Jeremy R. Knowles

Jeremy Knowles was educated at Magdalen College School, Oxford, and then served as a Pilot Officer in the Royal Air Force from 1953–55. He graduated in the Final Honour School of Chemistry from Balliol College, Oxford in 1959, subsequently being elected a Harmsworth Scholar at Merton College and then a Research Lecturer at Christ Church. He was awarded the degrees of M.A. and D.Phil. in 1961, and came as a Postdoctoral Fellow to the California Institute of Technology. Returning to Oxford in 1962, he was elected Fellow and Tutor of Wadham College, and was appointed to a University Lectureship in 1966. He was a Visiting Professor at Yale in both the Departments of Molecular Biophysics and of Chemistry in 1969 and 1971, and Sloan Visiting Professor at Harvard in 1973. In 1974, he joined the Harvard Faculty as Professor of Chemistry, and became the Amory Houghton Professor of Chemistry and Biochemistry in 1979. In 1983–84 he was elected Newton-Abraham Visiting Professor at Oxford University.

Professor Knowles was elected a Fellow of the Royal Society in 1977, and to the American Academy of Arts and Sciences in 1982. In 1984, he was elected to an Honorary Fellowship of Balliol College, and in 1990, to an Honorary Fellowship of Wadham College, Oxford. He became a Foreign Associate of the National Academy of Sciences, and a member of the American Philosophical Association, in 1988. He has been awarded the Charmian Medal of the Royal Society of Chemistry, the Bader Award and an Arthur Cope Scholar Award from the American Chemical Society, and the Prelog Medal.

Professor Knowles' research is in the area of bioorganic chemistry, and involves the use of chemical methods and approaches to the solution of biochemical problems. He works on the physical-organic basis for the extraordinary specificity and formidable rates of enzyme-catalyzed reactions, on the evolution of enzyme function, the isolation and characterization of enzyme: substrate reaction intermediates, and on the stereochemical course of enzyme reactions.

Professor Knowles' research interests have focused on the description of enzyme-catalyzed reactions in the language of physical organic chemistry. From his initial investigations of the mechanisms of serine and acid proteases, his contributions to the understanding of enzyme catalysis expanded to include phosphoryl transfer reactions, racemases, the enzymes of the shikimate pathway, the β-lactamases, and the more general consideration of the evolution of catalytic efficiency. In 1976 he developed the concept of evolutionary perfection in catalysis, a view that derived from the first complete description and evaluation of the energetics of an enzyme-catalyzed reaction: that of triosephosphate isomerase. His work on the stereochemical course of biological reactions involving phosphate esters and anhydrides, required the chemical construction of phosphate esters with the three peripheral oxygen atoms distinguished as ^{16}O, ^{17}O, ^{18}O and arranged in known geometry, and the development of subtle methods to determine the absolute ster-

eochemical arrangement of these isotopes after the enzyme-catalyzed phosphate transfer reaction. This work exemplifies a predilection both for the use of isotopes as minimal probes of mechanism, and for the unambiguity of stereochemical statements (whether applied to enzymic or non-enzymic processes). In the β-lactamase area, Knowles' group investigated the mechanism of action and mode of inhibition of this enzyme, to clarify the molecular basis for the principal source of penicillin resistance in bacteria, and to suggest how such resistance might be overcome. Most recently Knowles has been studying chemical evolution. The methods of genetic engineering have been used to destroy the 'perfect' arrangement of amino acids at the active site of an enzyme, and the gene has then been subjected to random mutation and selection in order to see if the catalytic potency of the enzyme can be reoptimized. In this way, the nature of protein 'sequence space' is being explored, and the relationships between protein structure and enzyme catalytic function are being probed.