

INTRODUCTION

This issue of *Bioorganic Chemistry*, and two issues that will follow, are all dedicated to honor Frank H. Westheimer, Morris Loeb Professor Emeritus at Harvard University, on the occasion of his 90th birthday on January 15, 2002. All of the articles in these issues have either one of Frank's former Ph.D. graduate students or one of his former postdoctoral fellows as an author or co-author. We were fortunate enough to be among this group of students. Frank is widely recognized as the "father" of mechanistic enzymology and one of the earliest authorities in the field of bioorganic chemistry.

Frank was born in 1912 in Baltimore, Maryland. He received his bachelor's degree in chemistry from Dartmouth College in 1932, a master's degree in chemistry from Harvard in 1933, and his Ph.D. degree in organic chemistry from Harvard in 1935. After a year's postdoctoral training in physical organic chemistry at Columbia with Professor Louis P. Hammett, he joined the faculty at the University of Chicago where he rose through the ranks to become full professor. He then moved to Harvard University in 1953.

Early in his research career, Frank quickly established himself as a scientist equally at home in the worlds of theory and experiment. In collaboration with Professor J. G. Kirkwood at Chicago, for example, he showed that through space electrostatic interactions can have profound effects on pK_a values, one of the cornerstones of modern physical organic chemistry as applied later to mechanistic enzymology. As early as the 1940s, he began to work on the enzymatic decarboxylation of acetoacetate which later led to his classic work on the enzyme acetoacetate decarboxylase from *Clostridium acetobutylicum*. In 1951, also at the University of Chicago, Frank collaborated with Professor Birgit Vennesland and graduate student Harvey Fisher on a series of studies of the stereospecific transfer of a proton or deuteron from the cofactor NAD⁺ to the product of the reduction of acetaldehyde (ethanol) catalyzed by alcohol dehydrogenases. Using deuterium labeling, they were able to demonstrate that the resulting monodeuterated ethanol was chiral at a center that is normally achiral. This chiral monodeuterated ethanol returned the same deuteron to the NAD⁺ when the reaction was reversed. A colleague described this work as "the first serious foray by a physical organic chemist into the enzymological area." Also while at Chicago, Frank invented the field of molecular mechanics (in the precomputer age) in order to calculate the barrier to rotation of a substituted biphenyl.

At Harvard, Frank and his co-workers discovered that five-membering cyclic esters of phosphoric acid (which are intermediates in the mechanism of action of bovine pancreatic ribonuclease, for example) hydrolyze millions of times faster than their acyclic analogues. This and related effects were explained by a theory calling for pentacovalent intermediates and pseudorotation about the phosphorus atom. This theory was developed by Frank and Edward Dennis, then a graduate student of Frank's. During this same period, Frank invented the field of photoaffinity labeling.