Enzyme Catalysis

Life at the cellular and higher levels results from the carefully controlled reactions of otherwise stable organic molecules. Enzymes are large molecular weight catalysts of cellular organic and inorganic reactions. My group is interested in understanding the mechanism for enzymatic catalysis of reactions that proceed through unstable carbocation and carbanion reaction intermediates. In solution, the overall activation barrier to reactions which proceed through such unstable intermediates is the thermodynamic barrier to formation of the intermediate. The major problem faced by enzyme catalysts is reducing the activation barrier for formation of reactive intermediates at an enzyme active site. Our work focuses on understanding the mechanism by which reactive intermediates for organic reactions are stabilized by interaction with the catalytic side chains at an enzyme active site.

In recent years X-ray crystallographic determination of an enzyme crystal structure has placed everything needed to explain catalysis by the examined enzyme in plain view. At the same time these static structures raise questions about whether one is gifted enough to *see.* Such insight can only come from the creative design of kinetic and other experiments to probe the dynamics of enzyme action, with the state view of enzyme structure. The design of such experiments and the interpretation of the experimental results is the prime objective of work in my laboratory.

Chemical Catalysis

Enzymes are very highly evolved examples of catalysts of chemical reactions. I am interested in understanding chemical catalysis because this is a significant intellectual problem, and because a broad understanding of such catalysis may lead to insight into the mechanism of enzyme action.

All of our work in this area is directed towards understanding the mechanism by which low molecular weight organic and inorganic catalysts stabilize the transition state for the catalyzed reactions. This has been the primary goal of our studies on electrophilic catalysis of proton and hydride transfer, and Brønsted general acid catalysis of heterolytic bond cleavage at carbon. Studies on the mechanism of the cleavage phosphate diesters, which are carried out in collaboration with Janet Morrow at Buffalo, have the additional goal of using insight gained from experiments to determine the mechanism by which metal ion complexes catalyze the cleavage of phosphate diesters to guide the design of new metal ion complexes of enhanced catalytic activity.

Reactive Intermediates

Carbanions and carbocations have attracted an enormous amount of attention over the last century, because these are the major intermediates of heterolytic reactions of carbon. The two principle problems encountered in the study of the formation of highly unstable carbanions and carbocations is the development of methods to measure equilibrium constants for reactions that generate a vanishingly small concentration of the intermediate at chemical equilibrium; and, for the determination of the rate constants for reaction of intermediates with halftimes as short as a picosecond. The solution of these problems in our laboratory for the formation and reaction of both carbocation and carbanions has allowed us harvest the wealth of useful data available to scientists fortunate enough to enter virgin territory.

Carbocation-anion pairs are an ephemeral species in aqueous solution, because the polar solvent water acts to attenuate the electrostatic attraction between the opposing charges. The methods that we have developed to estimate the lifetime to these species in continuously yielding new insight into their role as intermediates of solvolysis reactions.