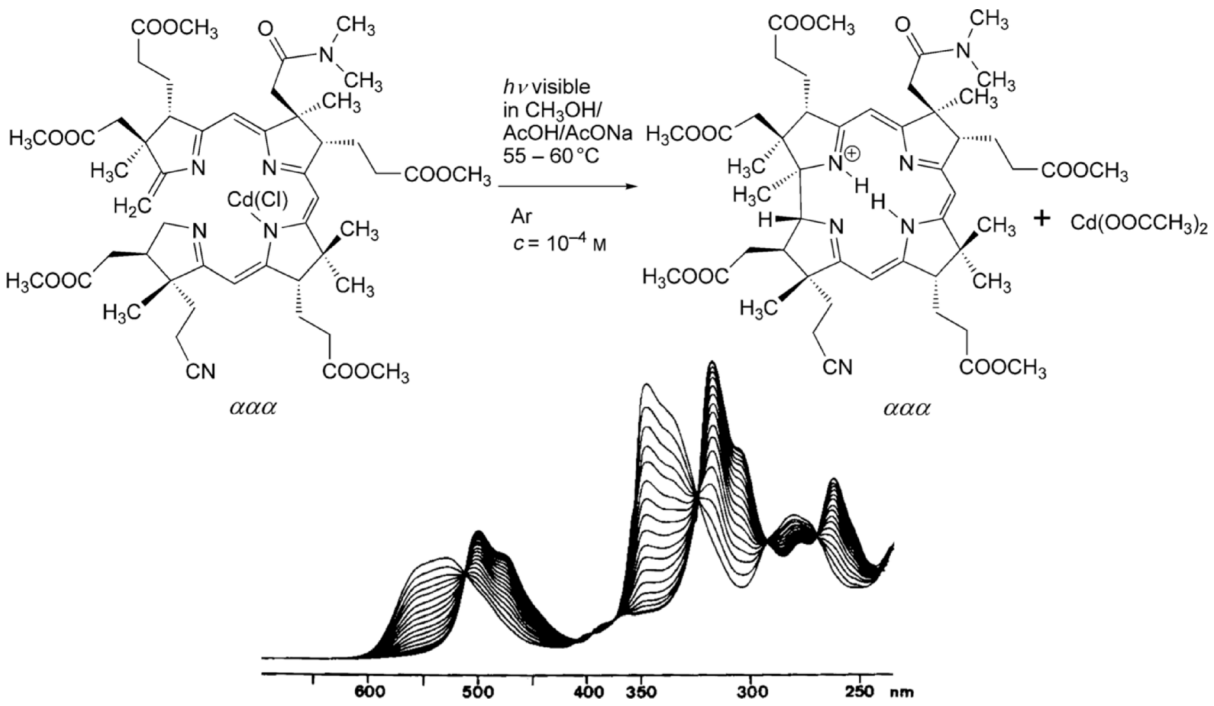

Scheme 1. Vitamin B12 Synthesis: Light-induced cycloisomerization to connect the A and D rings via an antarafacial 1,16-H shift followed by an electrocyclic ring closure (from *Helv. Chim. Acta* **2015**, *98*, 1921–2054).

which the bond between the A and D rings was formed via an antarafacial 1,16-H shift followed by an electrocyclic ring closure (Scheme 1). Although its total synthesis was successfully completed in 1972, Eschenmoser noted in a "chat session" recorded in 2022 that vitamin B12 remained a lifelong intellectual inspiration.

Drawing on lessons from his synthetic work, Eschenmoser turned his attention to the formation of corrin rings in nature. Model studies of non-photochemical variants of the cycloisomerization reaction he developed showed that corrins could be generated surprisingly easily from tetrapyrrole precursors by several potentially biomimetic pathways. In addition to elucidating credible biosynthetic routes to B12, these investigations led to the realization that such structures could have arisen spontaneously under prebiotic conditions. This line of research was subsequently extended to other classes of biomolecules, giving rise to plausible proposals for how other important biomolecules, including nucleotides, sugars, and amino acids, might have first formed billions of years ago. In asking why nature chose pentoses rather than hexoses as the backbone of its genetic polymers Eschenmoser also explored a series of information-carrying oligomers as alternatives to DNA and RNA, which afforded valuable insights into why the natural biopolymers ultimately prevailed in evolution.

Albert Eschenmoser was not only an outstanding scientist but also an exemplary educator and mentor to some 250 doctoral and postdoctoral researchers. His lectures in organic chemistry for undergraduate and graduate students were famous among ETH chemists as well as colleagues from all over the world. All those who had the privilege of working in Eschenmoser's research group will remember him as a demanding, critical, but also incredibly inspiring mentor. Indeed, he was a "Doktorvater" in the best sense of the word. It was of great concern to him to convey the central importance of ethical guidelines in science. He knew no compromise when it came to honesty, accuracy, and critical evaluation of his own research results. Moreover, his enthusiasm for chemistry, evident in discussions and in group seminars, was contagious. In difficult phases of a project, young colleagues were reminded of the work's importance and motivated to press on. His regular visits to the research labs were among the highlights of the group's daily routine. The informal, relaxed discussions during these visits provided unique insights into Eschenmoser's way of thinking, and his subtle, often enigmatic sense of humor often came to the fore. The duration of these coffee rounds depended on the course of the conversation—there was no set time limit. Their aftermath, formulas scribbled onto scrap paper or into notebooks, were kept as coveted trophies by many. As the term "Doktorvater" implies, Eschenmoser remained an important reference person in the lives of his former students even after they had completed their dissertations. He followed their professional development with interest and sympathy and was always ready to assist with advice.

Eschenmoser's accomplishments brought him international fame and countless invitations to lecture at universities, in companies, and at international conferences. Though always deeply rooted in Switzerland, even when abroad, Eschenmoser was appreciated, indeed admired and celebrated, by innumerable colleagues and friends around the world for his keen mind, curiosity, vitality, and unwavering integrity. He received national and international awards including the Marcel Benoist Prize (1973), the Robert A. Welch Award (1974), the Davy Medal (1978), the Tetrahedron Prize for Creativity in Organic Chemistry (1981), the Arthur C. Cope

Award (1984), the Wolf Prize (1986), the Paracelsus Prize of the Swiss Chemical Society (1999), the Franklin Medal (2008), and many others. He was a member of the most prestigious academies worldwide, including the German Academy Leopoldina, the American Academy of Arts and Sciences, the U.S. National Academy of Sciences, the Pontificia Academia Scientiarum (Vatican), the Royal Society of Chemistry, London, the Academia Europaea, the Göttingen Academy of Sciences, and the Croatian Academy of Sciences and Arts. He was also a recipient of the Austrian Decoration of Honor for Science and Art and an honorary member of the Royal Society of Chemistry, the Society of Austrian Chemists, and the Pharmaceutical Society of Japan. He was awarded honorary doctorates from the Universities of Freiburg, Chicago, Edinburgh, Bologna, Frankfurt, Innsbruck, Strasbourg, Harvard and the Scripps Research Institute.

Albert Eschenmoser shaped 20th-century organic chemistry as few others have. His intellect, his warm-heartedness and his fine sense of humor remain unforgettable.

Obituary

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