

The 1975 Nobel Prize for Chemistry

The 1975 Nobel Prize for Chemistry has been awarded jointly to John Warcup Cornforth and Vladimir Prelog for their researches on the stereochemistry of enzyme-catalyzed reactions and the stereochemistry of organic molecules and reactions, respectively.

Stereochemistry deals with the three-dimensional architecture of molecules. It is thus not a branch of chemistry but rather a point of view which pervades nearly all of chemistry, for nearly all molecules extend into the third dimension. Stereochemical problems range from evolution through biochemistry and pharmacology to technology. Even the senses of taste and smell respond differently to molecules which differ "only" in stereochemical architecture [(-)-carvone has a spearmint odor while (+)-carvone is the essence of caraway]. Indeed, the theme of stereochemical fit (as of a right glove with a right hand) versus misfit (left glove and right hand) is central to the workings of nature at the molecular level. Thus it is perhaps not surprising that the second Nobel Prize in Chemistry in 6 years has now been awarded for work in stereochemistry (the previous one being the 1969 prize given to Derek H. R. Barton and Odd Hassel).

It is in the biochemical applications of stereochemistry that Cornforth has made his mark. He is an Australian by birth (Sydney, 1917) and completed his predoctoral training at Sydney University in 1938. He then traveled to England where he received the doctorate degree at Oxford in 1941, working with Sir Robert Robin-

son. Cornforth began to lose his hearing at the age of 14, was almost deaf by the time he completed his studies at Oxford, and by the mid-1940's was totally dependent on written communication and lip reading. In 1941 he married Rita H. Harradence, also a Sydney University graduate and an Oxford Ph.D., and they have three children. Over the years his wife has been of invaluable help to him in communicating with his colleagues. She has also been his most constant scientific co-worker over a period of more than 35 years.

During World War II Cornforth worked at Oxford on the structure of penicillin and the chemical synthesis of steroids with Sir Robert Robinson, who received the Nobel Prize in 1947. This work culminated in a total synthesis of epiandrosterone. In 1946 Cornforth moved to the Mill Hill Research Laboratories of Britain's Medical Research Council where he stayed for 16 years developing his basic approach to the stereochemistry of enzyme processes. In 1962 he became director of the Milstead Laboratory of Chemical Enzymology of Shell Research Ltd., situated in Sittingbourne, Kent, near London. It was here that his detailed stereochemical studies on enzymatic processes were brought to fruition. From 1965 to 1971 he was also associate professor at the School of Molecular Science of the University of Warwick. In 1971 he became a visiting professor at the University of Sussex and last year joined the permanent faculty there as a Royal Society research professor. He became a member of the Royal Society in 1953 and has received the Corday-Morgan and Flin-toff Medals of the Chemical Society of London, the CIBA Medal, the Davy Medal of the Royal Society, the Guenther Award of the American Chemical Society, and the Prix Roussel.

Natural Products Structures

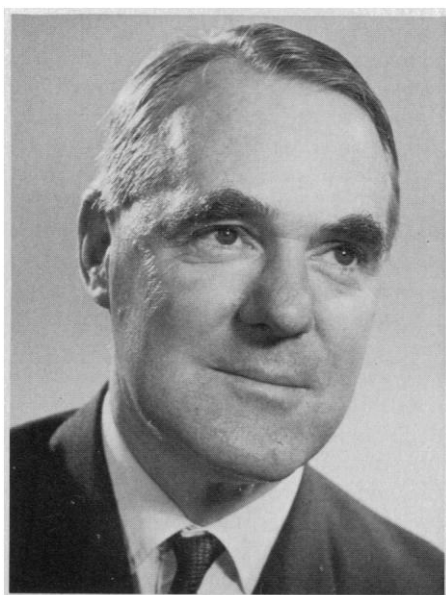
In his early studies Cornforth made many substantial and elegant contributions to the synthesis and elucidation of structure of a variety of natural products. Recently he has proved the structure of the terpenoid plant hormone abscisic acid (dormin) and personally completed its synthesis, reputedly in 11 days. During his initial studies on squalene he devised a new and now widely used general stereospecific synthesis of olefins. While these studies were in progress Cornforth was developing a deep and growing interest in enzyme-catalyzed biosynthesis of steroids and their precursors.

Clearly Cornforth's major scientific contribution has been the meticulously detailed elucidation of the biochemical

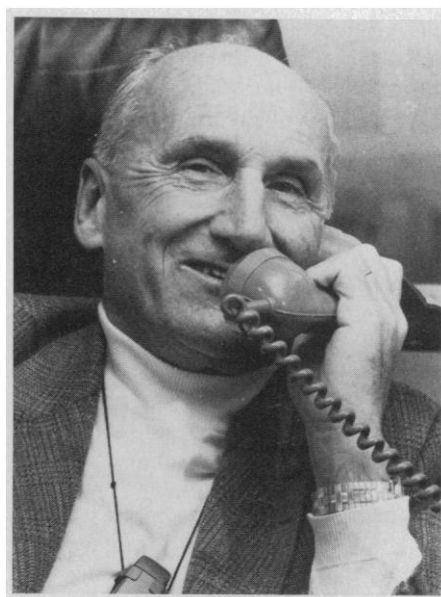
pathway for the synthesis of squalene from mevalonic acid. Through his research, more is known today of the mechanistic details of terpenoid biosynthesis than about any other biochemical process of comparable complexity.

By specific labeling of mevalonic acid, $\text{HOCH}_2\text{CH}_2\text{COH}(\text{CH}_3)\text{CH}_2\text{COOH}$, with deuterium or tritium in the two stereochemically distinct positions of each of the methylene groups at C-2, C-4, and C-5 and by following the label through the successive products of enzymatic elimination of H_2O and CO_2 , rearrangement, and condensation, Cornforth was able to determine the complete stereochemical course of squalene biosynthesis. This synthesis, which proceeds via isopentenyl, dimethylallyl, geranyl, and farnesyl pyrophosphates, has more than a dozen stereochemically definable steps of which all but one were determined as above. The last step was elucidated several years later by Cornforth when he succeeded (see below) in defining the stereochemistry at the chiral methyl group in the doubly labeled isopentenyl pyrophosphate $\text{CH}_3\text{C}(\text{CH}_3)(\text{CH}_2\text{OPP}) = \text{CHCH}_2\text{OPP}$, formed from 2-tritio-mevalonic pyrophosphate upon enzymatic incubation with D_2O .

That the mechanism of squalene biosynthesis should have been thoroughly elucidated by stereochemical labeling is so much the more remarkable in that squalene itself contains not a single chiral (asymmetric) center of the conventional type. Cornforth's achievement has additional significance since Konrad Bloch (Nobel Prize winner in medicine with F.



John Cornforth



Vladimir Prelog

Lynen in 1964) had shown that squalene is a biogenetic precursor of lanosterol and cholesterol. Thus, the mevalonic acid-to-squalene pathway is central not only to terpenoid but also to steroid biosynthesis.

Rita Cornforth made major experimental contributions to this beautiful work; she was personally responsible for the synthesis of the labeled mevalonate precursors. George Popják, now at the University of California, Los Angeles, was deeply involved in the biochemical aspects of these studies, in a collaboration which spanned 20 years. Among the many important papers resulting from this collaboration is one dealing with the question of which of the two hydrogens at C-4 in the dihydropyridine ring of NADH (reduced nicotinamide adenine dinucleotide) is transferred to the substrate in reductions involving the coenzyme.

More recently, Cornforth's attention has been focused on compounds bearing a chiral methyl group; that is, R- $\dot{\text{C}}$ HDT. The synthesis and especially the enzymatic assay of such compounds are major technical achievements in which Cornforth has had the able collaboration of Professor H. Eggerer and his students in Munich. This problem also has been attacked independently in parallel experiments by D. Arigoni and his co-workers at the Eidgenössische Technische Hochschule (ETH) in Zurich. Although the synthesis of chiral methyl compounds by itself is a most intriguing development, it is the brilliantly imaginative way in which Cornforth has made use of this chiral methyl group to trace the stereochemical consequences of enzyme processes, which has been the consummate achievement. Thus Cornforth has shown that the condensation of acetyl coenzyme A with (R)-3-tritio-oxaloacetate in the presence of R-citrate synthase gives an α -tritiated citrate from which is generated (R)-acetate, $\dot{\text{C}}$ HDT COOH , by cleavage in D_2O with citrate lyase. From this it follows that the enzyme-mediated carbon-carbon cleavage proceeds in a stereospecific manner with inversion. Thus, the enzyme process is inherently stereospecific even though the isotopically normal substrate citric acid and the product acetic acid are themselves achiral.

Cornforth is a very intense, incisive, and intellectual person, as well as a perfect gentleman in his scientific dealings with others. The scientific impact of his work has been carried more by his publications than his lectures. His public exposure has been less than that of others of comparable scientific stature because of his deafness. Cornforth is an excellent tennis player and chess enthusiast. He is reported to plan the downfall of his opponents at the chess

board in the same systematic fashion that he plans an assault on the solution of a biochemical problem. He is also a collector and author of limericks, which he sometimes generates at short notice to fit a special occasion.

Vladimir Prelog was born in Sarajevo (now part of Yugoslavia) in 1906, but received his university education at the Technical University in Prague, Czechoslovakia (Dipl. Ing.-Chem., 1928; Dr. Sc. Tech., 1929). After 6 years in the G. J.

Speaking of Science

Applied Math: Too Many Dehydrated Elephants?

Applied mathematicians, like pure mathematicians, are often lured by the formality and structure of the mathematical language. This love of elegance and abstraction can at times be detrimental, according to Mark Kac of Rockefeller University. (Kac has made substantial contributions to the fields of probability theory, statistics, analysis, and number theory.) In a recent series of lectures on probability theory that he gave at the University of Maryland, Kac stressed, as an underlying theme, that applied mathematics is becoming too fraught with formalisms and that this causes the field to become too ingrown.

Many of the most interesting problems in mathematics originated in the other sciences, Kac points out. For example, the meaty problems in probability and statistics came from physics, economics, and theories of games of chance. In order to remain vital, applied mathematics must continually be replenished with such problems. However, Kac believes that too many applied mathematicians deal exclusively with problems that are no longer tied to the real world. And this leads to a lack of vitality in applied mathematics, with the result that more and more is written about less and less.

Applied mathematicians traditionally approach problems arising from other disciplines by cleaning up the problems and rephrasing them in the language of mathematics. Many of these problems subsequently take on a life of their own and even lead to new and useful applications. This happened, for example, to Brownian motion. Once concerned with the motion of small particles, the theory of Brownian motion has been so formalized that it now exists as a mathematical subject unto itself, independent of its origins.

Although there is nothing wrong with the use of mathematical constructs, the tendency of mathematicians to reformulate problems in the most abstract way can lead to rather sterile research, according to Kac. The heart of the matter is that mathematicians often end up creating what Kac calls "dehydrated elephants." He refers to a cartoon, published during World War II in the *Saturday Evening Post*, in which two chemists are looking at a small pile of sand in the midst of formidable laboratory equipment. The caption read, "Nobody really wanted a dehydrated elephant but it is nice to see what can be done."

Of course, many applied mathematicians disagree with Kac's criticisms of their field and express surprise that he thinks applied mathematics is too ingrown. For example, Paul Smith, a statistician at the University of Maryland, denies that applied mathematicians in general, and statisticians in particular, are running out of interesting problems. He believes that many interesting new statistical problems are arising from interactions among statisticians and biologists and other scientists. Moreover, he emphasizes that many challenging problems that arose solely out of the internal structure of statistics remain to be solved. Smith, along with others, believes that it is wrong to condemn people who study pure statistical or other problems in applied mathematics that are divorced from problems that arise in the outside world.

Kac acknowledges that his is a maverick viewpoint. He speculates that the majority of people who study theoretical probability and statistics, as well as other areas of applied mathematics, have too much stake in what they are doing to worry about creating dehydrated elephants. Those who agree with Kac often point out that not only mathematicians but also investigators in other fields such as biology and physics should worry about the nature of their work. However, recognizing a dehydrated elephant when you create one is often easier said than done.—GINA BARI KOLATA

Driza laboratory in Prague, he returned to Yugoslavia to join the chemistry department of the University of Zagreb. After the German invasion of Yugoslavia in 1941 he left for Zurich, Switzerland, and joined the Laboratory of Organic Chemistry at the ETH in 1942, becoming professor in 1950. He is a naturalized Swiss citizen (and has become an ardent skier); he is married to Kamila Vitek and has one son.

Prelog's early contributions to chemistry were in the area of natural products and he has maintained a lifelong interest in this field. Among his early achievements at Zagreb was the synthesis of the remarkable hydrocarbon adamantane, heretofore isolated in minute amounts only from Moravian petroleum. Adamantane has a surprisingly high melting point (278°C) for its low molecular weight (138) due to its tetrahedral symmetry. Prelog's work on alkaloids about this time led directly to stereochemistry through his classical work on the relative and absolute configuration of quinine and its stereoisomers. He became interested in bridged nitrogen-containing rings (as in his work on Troeger's base) and other bridged ring systems (limitation of Bredt's rule concerning double bonds at bridgeheads). In 1953 he enunciated an important generalization for the assignment of absolute configuration of alcohols, through synthesis of their atrolactates, now known as Prelog's Rule. The significance of this rule is twofold: It pointed the way to a number of other empirical rules founded on the same basic general principles; and it led to the determination of the configuration of a number of important natural products. Among them is linalool, whose configuration was finally cleared up in a joint publication by Prelog and the two Cornforths.

The Cahn-Ingold-Prelog System

It soon became obvious that, even if one had a good method for determining configuration (the handedness, or, as we now call it, "chirality" of molecules), the means for imparting the resulting insight to one's colleagues were inadequate because there was no clear-cut definition of right-handedness and left-handedness on the molecular scale. Prelog teamed up with R. S. Cahn and C. K. Ingold in Britain to develop such a definition; the *R-S* system of naming stereoisomers is the result. This system is based directly on three-dimensional models rather than on projection formulas (which, as Ingold once put it, "are good slaves but bad masters"). All the world's chemical abstracting and indexing services now use the Cahn-Ingold-Prelog system.

While developing the *R-S* system, Prelog became interested in the underlying concepts of group theory, graph theory,

and the like, which he nowadays summarizes under the heading of "chemical topography." In following these interests Prelog and his group have synthesized a number of molecules with special symmetry properties including the so-called "vespirenes" with the rare D_4 symmetry as well as several molecules illustrating the still controversial concept of pseudoasymmetry. His current (and still continuing) work is directed toward putting stereochemistry on a sound mathematical basis.

When Prelog arrived at the ETH, Leopold W. G. Ruzicka, then professor of organic chemistry, had just received the Nobel Prize (1939) for, among other work, the synthesis of the carbocyclic large-ring compounds civetone and muscone, of importance in the perfume industry. Prelog became interested in synthesizing the more elusive medium-sized (8- to 11-membered) rings and solved this problem (simultaneously with R. Stoll) by application of the acyloin synthesis in 1947. He proceeded to investigate the reactions of these compounds and in 1952 (simultaneously with A. C. Cope in the United States) discovered "transannular reactions" in which an atom or group migrates across a medium-sized ring to a position proximate in space though four or five carbon atoms away. As a consequence of this work, Prelog became interested in conformational analysis; already in 1949, a year before the appearance of Barton's pioneering paper, he discussed the "Konstellation" (that is, conformation) of medium-sized rings, a problem which proved to be exceedingly complicated and was solved only many years later, mainly through the crystallographic work of Dunitz at the ETH.

Antibiotic Structures

Prelog has retained a lifelong interest in natural products which in recent years has been turned toward antibiotics, including such interesting molecules as rifamycin (used in the treatment of tuberculosis), the iron-containing sideromycins, boromycin (unique in that it contains boron), and the mold metabolite nonactin, which has a profound influence on the permeability of cell membranes for potassium ions. Stereochemical thinking is frequently interwoven in this work; thus in the course of a study of large cyclopolypeptides, Prelog and Gerlach discovered a new type of stereoisomerism called cyclostereoisomerism. Though to a lesser degree than Cornforth, Prelog has applied stereochemical principles to biochemical reactions. In the late 1950's he developed a theory (the diamond lattice model) of stereospecificity of ketone reductions with *Curvularia falcata*; in 1971 he published a paper on fatty acid synthetase, and his most recent

publication (1975) deals with enantioselective membranes.

Prelog is a cheerful, extroverted, stimulating individual with a great sense of humor and a good story or suitable saying for every occasion. (Example: "Never waste good thought on bad experiments.") He speaks excellent English and is widely sought after as a lecturer; our own long and fruitful intellectual association with him dates from his stay in the United States in 1950 when he delivered the Reilly lectures at the University of Notre Dame. Among his many other lectureships have been the Baker lectureship at Cornell (1967) and a visiting lectureship at Cambridge University, England (1975). He has been showered with honors, ranging from honorary doctorates (Zagreb, Liverpool, Paris) to medals (the Swiss Werner Medal, Belgian Stas Medal, French Marcel Benoist Award, British Davy Medal of the Royal Society, and the U.S. Roger Adams Award of the American Chemical Society are merely representative) to honorary membership in numerous national academies (he is a Foreign Member of the Royal Society, of the National Academy of Sciences of the United States, and the Academy of Sciences of the U.S.S.R., among others).

An American-Type Department

Prelog played a crucial part in making the ETH the outstanding institution in organic chemistry it is today. His interests in stereochemistry and reaction mechanism brought a modern structural and physicochemical point of view to a department which was already outstanding in natural products chemistry. As head of the organic laboratory (1957-1965) he developed a European-style one-professor institute into an American-type department with a number of co-equal professors and a rotating chairmanship. Over the years the ETH has attracted innumerable senior visiting scholars from all over the world. Prelog has maintained the long-standing close connection between the ETH and the Swiss chemical industry and is a member of the board of directors of the Ciba-Geigy Company in Basel.

Both Prelog and Cornforth have many friends in many countries, including the United States, who rejoice that the 1975 prize is going to two men who are not only great scientists but also great human beings.

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