Chimia 53 (1999)138–139

ISSN 0009–4293


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Vlado as Cheiron

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Over a period of several decades, *Vlado Prelog*'s laboratory was a mecca for academic guests from abroad, many of them from the United States, and it is my privilege to represent them today on the occasion of this commemoration. I intend to share some personal reminiscences of the time that I spent with my mentor at the ETH, over 40 years ago. In order to place my remarks in their proper perspective, however, it will first be necessary to outline *Prelog*'s vital contributions to the development of modern stereochemistry. As *William Klyne* remarked on the occasion of *Prelog*'s Nobel Prize in 1975: '*van't Hoff* is considered as the founder of 'chemistry in space'; *Prelog* has been the High Priest of this cult for the past 20 years.'

I would like to begin my tribute to the master by quoting a stanza from a poem that my son *Christopher* wrote on the occasion of *Prelog*'s 80th birthday celebration at the ETH-Zürich in 1986. The full poem was published in *Chimia* **1986**, *40*, 394 as part of a report on this celebration.

Of this I have never been surer,
And hence expect no one's demurrer
When I proclaim aloud
How we're all so damned proud
To have known the world's greatest Fachhörer.

Throughout his long and illustrious career, *Prelog* maintained a consuming interest in the chemistry of natural products. His involvement in stereochemistry was a direct outgrowth of this passion. It began with his studies of *Cinchona* alkaloids during his years in Prague, in the late 20s and early 30s, and continued in Zagreb with the first of his many scientific triumphs, the synthesis of adamantane, in 1941. In 1944, just a few years after his arrival at the ETH, *Prelog* had already published papers that specifically addressed questions dealing with stereochemical aspects of natural products. To give just one example, one paper published in that year is titled 'Über die Konfiguration der asymmetrischen Kohlenstoffatome 3, 4 und 8 der China-Alkaloide'. In hindsight, we can see in this title the foreshadowing of the *CIP* rules. The same year also saw the first of the many landmarks in pure stereochemistry that are identified with *Prelog*'s name: the famous resolution of *Tröger*'s base into its mirror-image components by chromatography on a column of lactose hydrate.

Just a few years later, in 1947, *Prelog*'s acyloin synthesis of medium-sized rings opened the way to a comprehensive study of many-membered ring systems. In the first Centenary Lecture of the Chemical Society, in 1949, *Prelog* showed, for the first time, how the methodology of conformational analysis can be employed to rationalize the physical and chemical properties of medium-membered ring compounds. This groundbreaking work led to an understanding of conformation-dependent steric effects on structure and reactivity. During that time, *Prelog* also succeeded in formulating an empirical rule, now known as *Prelog*'s Rule, governing the stereochemical direction of the asymmetric atrolactic acid synthesis. The underlying idea behind this rule was that the relative steric bulk of the groups attached to the carbinol carbon was responsible for the direction of the asymmetric synthesis. It is commonly assumed, nowadays, that the course of asymmetric syntheses is, in general, controlled by differential non-bonded interactions. *Prelog*'s pioneering concept, therefore, represented a breakthrough of major proportions.

It seems appropriate here to quote another stanza from *Christopher*'s poem:

Combining his sense of the practic
With his vision of scale galactic,
He made *Prelog*'s Rule
An imperative tool
By concocting a brew atrolactic.

So, by the end of the 1950s, stereochemistry had clearly become the dominant theme in *Prelog*'s work. It was around that time that I was able to spend the academic year 1957–58 as his guest in the Laboratorium. *Prelog* had found his first inspiration in organic chemistry by working with *Rudolf Lukeš* in the 1920s, and this experience had taught him, as he tells us in his autobiography 'My 132 Semesters of Chemistry Studies', that 'the best way to study science is as an apprentice to a master who is a model both in his field and in his personal characteristics'. So it turned out that, by good fortune, I had come to the right place at the right time, to apprentice myself to the right master.

To be under *Prelog*'s spell proved to be a memorable experience. Forty years have passed and memories tend to warp and blur. But I still remember those glory days as though it were yesterday. The air at that time was electric with the excitement generated by a constant stream of galvanizing discoveries, by the race to beat the scientific competition, and by the hubbub of incessant scientific discussions. The wonderfully stimulating atmosphere was due entirely to *Prelog*'s nurturing influence and charisma. As first among equals, or 'Dorfältester' as he liked to characterize himself, *Prelog* presided over a stable of brilliant young students and of Dozenten, like *Albert Eschenmoser* and *Duilio Arigoni*, who were to achieve world-class reputations. The conviviality in this hothouse of ideas, and the affection, deep

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admiration, and respect that the denizens of the Laboratorium felt for each other was promoted as much by *Prelog*'s intellectual leadership as by his human kindness, his genial manner, his genuine modesty, and his utter lack of pretentiousness. An article in the July 6, 1998, issue of *Chemical & Engineering News* carried the headline 'Talent thrives at the ETH-Zürich' and described the Swiss Federal Institute as it is today as a scientific 'paradise'. It surely was a paradise 40 years ago. And there can be no doubt that *Prelog* was the architect who layed the groundwork for this happy state of affairs.

The highlight of my visit was the stimulation afforded by innumerable lively discussions with the master, who, with fatherly benevolence, had taken me under his wing. What seemed uppermost in his mind in those days was the need to impose a logical structure on stereochemistry so as to bring reason and order to a field dominated at that time by rank empiricism, pragmatism, and intuitive, not to say sloppy, thinking. The time seemed ripe to provide stereochemistry with a conceptually sound foundation. *Prelog*'s main motivation, as I saw it, was his thirst for reason and order, coupled with a sense for the aesthetic – he even taught me how to erase a blackboard properly, that is, in parallel vertical strokes – and this is what led him on a quest to frame the principles of stereochemistry in the language of geometry, and to the development of what he called the geometric foundation of stereoisomerism and, at other times, chemical topology. It was also around that time that the 'cult' of chemistry in space, in *Klyne*'s formulation, began to take shape. We called it 'chirosophy', and *Prelog* was the undisputed leading light and star attraction among the coterie of chirosophists (or chirosophers) like *André Dreiding* and *Jack Dunitz*, among others, who shared his objectives.

Among these was the need to give precise meaning to the shape of the stereomodel. In part, this entailed cleaning up stereochemical nomenclature, or to 'purify the stereochemical vocabulary', as *Günter Helmchen* recently put it. For example, in his careful and meticulous way, *Prelog* followed the mathematician *Felix Klein* in drawing a distinction between molecular geometry and topography. He was most decidedly not a friend of the semantically challenged, and he tried with some success to rid the language of stereochemistry of questionable expressions such as 'optical isomers' and 'antipodes'. I have to confess, however, that, in this quest for terminological exactitude, there were also some occasions where hotly debated arguments were in the nature of theological disputes and tended toward medieval scholasticism. In any event, *Prelog*'s most significant efforts in this direction consisted in the introduction of logically unassailable and internally consistent stereochemical notations. In 1953, together with *Barton*, *Hassel*, and *Pitzer*, he proposed the axial/equatorial terminology to describe the spatial arrangement of cyclohexane bonds. In 1956, together with *Cahn* and *Ingold*, he proposed the *R/S* terminology, now familiar to everyone as the *CIP* system, to specify the configuration of stereoisomers. And in 1960, together with *Klyne*, he proposed the *syn/anti*-clinal/periplanar terminology to describe steric relations across single bonds.

Beyond all of this, however, *Prelog* saw the need for a systematic classification of stereoisomers, for a way of cataloguing the innumerable stereoisomers of an organic compound of known constitution. It was a challenge that he tackled with the characteristic enthusiasm and thoroughness that was the hallmark of all of his work. As he expressed it to me in a metaphor, the objective was to construct a comprehensive chest of drawers, each drawer labeled with a particular class of stereoisomer and containing the appropriate stereomodels. This exercise in systematic taxonomy was to remain his main passion in the years to come. It resulted in the construction of theoretical models of stereoisomers from various combinations of simplexes, and it inspired the synthesis of novel types of stereoisomers – cyclostereoisomers, vesperenes, and molecules possessing so-called elements of pseudoasymmetry.

Discussions with *Prelog* proved to be not only instructive and stimulating, but invariably good fun. He was renowned for his inexhaustible supply of jokes, anecdotes, and aphorisms. Here is another relevant stanza from *Christopher*'s poem:

But *Prelog*'s no mere academic.
His gifts far transcend just the chemic.
His skilled craftsmanship
Of the quick-witted quip
Makes contagion of mirth epidemic.

It would be doing *Prelog* an injustice, however, to describe him as merely a brilliant and witty raconteur. His was that, to be sure, as well as a master of the fast repartee, but he was much more than that. His stories, told with his wry and self-deprecating sense of humor and his well-tuned feeling for the ironic, were always captivating and precisely honed to fit the occasion. But rarely were they merely entertaining – there was always a message buried in the pleasantry. The intellectual rigor of his arguments remained uncompromised, but the avuncular manner helped to make the medicine go down more easily. And this was his genius as a teacher.

The last chapter of *Roald Hoffmann*'s book 'The Same and Not the Same' is entitled '*Cheiron*'. *Cheiron* was the wisest, the most righteous, and the most learned of all the centaurs, famous for his knowledge of medicine and for his skill in hunting, music, and the art of prophesy. But above all, he was a great teacher. *Cheiron* became the foster father and tutor of many great heroes of Greek mythology who learned those arts from him: *Peleus*, *Achilles*, *Asclepius*, *Castor*, *Jason*, *Theseus*, *Heracles*, *Odysseus*, and many others. In this chapter, *Hoffmann* said: 'The teacher in me likes this teacher'. I chose the title for my talk with this sentiment in mind, but also, of course, because it happens fortuitously to convey *Prelog*'s intense preoccupation with chirality in chemistry. Over the years, this subject had become of paramount concern to him; indeed, it is the title of his *Nobel* lecture. But to return to the name of the centaur: *Hoffmann* did point out that 'The Centaur's name comes from the Greek word for hand', but he did not explain the reason for giving the centaur this name. What does handedness have to do with the centaur's activities – which, by the way, included activities such as archery and music for which he surely needed both hands? It all seemed quite mysterious to me, so I consulted my colleague at Princeton, *Robert Fagles*, who is in the Comparative Literature department. *Fagles* had recently published a widely acclaimed translation of the Iliad and the Odyssey, so I thought that he might be the right person to ask. Although the question was new to him, he came up with an answer immediately: he speculated that the name probably meant to convey 'the one whose hands one is in', in other words, the teacher. Just like our *Vlado*.

Upon his death, *Cheiron* was placed by *Jupiter* among the stars, where he now appears in the shape of the constellation *Sagittarius*. The memory of the teacher whom we are honoring today will shine just as brightly in the annals of science, and among those of us who had the privilege of having known the world's greatest Fachhörer.