Stephen Benkovic

Stephen J. Benkovic was born in Orange, New Jersey in 1938 and received his undergraduate degree at Lehigh and his Ph.D. at Cornell. After a period as a postdoctoral research associate at UC-Santa Barbara, he joined the faculty at Penn State University in 1965. He now holds the rank of Evan Pugh Professor, and was awarded the Eberly Chair in Chemistry in 1986. He has been recognized by numerous national and international awards, including Alfred P. Sloan and Guggenheim fellowships, the Arthur C. Cope Scholar Award, and the Alfred Bader Award in Bioorganic Chemistry. In addition, Professor Benkovic was elected to the National Academy of Sciences in 1985.

His career began with the joint authorship with Thomas Bruice of the now classic two-volume set of texts entitled "Bioorganic Mechanisms," which was the first authoritative review of this subject material. These texts framed this field and set the stage for its explosive development. Since that time Professor Benkovic has led its evolution, beginning with his work in novel model studies for enzymic group-transfer reactions and his original, incisive experiments in mechanistic enzymology. These efforts have continued with the pioneering use of site-specific mutagenesis to probe enzyme function and his role as one of the originators of catalytic antibodies. His expanse of interests, and the willingness to wrestle with new problems and appropriate unfamiliar methodologies have been hallmarks of Benkovic's science.

In mechanistic enzymology, Benkovic has made a number of fundamental contributions that have altered our conception of various biological processes. For example, he realized that the anomeric specificity of glycolytic enzymes as depicted in various biochemical texts was presumed rather than demonstrated. Using ingenious rapid quench methods, he established the anomeric specificity of phosphofructokinase, fructosebisphosphatase, aldolase (with K. Schray), and phosphoglucoisomerases (with K. Schray and I. Rose), and showed that the gluconeogenic/glycolytic flux was partially regulated by requiring differing anomers at the key phosphofructokinase/fructose bisphosphatase step.

In the area of folate-requiring enzymes, his group has made far-reaching contributions that have altered the course of research. In de novo purine biosynthesis they showed that both transformylases use 10-formyl tetrahydrofolate as the one carbon source, correcting earlier views. Furthermore, it was proved that glycinamide ribonucleotide transformylase was a multifunctional enzyme (possessing three activities) and thus probably part of a larger purine biosynthetic complex. Both discoveries have had a significant impact on the development of a new generation of antifolates for use in cancer chemotherapy.

Benkovic has also been a leading proponent of the use of rapid quench or stopped flow kinetics as opposed to steady-state methods, techniques he employed to elucidate the kinetic sequence for two very important enzymes. One of these was DNA polymerase I (with K. Johnson) in which the first complete kinetic characterization of a DNA

polymerase enzyme was accomplished. These experiments furnished the first direct support for the fact that fidelity of the enzyme is achieved by a multiplicative combination of discrimination in the chemical step and the nonselective exonucleolytic removal of the mismatched base. These conclusions are startling and are in opposition to long-cherished concepts that viewed the fidelity of polymerases as arising primarily from discrimination in the binding of deoxynucleotides.

In his recent work in the areas of site-specific mutagenesis and catalytic antibodies, the Benkovic group has made a number of distinguished achievements. They elucidated and evaluated the minimal kinetic scheme for the reaction catalyzed by dihydrofolate reductase from E. coli (with K. Johnson). This basis set, coupled with the construction of numerous active site mutants, permitted the evaluation of: (1) the importance of individual hydrophobic residues in substrate and drug binding, (2) the efficacy of the enzyme in converting binding energy into catalytic function, and (3) by comparison to the L. casei enzyme, the importance of the surface of the active site ensemble in contrast to individual amino acids in dictating the free energy profile for the reduction. The concept of active site cavity shape will greatly influence future drug design.

The demonstration of the catalytic ability of antibodies has been revolutionary and has spawned a new field of research (with R. Lerner). Appropriate transition-state analogs have been elicited to promote intramolecular cyclization reactions with apparent absolute stereochemical control, to catalyze a biomolecular aminolysis reaction and amide hydrolysis, and to act as stereospecific lipases. These represent the first times that such reactions were promoted by antibodies. Recently this team has been able to express the entire heavy chain component of an immunologic response in bacteria, thus setting the stage for screening large numbers of antibodies for catalytic activity by plate assays. This exciting development holds great potential, since the entire antibody repertoire can now be examined for superior catalysts and the evolution of their catalytic ability tracked. Finally, this team created the first metalloantibodies by transplanting through site-specific mutagenesis a metal ion binding motif into a preexisting Fab molecule.

Thus, Benkovic's work speaks for itself. His accomplishments, highly original and of unusual breadth, have had a profound impact on the way we think about how the proteins function as catalysts. His papers are fine examples of intellectual creativity, careful reasoning, and insightful experimental design. They are written in a graceful, scholarly fashion that assembles all of the data lucidly to present a coherent, unifying rationale. Most impressive overall are the breadth of techniques used, the freshness of his ideas, and a remarkable sense of what questions to ask.