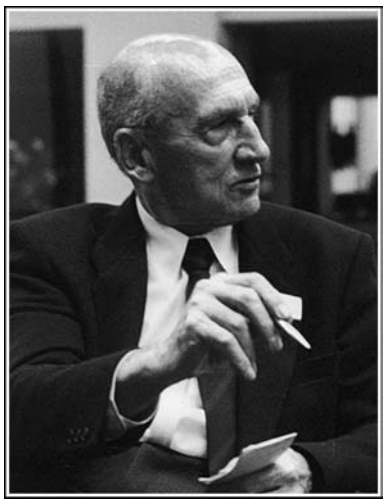
NEKROLOG OBITUARY

Vladimir Prelog

(Sarajevo, July 23, 1906 – Zürich, January 7, 1998)



In the twilight, all of a sudden,
Unwatched by anyone from below,
A cloud
Appeared above the town.

It was swung by high wind
And it started to glow,
But all men's eyes were pointed
To the earthly matters.

And everybody went their way:
After power, gold or bread,
And the cloud, bleeding beauty,
Went its way in the sky.

And it floated higher and higher,
As if to reach God;
It was swung by high wind,
The wind dispersed it.

The Cloud, Dobriša Cesarić

For those who knew well Vladimir Prelog, retired professor of Eidgenössische Technische Hochschule (ETH) in Zürich, as well as those who met him only occasionally, it is hard to believe that our Professor, though almost 92, really left us on January 7, 1998, in the same quiet way as he always lived. Even at his age, with his physical strength declining, he was still a lively, optimistic, witty, cordial, accessible and above all modest person, interested, besides chemistry of course, in music, theatre, literature and social trends. He was a real intellectual, one of the greatest chemists of this century, winner of the Nobel Prize for chemistry.

Vladimir Prelog was born in Sarajevo on July 23, 1906. After finishing elementary school in Sarajevo, he attended grammar school in Osijek and then in Zagreb. He graduated from the Prague Institute of Chemical Technology, where he also obtained his doctor's degree in 1929. After running a laboratory for the production of rare chemicals in Prague, he started his academic career at the Technical Faculty in Zagreb, first as assistant professor (1935–1940) and then as associate professor of organic chemistry (1940––1941). In December 1941 he joined Professor Leopold Ružička in his laboratory at the Eidgenössische Technische Hochschule (ETH) in Zürich, where he quickly climbed the hierarchical ladder and in 1957 succeeded Ružička as head of the Institute. He extended and modernized the Institute and democ-

ratized it by introducing collective management. He retired in 1976 and, since there is no status of professor emeritus at ETH, he enrolled further semesters as a *»Fachhörer«,* thus remaining active up to the end of his days.

In 1933 he married Kamila Vítek, with whom he has a son – Jan (1949).

Though he had no Alpine garden like Ružička, Prelog loved flowers. Pearly pink »Mercedes« roses on his desk and a red amaryllis, tended by his secretary of many years Dagmar Westen, adorned his office. These were later replaced by a large Christ's thorn and an orchid. He was also fond of sweets. Especially cakes and bayadere chocolates, as well as fruit salads, with some maraschino if possible. He did not drink in principle, however he could not refuse a welcome glass of home-made plum brandy or a toast with Riesling from my cellar.

He was cordial and accessible and liked to socialize. He was known for his historical memory. He knew personally almost all prominent chemists of this century, and he used to entertain company telling funny stories and anecdotes about them until early hours in the morning. He was a source of proverbs and sayings. He was suggestive in explaining, argumenting, requesting and also in disagreeing. He was gentle and knew how to reassure, encourage, relax and console.

He was always ready to take visitors round the ETH laboratories or to show them and explain the small collection of chiral objects in his office: quartz crystals, snail shells or fossilized ammonites.

Still, Prelog loved chemistry above all. He swore his allegiance to chemistry when he was fifteen and at grammar school by publishing his first scientific paper and he lived happily with it ever after. The following old Chinese proverb seems applicable to Prelog: *»If you want to be happy one evening, buy a bottle of wine, one week, slaughter a pig, one year, get married, but if you want to be happy for the whole of your life, you must love your work.«*

Indeed, Prelog loved his work, which resulted in more than 30 patents and 400 publications. He frequently stressed that success in work required, in addition to some talent, a great deal of hard work and also a great deal of luck. Luck to have a good teacher, good associates, understanding of the working environment and, finally, luck of having chosen the right theme. A theme that is neither very outdated nor too much advanced for the time in which you live. He modestly said that he had just that kind of luck and that he changed his research themes according to the trends of time.

»The world is chiral and clinal; enjoy
the symmetry wherever you find it.«
Vladimir Prelog

Prelog's major contribution to science refers to the field of organic chemistry of natural compounds and the stereochemistry of organic compounds and reactions, and especially to the search for symmetry and order in the world of chiral and asymmetric chemical compounds, which permeates his overall work.

In Prague, after his dissertation in which he clarified the structure of the aglycone of glycoside rhamnoconvolvuline, his first research choice was the study of the chemistry of cinchona bark alkaloids, which he later carried on in Zagreb, and even in Zürich. There he published 26 papers.

»At Zagreb his work was frenetic
To make adamantane synthetic
A molecular cathedral
Of shape tetrahedral.....«

Christopher Mislow

When he returned to Zagreb in 1935, along with antibacterial sulfonamides, bicyclic derivates of quinuclidine, antimalarial quinine, Prelog and his associate and good friend Rativoj Seiwerth synthesized adamantane, a miraculous, natural, diamond-like substance. The solution of this demanding problem raised highly Prelog's standing in the scientific circles of that time. He immediately established close co-operation with the small chemical factory »Kaštel«, for which he patented his inventions. In 1937, very soon after it was done in the world, upon Prelog's suggestion, »Kaštel« launched sulphanilamide, under the name *Streptazol*®, on the market. He also established a research department at »Kaštel«, which included a chemical, a farmacological and a bacteriological laboratory. After World War Two, »Kaštel« evolved into »Pliva«, which employed and still employs most of the chemists who specialized with Prelog.

»From there on to Zürich he went
To continue his rapid ascent
Towards the brilliant career
Which has brought us all here...«

Christopher Mislow

He arrived in Zürich, where he was met by L. Ružička, in December 1941. They worked together on isolation and determination of the structure of natural substances of animal origin, obtained from urine extracts of pregnant mares and pig testes, mainly steroid structure compounds. Thus, 3-α-androstenol was isolated from the latter extract, a substance of much more intensive odour than civetone, which was very similar in structure both to civetone and to the androgenic hormone androstene. It was much later that 3-α-androstenol found application as a sexual attractant in pig-breeding and parfurmery. It was also determined in truffles.

Soon, however, Prelog went his own way. After the war, various materials of plant origin became available. Prelog used them to isolate and determine the structure of compounds from the series of china-, strychnos-, solanum-, veratrum-, erythrina- and other alkaloids. Studying the hypothesis whether poorly accessible, civetone and muscone related, bi- and tricyclic compounds with 9–11 C-atoms in the ring also possess similar odours, Prelog developed fundamental studies of these medium-size cyclic compounds both with re-

spect to their possible preparation (acyloin synthesis) and to their stability and reactivity. He defined the limits of Bredt's rules.

These studies resulted in the technique of isotope labelling for the needs of following the course of chemical reactions and, thus, Prelog became a co-founder of the application of the secondary deuteric isotope effect technique in studies of the mechanism of chemical reactions. S. Borčić brought this method to Zagreb and, jointly with D. Sunko, and later K. Humski, developed this area of physical organic chemistry (at one time known as the Zagreb School).

By his conceptual approach to the stereochemistry of large ring compounds, Prelog opened another area, that of conformational analysis. Namely, for detailed location of an atom in a molecule it is not enough to know only its structure and configuration, but also its conformation, *i.e.* the spacial arrangement of atoms conditioned by the free rotation around all single bonds. In 1960, Klyne and Prelog proposed the unambiguous, and today generally accepted, nomenclature of conformations, which now bears their names. Prelog is considered one of the co-founders of conformational analysis.

Stereochemical approach to the compounds and reactions led Prelog to the study of asymmetrical McKenzie reactions. Prelog observed the formal relations and established that the reagent attack at the carbonyl group C-atom always occurred from the side of the smaller substituent on the chiral C-atom of the alcohol, lying beyond the paper plane. This rule is now included in all textbooks and is known as *Prelog's Rule.*

Microbial cultures abound in interesting compounds. Prelog isolated and determined the structures of the macrolide narbomycin, the degradation product of which, known as the *Prelog-Djerassi* lactone, plays an important role as a reaction intermediate in the syntheses of macrolides. This is followed by nonactin, echinomycin, antibiotic ferrimycin, with a series of structurally related ferrioxamines, and antibiotics rifamycins and boromycin.

As a logical sequel to his work on products of microbial origin and studies of asymmetric reactions, Prelog systematically studied reductions of simple ketones by microorganisms and enzymes. He came to, for that time far-reaching, conclusions, according to which the enzyme (dehydrogenase) releases a hydride ion equivalent towards the *re*-side of prochiral ketone. This rule is currently used to predict the stereospecificity of reductions involving either microorganisms or isolated enzymes. Also this rule is now found in technical and scientific literature under the name *Prelog's Rule.*

Into the field of stereochemistry dealing with the geometric characteristics of models, *i.e.* geometric shapes representing the current topography of a molecule, Prelog introduced the term *Chemical Topology.* One of the major molecular properties in terms of topography is their optical activity, a consequence of the geometric property known as chirality. Since chirality is not restricted to three-dimensional space, but is possible in a space of any dimensions, Prelog designed a catalogue of chiral and achiral geometric

shapes, which may be isomorphic or homomorphic to geometric models. While designing this catalogue, he also developed a new approach to stereochemistry, which is based on the simplex theory. The strength of this approach is not only in its application to stereochemistry, but also in prediction of unknown molecules, which were subsequently synthesized by Prelog and his co-workers (*e.g.* vespirenes, diastereoisomeric α-phenylethylamine derivates with a pseudoasymmetry axis or plane, and cyclostereoisomeric cyclohexaalanils).

This conceptual and topological approach expresses, in a way, the aesthete Prelog's search for harmony and symmetry in the chiral and clinal world of molecules.

Prelog recognized the need for unambiguous specification of the configuration of stereoisomers and, jointly with Robert Sidney Cahn and Sir Christopher Ingold, he developed a system of rules for assignment of descriptors (*R, S, M, P, r, s, m, p, E, Z*). The system, known as CIP [C(ahn)-I(ngold)-P(relog)] rules for specification of molecular chirality – rules of stereoisomer nomenclature. It was adopted, as a convention, on Friday, 13 May 1966 at the *»2nd EUCHEM Conference on Stereochemistry«* in Bürgenstock, Switzerland, one of the most prestigious conferences of today, a co-founder of which was also Prelog. Jointly with Helmchen, Prelog updated the CIP rules in 1982.

According to the editorial board of the renowned journal *Angewandte Chemie*, with P in the CIP-rules Prelog erected his own monument while still alive. Finally, the CIP-rules, along with his conceptual and topological contributions to chemistry, paved the way to Prelog's Nobel Prize for chemistry (1975) for his research in the stereochemistry of organic reactions and molecules.

After his retirement in 1976, working with a restricted number of coworkers, almost exclusively from Zagreb, Prelog was engaged in studies of the enantioselective complexation of chiral ammonium salts with lipophilic esters of tartaric acid and the fascinating chiral poly-(9,9'-spirobifluorene) crown ethers, whose picture became the »cover girl« of the September issue of *Angewandte Chemie* in 1985. It was in this field, of utmost importance for the understanding of analogous biochemical processes, that Prelog's last experimental work was done. It culminated in a proposed model, presented as a diamond lattice, of stereoselective complexation of tartaric acid esters with amino alcohols. Thus, Prelog's research areas got entwined and *»Prelog's research wheel«* turned back to the beginning, that is, to adamantane and its diamondoid structure.

Prelog was very attached to his native environment. He was the first to teach his associates from the University of Zagreb the science, skill and art of organic syntheses. Co-operating with »Kaštel«, Prelog laid the foundations of synthetic production and of organized scientific work at »Kaštel«, which was actually the germ of the »Pliva – Research Institute«. Though his departure for Switzerland interrupted his work in our circles, Prelog man-

aged to establish **Prelog's Zagreb School of Organic Chemistry** in only seven years of his scientific activities in Zagreb. This period resulted in 48 published scientific papers and 6 patents, as well as 5 dissertations written under his guidance. It is worth mentioning that Prelog's group with their 10 papers was the research team with the largest number of papers published in the distinguished journal *Berichte der Deutschen Chemischen Gesellschaft* in 1941.

Even after he left for Zürich, Prelog continued to monitor the development of his school. He maintained contacts with his former co-workers and also made it possible for many young organic chemists to come as welcome guests or associates to his laboratory at the ETH. They have all returned to this country. »All scientists from Croatia that stayed for some time with Prelog could feel his enthusiasm, his complete dedication to research work, as well as his wish to disseminate modern knowledge and current scientific problems to our scientific environment. In this respect, he certainly influenced all of us that worked in his ETH laboratory while it is up to others to evaluate our contribution to the spreading of such approach to research work and relationships among colleagues« (Vitomir Šunjić).

In this manner, Prelog made a large contribution to the further development of organic chemistry in these parts and Prelog's Zagreb School of Organic Chemistry still continues imparting the teaching of its founder.

Prelog actively followed the developments in this country. Whenever he visited his homeland, Prelog liked to meet and informally socialize with his former associates, students who specialized or prepared their doctor's dissertations with him. Generations of Croatian chemists collaborated in some way with Vladimir Prelog. He paid visits to the Universities of Zagreb and of Osijek. He also visited the Croatian Academy of Sciences and Arts, Institute »Ruđer Bošković«, Pliva, INA Oil Industry, Borovo and the Croatian Chemical Society. He took part in the debate on science in these parts, stopped at the Faculty of Science in Zagreb. He was honorary chairman of »Ružička's Days«, »Meetings of Croatian Chemists«, *Almae matris alumni* and life honorary president of the Advisory Board of the journal Croatica Chemica Acta. He gave interviews to the press, radio and television. He donated books and magazines from his own library to his former department at the Faculty of Chemical Engineering and Technology and the Croatian Academy of Sciences and Arts. Still, his visits to the Department of Organic Chemistry of the Faculty of Chemical Engineering and Technology in Zagreb, where he used to work, were particularly touching and his samples preserved there, »covered with almost the same dust as 50 years ago«, when they were synthesized, evoked memories of bygone days in him.

Prelog was a honorary member of many associations and academies, among which the Croatian Academy of Sciences and Arts and the Papal Academy. He received honorary doctorates from a number of universities from all over the world, among them also from the Universities of Zagreb and Osijek. He also got the Božo Težak Medal of the Croatian Chemical So-

ciety. His basic institution, the ETH, founded »Prelog's Lecture« in 1986, an event held each year and accompanied by the awarding of Prelog's Gold Medal. The Croatian Chemical Society and »Pliva« established in 1996 the organic chemistry award »Vladimir Prelog« for young researchers under 36. On the occasion of Prelog's 80th birthday, chemists from all over the world organized three scientific gatherings in his honour – in Israel, Switzerland and in Croatia. To mark his 90th anniversary, his colleagues dedicated to him their papers in the special issue »*Surprise Festschrift*« of Croatica Chemica Acta.

Prelog worked quietly and unobtrusively during his whole life and, like no one so far, he gladly disseminated new knowledge in Croatia. Recognitions came also from outside the profession. He is an honorary citizen of Zagreb and Osijek, and he also obtained several high state decorations.

Prelog was an agnostic, tolerant to everybody, except for militant extremists of any persuasion. It was for this reason that, at the very beginning of the Croatian patriotic war, he raised his voice against the atrocities and barbarism, both in personal contacts and over the public media. In all his protests, however, he was true to himself, clear, simple, dignified and did not provoke further conflicts. This was one of his life skills. By the clarity of his expression, regardless whether he was requesting or explaining or was fed up with something, Prelog captured his collocutors. He also captured me, wholly and without reservation.

Our Vladimir Prelog, Vlado, Pg, or »King of Chemistry« (Barry Sharpless) has left us. In the same quiet way as he lived, he was buried with only his closest family attending the funeral. Vladimir Prelog, the living history of chemistry thus moved into the history of chemistry. He has certainly already looked up many of his teachers and collaborators out there, for instance, Kuria, Lukeš, Ružička, Woodward, or some of his students that died too early, such as Borčić or Oppolzer. He is sure to be talking to them – about what else but chemistry or, as Sir Derek Barton put it, about good old times when the students really worked hard.

The teacher of generations of undergraduates, doctoral and postdoctoral students will not impart his knowledge any more. Scientific public has lost a brilliant scientist, many of us much more than that – a dear friend. He will be missed also by ordinary people who used to meet him and for whom he always had time and understanding. My family and I will always remember him.

I hereby express gentle words of condolence to his wife Kamila and his son Jan who will miss him most of all.

Miljenko Dumić