Thomas C. Bruice

1925–2019

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Stephen J. Benkovic
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NATIONAL ACADEMY OF SCIENCES

THOMAS CHARLES **BRUICE**

August 25, 1925–February 15, 2019

Elected to the NAS, 1974

Photography by Tony Mastres UCSB

By Stephen J. Benkovic and Paula Yurkanis Bruice

Thomas C. Bruice was one of the fathers of bioorganic chemistry. His productivity was prodigious, as was his creativity, which led to more than 600 papers whose wealth of discovery contributed to a foundation for the development of bioorganic chemistry. His papers fell broadly into several distinct categories: How do enzymes achieve their enormous catalytic rate advantages relative to a nonenzymatic reference state? What are the mechanisms used by various coenzymes to catalyze specific transformations? How are general acid-base catalysis and transition-state stabilization harnessed by enzymes to facilitate various reactions?

Tom's research was recognized by the election to both the National Academy of Sciences (1974) and the American Academy of Arts and Sciences (1976). He also was a Fellow of the American Association for the Advancement of Science and a Fellow of the Royal Society: Chemistry. Among his many awards were, the Tolman Medal (1979), the Repligen Medal for the Chemistry of Biological Processes (1987), the Arthur C. Cope Scholar Award in Chemistry (1987), the Alfred Bader Medal for Bioinorganic and Bioorganic Chemistry (1988), the Renaud Award (1988), the James Flack Norris Award in Physical-Organic Chemistry (1996), the Distinguished Alumnus Award from the University of Southern California (2005), the National Academy of Sciences Award for Innovative Research in the Chemical Sciences (2005), and the Linus Pauling Medal (2008). He also was listed as one of the "World's 50 Most Cited Chemists" (1992).

Early Life and Education

Tom was born in Los Angeles on August 25, 1925. His father left the family three years later. His mother, who had only a sixth-grade education, had to put Tom in foster care. When he was eight, he went to live at the McKinley Home for Boys, a facility in Van Nuys for 200 boys who either had no parents or had parents unable to take care of them. There he attended school for the first time. During his four years at McKinley, his

mother often took him to plays and concerts in Los Angeles on the weekends, which led to Tom's lifelong interest in the performing arts and classical music. When his mother remarried, Tom left McKinley to live with her and his stepfather.

Tom's high school chemistry teacher at Manual Arts High School in Los Angeles introduced him to two older boys, and Tom joined their home lab, a small building in one of the boys' backyard. The father of one of the boys paid to equip the lab and also paid for a subscription to the *Journal of the American Chemical Society* (*JACS*). The boys learned by repeating syntheses published in *JACS*, making a hood by placing a large fan in a wall. They went through *Chemical and Engineering News* and, using their printed personal stationary, asked for any chemical that was offered for free. Tom also frequently visited the Department of Chemistry at the University of Southern California (USC) to try to obtain supplies for the lab. Norman Kharash, a professor of chemistry and Tom's future mentor, let him do experiments in his lab and another USC professor arranged for him the take a biochemistry course when he was in the tenth grade. Tom's weekends were spent body surfing at California beaches. A talented track and field competitor, one of the things Tom was most proud of was his third-place finish in the high hurdles in the Los Angeles Championships in his junior year.

Tom enjoyed many days surfing at Santa Barbara, California. (Photo P. Y. Bruice.)

Rather than returning for his senior year of high school, Tom enlisted the U.S. Navy in August 1943, carrying letters of support from two USC professors, which allowed him to enter the Navy as a hospital corpsman. He served in the Navy until 1946, principally in the South Pacific. Tom had been assigned as a medic to the First Marine Division, which was preparing to board ship for the invasion of Tokyo when it received word that the Japanese had surrendered.

Tom returned to Manual Arts High School to enroll for his senior year. But when the principal found him sitting on his secretary's desk, smoking, and flirting with her, he suggested Los Angeles City College (LACC) would be a better fit. After two years at LACC, Tom transferred to USC, using the GI Bill to pay for his education. In 1948, he married his high school sweetheart, Madge Freudenberg, with whom he had three

children. He and Madge were divorced in 1971. Tom received a bachelor of science from USC in 1950 and a Ph.D. in 1954. Because of his dual interests, he was allowed to have two mentors, Norman Kharash (organic chemistry) and Richard Winzler (biochemistry). One study Tom published with them was the first linear-free energy correlation for drug activity, providing the inspiration, fifteen years later, for the Quantitative Structure-Activity Relationship (QSAR) method used currently in drug design.[1] Tom was awarded funds from the National Research Council for postdoctoral work at the University of California, Los Angeles, where Ted Geissman allowed him to work independently in his lab.

Tom's doctoral thesis with Kharash and Winzler on sulfenic acids provided no hint that in his first papers as an assistant professor at Yale University he would report that the imidazole base in histidine could catalyze the hydrolysis of esters. From then on to the end of his career, Tom was intensely focused and unsparingly driven to decipher how enzymes catalyze reactions.

Tom was one of a handful of chemists who introduced physical organic chemistry approaches into biochemistry. He invented the term *bioorganic chemistry* in order to bring together the disciplines of organic chemistry and biochemistry at a time when the idea appeared outlandish to many. Not only did biochemists have little knowledge of enzymatic mechanisms, but organic chemists had little knowledge of the reactions that enzymes catalyze and were only beginning to describe plausible mechanisms for organic reactions.

Tom started his career in the Department of Biochemistry at Yale Medical School in 1955. Two years later, he moved to the Department of Biochemistry at Johns Hopkins Medical School, and in 1960 to the Department of Chemistry at Cornell University. His fourth winter at Cornell caused him to look for a school where he could surf. He joined the faculty at the University of California, Santa Barbara in 1964, giving up the Life-Time Investigator Award he held at Cornell and bringing all but two of his graduate students and postdocs with him. His laboratory was a short walk to a surfing beach. When the surf was up, Tom and his students could be seen marching to the beach with their surfboards on their heads.

In 1970, one of Tom's former postdocs, an assistant professor in the Department of Pharmacology at Yale Medical School, introduced him to Paula Yurkanis, a postdoc in the department. Tom and Paula were married in 1971, and he became a father to her three small children.

Tom and Paula with Meghan.
(Photo Prof. Rex Pratt.)

Early Studies

From 1957 to the mid-1970s, Tom published nearly one hundred papers in which he provided a fundamental understanding of the catalytic processes involved in group transfer reactions[2,3] and the importance of the juxtaposition of reactants to accelerate the rate of their reaction.[4,5] His initial studies focused on ester and amide hydrolysis and aminolysis and led to discoveries that included: the role of general-acid and general-base catalysis in such reactions; that imidazole could act as a nucleophilic catalyst for ester hydrolysis; that acyl transfer reactions generally proceed through a tetrahedral intermediate; that metal-ion ligation of water provides a metal-bound HO^- that is a better nucleophile than H_2O for hydrolytic reactions; and the unique chemistry of acyl transfer from thioesters as models for acyl CoA. He disproved the popular "push-pull" and "orbital-steering" mechanisms of the 1960s and 1970s. In 1968, Tom published a paper on micelle catalysis that was a forerunner of the present intense interest in liquid condensates.[6] To mimic glycosidase mechanisms, Tom evaluated the role of ring strain, planarity, general-acid catalysis, and acetamido participation in the hydrolysis of hexoses.[7,8] This period culminated with his studies of arene oxides, which provided a fundamental understanding of the formation and reactivity of these compounds and a chemical basis for understanding why certain aromatic compounds are carcinogenic.[9]

It was known that some enzymes require coenzymes (for which vitamins are the precursors) for their catalytic activity, but how these coenzymes catalyze reactions was not understood. The role that Tom played in the elucidation of coenzyme chemistry is truly remarkable. His studies of pyridoxal catalysis defined the chemistry of the various reactions supported by vitamin B_6,[10] and those of CO_2 transfer by biotin were pertinent for the development of mechanisms for vitamin H-dependent enzymes.[11] Additionally, Tom's first synthesis of a water-soluble $Fe_4S_4(SR)_4^{2-}$ cluster allowed him to perform kinetic studies that showed its behavior to be similar to enzyme-bound clusters.[12,13] Tom's investigations of nicotinamide reactions[14] showed that the chemical pathway (radical or hydride transfer) was dependent on the oxidation potential. He was the first to show that hydride tunneling is a function of the distance between NAD(P)H and substrate.[15] And finally, when Tom entered the field of flavin cofactors, the literature was so confused that the subject was generally bypassed in graduate courses. His research revealed the

chemical pathways for many enzymatic transformations requiring flavins. For example, he established the importance of both radical intermediates and covalent adducts in flavin oxidation of carbon acids; he introduced deazaflavins; he prepared 4a-hydroperoxyflavin (4a-FlHOOH) and established that it was identical to that formed by mixed function oxidase enzymes; he also established that the free energy of activation for oxygen transfer from 4a-FlHOOH was based on the pK_a of the 4a-FlHOH leaving group; and he discovered the unprecedented phenomenon of dioxygen transfer from 4a-FlHOO- to nucleosides.[16,17]

Little attention had been paid to hydrolysis of alkyl phosphodiesters even though they are the connectors in both DNA and RNA. Tom determined the mechanisms for their hydrolysis.[18] His contributions to our current knowledge of the formation, chemical characteristics, and reactions of hypervalent metal-oxo porphyrins are too numerous to describe.[19,20] Briefly, he determined the oxidation potentials and chemical and kinetic behavior of $(P^{-})M^{II}(X)_2$, $(P)M^{II}(X)2$, $(P)M^{III}(X)_2$, $(P)M^{IV}(X)_2$, and $(P^{\cdot+})M^{IV}(X)_2$, [X = HO^{-} or H_2O] for Cr(III), Fe(III), and Mn(III) tetraphenylporphyrins and the kinetics associated with their oxygenation by a variety of oxidizing agents.

Later Studies

Tom was never hesitant to explore new areas and learn new methods, even towards the end of his career. At that time, he made an abrupt shift from bioorganic model studies to molecular dynamics and began to use computational approaches to evaluate reaction trajectories, structures, and atomic motions in enzymatic reactions.[21] At the age of approximately 70, he turned a major portion of his research toward computational enzymology. For example, the mechanism of methanol dehydrogenase could not be determined using traditional experimental methods. Tom was able to elucidate the multistep catalytic sequence using X-ray coordinates of the enzyme-coenzyme complex and MD and QM/MM methods. This may well be the first determination by simulation of the structures and free energies involved in an enzymatic reaction. His laboratory also developed nucleic

At age 70, Tom turned a major portion of his research toward computational enzymology. (Photo P. Y. Bruice.)

acid analogues that contain positively charged guanidinium linkages designed to act as antisense and antigene agents.[22]

During this period, Tom returned to his first major interest: the factors underlying the enormous catalytic advantage exhibited by enzymes. His group determined the ground-state conformations for a number of enzymatic and intramolecular reactions via MD computations. The near attack conformers (NACS) in these ground states closely resemble the transition state that can be reached only from the NAC. Thus, it was shown that the free energies for NAC formation determined a major part of the free energy of the overall reaction.[23]

Reflection

For me (SJB), one of the outstanding remembrances of Tom derives from our collaboration on the *Bioorganic Mechanisms* texts that served to help establish this field.[24]

Tom was a man of intense energy. All his activities were pursued with passion, whether it was his science, his driving a Corvette at unsafe speeds, or playing touch football against hapless graduate students who lacked his physical strength. To many perceived competitors, Tom was combative and aggressive. He was uniquely honest and demanded the best from his graduate and postdoctoral associates; he did not tolerate incompetence. Those who met his standards were rewarded with the joy and deep satisfaction of learning how to accomplish excellent science. Tom was a strong supporter of one's career choice, and for many of us, a close personal confidant. He befriended us when we encountered failures and losses, revealing a warm tender side often not visible. He rejoiced with us in our accomplishments. Like many who have pioneered new areas in science, Tom's discoveries are no longer specifically cited. They now underpin so much present research in bioorganic, bioinorganic, and chemical biology that they are taken for granted. I, who enjoyed a special kinship with Tom Bruice, will miss brainstorming his insightful judgments and, most of all, his unselfish and warm friendship.

Tom is survived by his wife, Paula, his children, Tom, Ann, Carl, Meghan, Kenton, and Alec, and thirteen grandchildren.

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