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The 50th Anniversary of the Cahn–Ingold–Prelog Specification of Molecular Chirality

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In 1964 I was searching for a place to pursue a doctoral thesis. At that time I was carrying out my diploma thesis at the Technische Universität Hannover in the group of Walter Theilacker. I was working on the task of preparing the first long-lived dialkylarylmethyl radical, in which I did not succeed. My bench neighbor Horst Böhm, a PhD student, was more successful. He was able to determine the very low rotational barrier of 2,2′-dimethylbiphenyl, a difficult problem even today, by carrying out ingenious experiments that involved polarimetry at below −30 °C: $E_A = 15.1 \pm 0.4\ \mathrm{kcal\,mol^{-1}}$. Horst took inspiration from Eliel's *Stereochemistry of Carbon Compounds* (1962), which was usually on his desk and often consulted. His enthusiasm was infectious, and I started also to study this book. It was full of references and had an index of names. Only four authors had four lines in the register: Eliel, Allinger, Djerassi, and Prelog. Horst told me that Prelog was considered the "pope of stereochemistry" and that the ETH Zürich was one of the world's top universities. I applied and was accepted to start work in 1965.

My new home was lab D110, the lab nearest to Prelog's office. My labmates were the habilitands Hans-Herrmann Westen and Hans Gerlach, and slightly later the PhD student Georges Haas. I encountered a lab that was partially covered with sheets of paper, versions of the manuscript of the publication that eventually appeared in April 1966. Professor Prelog, "Pg" among co-workers and addressed as "Vlado" by American postdocs, usually hurrying along in a white, unbuttoned lab coat, and often came in for last-minute changes, which were accompanied by discussions and anecdotes, which Prelog loved to tell.

First Steps—London 1951

I learned that the system was initiated by Robert S. Cahn (London), the editor of the *Journal of the Chemical Society*, in order to cope with an increasing number of structures, the configuration of which could not be adequately described by the Fischer–Rosanoff D,L convention. He asked Christopher K. Ingold of University College London for help, and Ingold, an intellectual giant, came up with the rudiments, published by the two in 1951,[1] of what later became the CIP system. However, they kept the descriptors D and L. Prelog came in not only because of his extensive research on various stereochemical issues, but also because he succeeded his teacher Emil Votoček (Prague) in the 1950s as member of the IUPAC Commission on the Nomenclature of Organic Chemistry. The collaboration began in 1954 at a conference in the Manchester area, which was concluded with a dance. Among the people who were not dancing, Prelog spotted Ingold and Cahn, whom he knew from the IUPAC commission. A lively discussion and criticism of their system closed with the invitation to join the team.

The R,S System—1956

The result appeared in the journal *Experientia* only two years later.[2] In the meantime, Bijvoet (1951) had determined, for the first time, the absolute configuration of an organic compound. Furthermore, a variety of new description types were introduced, for example, pseudoasymmetric units, chirality axes, and chirality planes. All this required a fundamental distinction from the Fischer system, which was made visible by introducing the descriptors *R* and *S*. Adoption of the *R*,*S* system, as it was called before 1966 by the chemical community, was by no means guaranteed as other scientists developed rules for the same purpose. Here, membership of the aforementioned IUPAC commission was of great importance, because among its members were editors of important journals and handbooks, for example, Cahn, and Friedrich Richter, the Editor of the "*Beilstein*", who adopted the *R*,*S* nomenclature and applied it to numerous examples. The *Beilstein* editors encountered a number of difficulties, which were regularly discussed with Prelog, who transferred the experience to Cahn and Ingold. Finally all this evolved into a new manuscript, to which Hans-Herrmann Westen contributed considerably.

The CIP System—1966

The publication "Specification of Molecular Chirality"[3] in *Angewandte Chemie* was an immediate and lasting success. The title was to change the everyday language of chemists by bringing the term chirality to their attention. This term had been created by Lord Kelvin in the 19th century and was "discovered" by Kurt Mislow. A former

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guest professor at the ETH and friend, he generously left it to Prelog to unveil it to the chemical community.

The article was a comprehensive outline of the system with numerous examples and in-depth explanations of problematic specifications, many of which had been brought forward by the Beilstein experts as well as chemists from all over the world. Most examples referred to molecules that had chiral centers with four ligands. An extension to coordination compounds with up to six ligands, mostly octahedral complexes, considerably widened the scope. The system was further extended to include conformations as well as helical stereomodels, which were specified with the new descriptors *M* (minus) and *P* (plus). It was clearly recognized that compounds with a chiral axis, for example, biaryls, can be specified either by using a model based on an elongated tetrahedron, descriptors a*R* and a*S*, or by the conformational approach, descriptors *M* and *P*. A similar treatment was already in use for the chirality plane. It was an unfortunate coincidence that a*R* corresponds to *M* in case of the axis. This is not known to many users and has caused numerous erroneous descriptions.

Revision of the CIP System—Developments Beyond 1966

The 1966 article coincided with important developments. The concept stereotopicity ("prochirality") was introduced by Mislow, Hanson, and others in 1965–1967. The development of computer programs for synthesis planning brought in mathematicians, who found the CIP rules not sufficiently precise. In particular, a number of cyclic compounds caused serious problems.

Challenged by the critics, Prelog developed a keen interest in fundamental geometry, which he absorbed from books of the great mathematicians of the 19th century, in particular Felix Klein and A. F. Möbius, and he sought the company of mathematicians and physicists. The theoretical physicist Ernst Ruch, for example, was often invited to the ETH. The main results obtained after 1966 were summarized in three publications. In 1972, "Pseudoasymmetrie in der organischen Chemie" appeared.[4] Therein two-dimensional stereochemistry was introduced and stereotopicity was combined with the CIP specification. Pseudoasymmetric stereoisomers are rarely encountered; however, their description marks a clash between the viewpoints of symmetry and permutation of ligands. Some of our proposals were somewhat bold and raised criticism from Kurt Mislow, who later published an analysis of the problems together with Jay Siegel.[5]

It took ten years to finish what we called our opus magnum.[6] Therein the geometrical basis of the CIP system was clarified. This paper revived the largely unknown term stereogenic unit, which was immediately accepted by the community. Most importantly, the specification of cyclic stereomodels became possible by an unambiguous procedure to transform cyclic into acyclic ligands through a hierarchical tree graph; mathematicians could now codify the CIP system. In the late 1970s "acyclic stereocontrol" caused considerable problems with respect to stereodescription. Dieter Seebach took the initiative to apply the revised CIP description.[7]

Later stereochemistry grew in many directions. For example, fullerenes are often chiral and their description by the CIP system is possible. For topological stereoisomerism and some areas of coordination chemistry limits are possibly reached.

When asked for the value and future of the CIP system, Prelog might have answered with an anecdote, such as this one.[8] It so happened that he met Sir Robert Robinson at Zürich airport. Robinson: "Hello, Katchalsky. What are you doing here in Zürich?" Prelog: "Sir Robert, I am only Prelog, and I live here". Robinson: "You know, Prelog, your and Ingold's configurational notation is all wrong." Prelog: "Sir Robert, it can't be wrong. It is just a convention. You either accept it or not." Robinson: "Well then, if it is not wrong, it is absolutely unnecessary."

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