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WILLIAM PLATT JENCKS
1927–2007

A Biographical Memoir by

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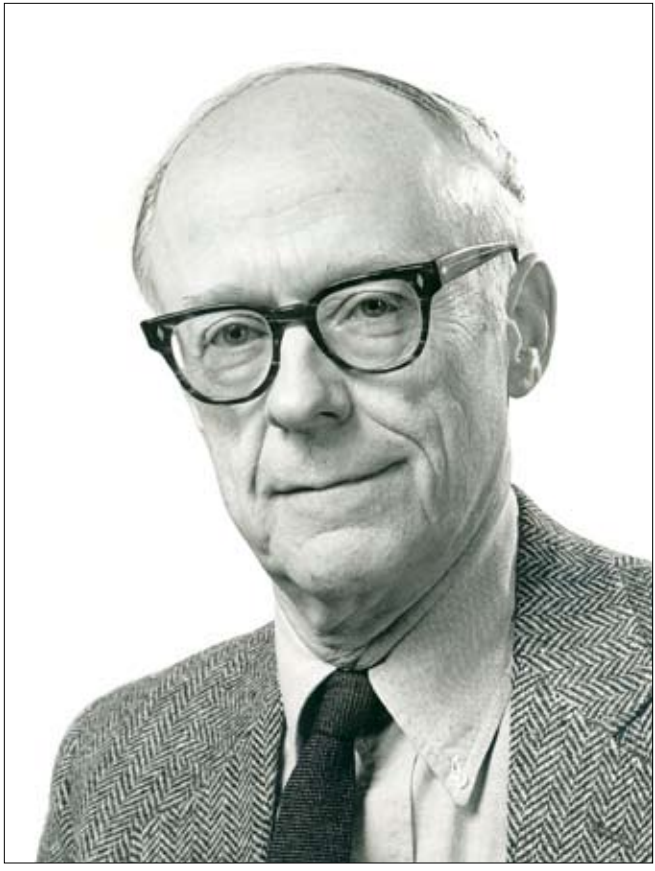
Biographical Memoir



William O. Jones

WILLIAM PLATT JENCKS

August 15, 1927–January 3, 2007

BY JACK F. KIRSCH AND JOHN P. RICHARD

THE FIELD OF ENZYMOLOGY was profoundly affected by the death of Bill Jencks on January 3, 2007, after a 17-year struggle against Alzheimer's disease. Jencks was a major innovator, superb teacher, devoted husband and father, and helpful friend and colleague. Those of us who had the privilege of working with Bill, or of knowing him professionally, are poorer for his passing.

Bill Jencks was born on August 15, 1927, in Bar Harbor, Maine. He earned an M.D. from Harvard Medical School in 1951, and interned at Peter Bent Brigham Hospital in Boston. He next spent a postdoctoral year in studies in biochemistry and chemistry at Massachusetts General Hospital with Fritz Lipmann. Lipmann thought that the Korean War would be a waste of Bill's talent, and helped to have him assigned as a staff member at the Army Medical Service Graduate School Department of Pharmacology at Walter Reed Army Medical Center in Washington, D.C., where he was later appointed as chief of staff. After two years he returned for a further year in the Lipmann laboratory, and then pursued additional postdoctoral studies at Harvard University with Robert Woodward in the mid-1950s. He joined the Brandeis University faculty in 1957, where he served as assistant professor, associate

professor, and full professor of biochemistry and retired in 1996 as professor emeritus of biochemistry.

Jencks was the recipient of several of the highest honors from the chemical and biochemical community, including memberships in the National Academy of Sciences (elected in 1971), American Philosophical Society, and foreign membership in the Royal Society. His numerous awards include the Eli Lilly Award in Biological Chemistry, Repligen Award in Chemistry of Biological Processes, and James Flack Norris Award in Physical Organic Chemistry. Bill Jencks is survived by his wife, Miriam, his children, Sara Helen and David, and his grandson, Benjamin.

Bill Jencks was born into a cultured family. His parents' divorce, and the subsequent remarriage of his mother and her move to New Mexico led to a structured upbringing and schooling in Baltimore, punctuated by a less organized regimen on trips west to visit his mother and stepfather. He apparently received little career counseling, and decided to enter Harvard Medical School after his junior year, because he "couldn't think of what else to do" (Jencks, 1997). His research began the summer following his first year of medical school with a study of lobster shell pigments carried out under the direction of a family friend, George Wald, at the Marine Biological Laboratory in Woods Hole. Noncovalent interactions between the red carotenoid astaxanthin and a protein receptor cause its color to change to blue, while cooking the lobster denatures the protein and releases the red carotenoid. The insight gained from this work into the possibility of profound effects of protein-ligand interactions on molecular structure served him well throughout his career.

Jencks came to view medicine as "a very broad field in which it would be difficult to obtain definitive answers to fundamental problems" (Jencks, 1997). His accomplish-

ments, while searching for a more appropriate calling, were impressive. His work with E. L. Durham at the Walter Reed Army Medical Center showed that males who had suffered a myocardial infarction had relatively low levels of serum high-density lipoproteins and high levels of low-density lipoprotein compared with normal controls. These observations have served as the basis for current therapeutic treatments of people at risk for heart disease.

Jencks found his career calling in the laboratory of Fritz Lipmann, where he pursued a seeming curiosity in the standard hydroxylamine assay for activated acyl groups. This was the progenitor of his long interest in the physical organic chemistry of acyl transfer reactions. The explanation for these observations was worked out in detail in subsequent independent research in the Woodward laboratory. While at Harvard, Jencks came under the influence of Frank Westheimer, who pioneered the use of physical organic chemistry to explore enzyme reaction mechanisms.

In 1957 Bill Jencks was encouraged to contact Nate Kaplan and Martin Kamen, who were starting a department of biochemistry at Brandeis University. He did so and joined this department shortly thereafter. During his 39 years on the faculty at Brandeis, Jencks worked to understand the mechanisms by which enzyme catalysts facilitate the chemical reactions of molecules that are not otherwise inclined to react at a useful rate. His last substantial scientific work at Brandeis, from nearly 400 papers, appeared in 1995. Jencks's papers continue to be widely read and cited; several with the highest current levels of citations were published 30 or more years ago.

The immensity of the problem of enzymatic catalysis that faced a new investigator in 1957 is difficult to appreciate in 2010. It was known then that enzymes are proteins, but their precise chemical compositions were only beginning to

be determined, and no three-dimensional structures were available. The understanding of the mechanisms for even the simplest chemical reactions was likewise poor, and there were few ideas about how enzymes might accelerate their rates. Instrumentation was primitive, not widely available, and the procedures for funding scientific research were just being developed. The field of mechanistic enzymology began an impressive surge guided by Jencks and just a few others (particularly F. H. Westheimer, T. C. Bruice, and M. L. Bender). A very large fraction of the currently active investigators in this area are direct academic descendents of one or more of those pioneers.

Bill Jencks chose to work on big problems but free of the requirement for vast resources by those who now do big science. His choices were not strongly influenced by current fashion, and were guided by intense personal curiosity and belief in the significance of the anticipated results. His major book, *Catalysis in Chemistry and Enzymology,* was published early in his career (1969) and reprinted in 1987. Forty years later it can be found on the bookshelf of nearly everyone harboring a serious interest in enzymology.

Jencks wrote in his text, "The problem of the mechanism of enzyme action may be approached in three ways: by theorizing, by examining the properties of enzymes, and by examining the nature of chemical reactions and their catalysis" (Jencks, 1969). Many of Jencks's early independent papers focused on studies of chemical reaction mechanisms that were directly relevant to the mechanism for enzymatic catalysis of related reactions. However, he knew that it was necessary to study enzymes in order to understand their mechanism. With typical modesty he compared his position in 1969 to that "of the drunk on his hands and knees under the corner street light who, when approached by a citizen asking his intentions, replies he is looking for his

keys here, rather than in the poorly illuminated center of the block where they were lost, because the light is better at the corner" (Jencks, 1969).

Work in the Jencks laboratory was divided between the study of enzymatic reaction mechanisms and of the mechanism of the reaction of small molecules that might serve as models for enzymatic reactions. These were truly interdisciplinary studies, and provided the graduate students and postdoctoral fellow working in his laboratory with unique insights into catalysis not easily gleaned from focused chemical or enzymatic studies.

In his earliest work Jencks examined the roles of reactive amino acid side chains in catalysis of the reactions of small molecules in water. One aim was to define the possible roles for these side chains at enzyme active sites. Jencks and Carriuolo showed that imidazole can act as either a covalent nucleophilic catalyst, or as a Brønsted general base catalyst of the hydrolysis of esters (Jencks and Carriuolo, 1959). These two functions are also observed for the imidazole side chain of histidine in enzyme-catalyzed reactions. Early studies on the mechanism for nucleophilic and electrophilic catalysis of hydrolysis of phosphate esters and phosphoroamidates (Jencks and Gilchrist, 1965), for reactions of pyridoxal (Cordes and Jencks, 1962), and for condensation of formaldehyde with tetrahydrofolic acid (Kallen and Jencks, 1966) provided important insight into the mechanism for the corresponding enzyme-catalyzed processes. Jencks revisited the problem of the mechanism for nucleophile addition reactions to phosphate esters later in his career, and published several seminal papers on the distinction between the stepwise and concerted mechanism for phosphoryl transfer (Skoog and Jencks, 1984) and on the imperatives for catalysis of these nucleophile addition reactions (Herschlag and Jencks, 1990).

Jencks had an ability to simplify and generalize analyses of complex kinetic data for nonenzymatic reactions that enabled him to resolve simple and fundamental questions about reaction mechanisms. In 1972 he formulated the libido rule, which defines the conditions that must be satisfied to observe concerted Brønsted general acid-base catalysis of carbonyl addition and other complex reactions. This simple rule states that "concerted general acid-base catalysis of complex reactions in aqueous solution can occur only (a) at sites that undergo a large change in pK in the course of the reaction and (b) when this change in pK converts an unfavorable to a favorable proton transfer with respect to the catalyst" (Jencks, 1972). This rule allows an investigator to use the knowledge of a few pKas to quickly gauge whether a reaction is a candidate for catalysis by added buffer acids or bases, or by the acidic and basic amino acid side chains at an enzyme active site.

Jencks developed "clocks" to probe the lifetimes of tetrahedral intermediates resulting from nucleophile addition to the carbonyl group. This work led to the demonstration of simple relationships between intermediate lifetime and the mechanism for Brønsted acid-base catalysis of carbonyl addition reactions (Jencks, 1976). The most important of these relationships is that changes from stepwise to concerted mechanisms for acid-base catalysis are often controlled by the lifetime of the intermediate: reactions follow a stepwise mechanism when the intermediate can exist for a time that is greater than that of a bond vibration, and a change to a concerted mechanism is enforced when the intermediate is too unstable to exist in a potential energy well for ca. 10^{-13} second, the time of a bond vibration (Jencks, 1980). Jencks and coworkers developed clocks for the lifetimes of carbocation intermediates of organic reactions (Richard and Jencks, 1982; Amyes and Jencks, 1989), and Jencks worked until

the end of his career to provide experimental evidence for these relationships between reaction mechanisms and intermediate lifetime. He reported several changes from stepwise to concerted mechanisms for nucleophilic substitution at aliphatic carbon that occur as the lifetime of the putative carbocation intermediate becomes shorter than 10^{-13} second. Similarly, the mechanisms of E1cb-type elimination (Banait and Jencks, 1990) and retroaldol (Thibblin and Jencks, 1979) cleavage reactions were found to be enforced by the impossibly short lifetime for putative carbanion reaction intermediates. Jencks forcefully advanced the position that the defining characteristics of a reaction mechanism are the number and the types of the reaction intermediates. His ideas about how mechanisms change from stepwise to concerted have served as the basis for recommendations by the International Union of Pure and Applied Chemistry (IUPAC) on the symbolic representation of reaction mechanisms (Guthrie and Jencks, 1989).

The enormous body of kinetic data generated by Jencks and coworkers define the stability of the transition states for a wide range of chemical reactions. Jencks was intrigued by proposals that certain features of the structure of these transition states could be defined through systematic studies of the effect of small changes in reactant structure on transition state stability, and he invested considerable time in developing and testing models to rationalize changes in transition state structure (Jencks, 1985). He worked with his son, David, to develop a largely empirical and self-consistent model to rationalize these experimental results (D. Jencks and W. Jencks, 1977). As we move through the 21st century, calculations by large computers supplement—but cannot supplant—experimental results from the study of reaction mechanisms. The appeal of these calculations is that they have the potential to provide transition state structures in

greater detail than those determined by Bill Jencks and others in painstaking structure-reactivity studies. This experimental work should be treasured and expanded upon as a reality check for these computational studies.

In 1975 Bill Jencks published a seminal review in *Advances in Enzymology and Related Areas of Molecular Biology* that summarized his thoughts on the strategies employed by enzymes in catalyzing chemical reactions (Jencks, 1975). In this review he considers the "proposition that the intrinsic binding energy that results from the noncovalent interaction of a specific substrate with the active site of the enzyme is considerably larger than is generally believed. An important part of this binding energy may be utilized to provide the driving force for catalysis, so that the observed binding energy represents only what is left over after this utilization" (Jencks, 1975). It is now widely accepted that apparent transition state binding energies of >30 kcal/mol are sometimes required to account for the stability of the transition states (Radzicka and Wolfenden, 1995). It is less widely appreciated that the functionalities present in relatively small ligands such as orotidine 5'-monophosphate are sufficient to obtain binding interactions of 30 kcal/mol with an enzyme such as orotidine 5'-monophosphate decarboxylase (Radzicka and Wolfenden, 1995).

Bill Jencks described in his classic review many of the possible mechanisms by which the intrinsic binding energy of nonreacting portions of a substrate might be utilized in the stabilization of a transition state for reaction at a distant substrate fragment (Jencks, 1975). He emphasized that part of the entropic cost of freezing translational and rotational motions in sequestering a pair of reactive molecules at an enzyme active site is paid for in the utilization of intrinsic substrate binding energy, and recovered as a reduction in the activation barrier associated with a change from a bimolecular

solution reaction to an effectively unimolecular reaction at the enzyme active site (Page and Jencks, 1971; Jencks, 1981). He advanced the notion that appendages added to smaller biological molecules, such as the addition of coenzyme A to the acetate group or of phosphates to sugars, provides binding energy that is utilized not only in the stabilization of the Michaelis complex but also to activate the enzyme for catalysis. He confirmed this directly by a careful analysis of the contribution of the different parts of coenzyme A to enzymatic rate acceleration for catalysis by 3-oxoacid coenzyme A transferase (Whitty et al., 1995).

The rapid evolution in our understanding of the mechanism of enzyme action during the more than 50 years since Bill Jencks began his independent research program may appear as a revolution to young scientists entering the field. Indeed, enzymologists have derived great satisfaction from the solutions of so many important problems related to enzyme mechanisms made possible by rapid advances in the solution of enzyme structure by X-ray crystallography and creative use of site-directed mutagenesis. This progress has been accompanied by nervousness that the scope for original discovery has been reduced in proportion to the number of important problems solved. However, in our opinion, many important questions about the origin of the rate acceleration for enzyme-catalyzed reactions remain unanswered. In this regard, Bill Jencks's penetrating insight into how enzymes work is missed by all who appreciate the magnitude of his intellect.

The question of the mechanism by which movement is brought about in biological systems fascinated Bill Jencks. More specifically he asked the following question: "How does ATP hydrolysis bring about movement in muscle contraction and in many other systems in which movement occurs?" (Jencks, 1997). His work on this problem led to the devel-

opment of a simple and general model to rationalize the coupling of ATP hydrolysis to the movement of Ca^{2+} across intact sarcoplasmic reticulum vesicles (Jencks, 1992; Makinose, 1973). The model is based upon alternating changes in the catalyst specificity for the binding of Ca^{2+}, caused by the hydrolysis of enzyme-bound ATP and the specificity for hydrolysis of enzyme-bound ATP, caused by movement of Ca2+ across the sarcoplasmic reticulum. It is a general model that holds for any enzyme-catalyzed processes that couple the hydrolysis of ATP to a second vectorial motion, of which transport of Ca^{2+} across the membrane is but one of many examples.

Our most vivid memories of Bill Jencks are associated with his extraordinary ability as a teacher. His classroom lectures covered not only "the known" but also "the what had to be learned." Critical thinking was instilled by example. His course on enzyme mechanisms became the basis for the syllabi of the lectures taught by many of his students and postdocs. He assembled a handbook on how to read the literature and to keep a notebook, which was distributed not only to his research group but also to many others at Brandeis. Quite a few have passed the volume to succeeding generations. Bill's literature notebook, which he sometimes referred to as "my brain," consisted of categorized loose-leaf pages with one- or two-line summaries of the many papers that he had read. Some of these were flagged with an exclamation point indicative of an important result, and some bore a question mark signifying that he didn't understand the paper or that he saw an important flaw in it. He was unselfish in providing help to his colleagues. The morning and evening scientific sessions of Gordon Research Conferences (GRC) are punctuated by long afternoon breaks that most conferees use mainly for recreation. Bill was a faithful participant in the Enzymes, Coenzymes, and Metabolic Pathways GRC. Most afternoons

he could be found in the lounge area outside the Kimball Union Academy dining hall with a line of participants seeking his advice. The wait was invariably rewarded with insight and constructive comments.

The experiences of the students and postdocs who worked in his laboratory were exceptional. With an average group size of 10 coworkers, Jencks's laboratory was modest by modern standards. Each laboratory member worked on a unique problem, and could expect to be the sole author on papers describing the work. Communication with Bill was constant, intense, and at an intellectual level that most of his students could only hope to encounter again by building a laboratory modeled after the one at Brandeis. He met daily with new arrivals to the laboratory as long as necessary for a satisfactory level of independence to form. His door was always open, and he made one feel like it was never an intrusion to walk in at any time. He instilled the highest standards in the exercise of laboratory experimentation and in the crafting of research reports. Full credit must be given to others; references must be checked against the original papers, not review articles; and you should read your manuscript through the imagined eyes of your major competitors. Quite a number of his former coworkers have remarked that they still imagine Jencks looking over their shoulder as they write. These students and postdocs thus benefited enormously from their interactions with him, and a large number currently hold influential positions in academics and in the chemical and pharmaceutical industries.

Jencks had strong views about the obligations of the scientist to the taxpayers who support our research. These were never preached, just inculcated by example. One of us (J.F.K.) recalls a day when he was offered a pair of well-used stamped metal bookends from Jencks's office after the latter had purchased some better ones with his own money.

J.F.K. said that he didn't need them at his desk but could use them in his apartment. Bill didn't say no, but offered that the moral decision was up to J.F.K. Needless to say, the bookends remained at his desk at Brandeis. On a recent visit to Brandeis the Friedland building, which housed the Jencks lab in the early days, was in the final stages of demolition, and J.F.K. observed that one final slab of concrete remained standing, and anchored to it for eternity were the bookends bound by the Jencks-implied moral imperative.

Bill Jencks made superb use of his great intellectual gifts while living a life that was rich and full in every respect. He was devoted to his wife and two children, and they to him. He was well read, traveled widely, and worked to absorb the history and character of places visited. Jencks was an English major at Harvard and acquired an interest in 19th-century literature and plays. Early parties at his house often included group readings of plays by authors such as Sheridan and Shakespeare. He had an intense devotion to music, particularly that of Mozart and Bach. Fittingly his memorial concert at Brandeis consisted of a program of Bill's favorite Mozart compositions performed on a fortepiano. Bill, influenced by R. B. Woodward, originally eschewed physical exercise, claiming it to be a waste of time, but later in life he took up jogging. Preparation consisted of loosening his tie, and exchanging his leather for running shoes. Bill was not a competitive runner, and he remarked with near disbelief that after some months of this exercise that he actually passed another jogger. We will miss this remarkable man.

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