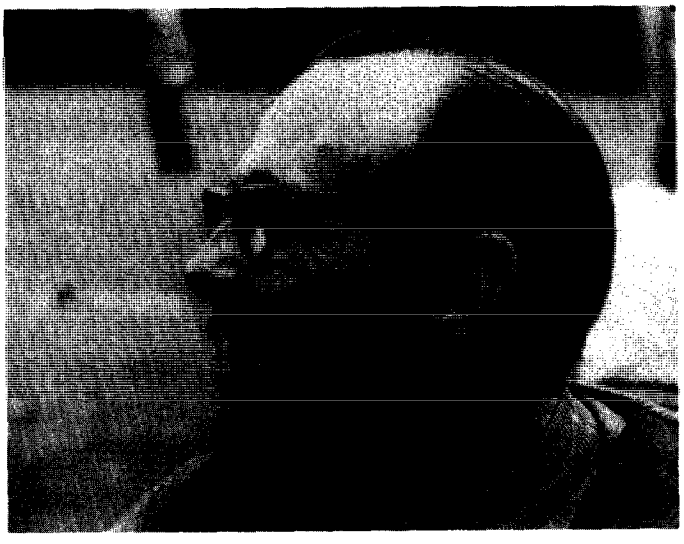
BIOORGANIC CHEMISTRY 17, 252–256 (1989)

IN MEMORIAM

Myron Lee Bender
(May 20, 1924–July 29, 1988)



Editor's Note

Irving M. Klotz, a longtime colleague of Myron's, perhaps summarized it best when he noted in a memorial service:

> Each of us arrives on this earth endowed with some advantages and some handicaps. And we leave when our infirmities overwhelm us. During the intervening years each of us has the opportunity to create something for himself, for his family and associates, and for present and future generations. Myron Bender added far more than one man's share to the world's store of scientific knowledge and understanding. Researcher, teacher, writer, he functioned with distinction in all these activities.

Myron Lee Bender was born and raised in St. Louis, Missouri, and obtained both B.S. (1944) and Ph.D. degrees (1948) from Purdue University (his Ph.D. thesis research was performed under the direction of Henry B. Hass). Following a postdoctoral research year with Paul D. Bartlett at Harvard University, a second year as an AEC fellow in Frank H. Westheimer's laboratory at the University of Chicago, and a year on the faculty at the University of Connecticut, he accepted in 1951 a position in the Department of Chemistry of the Illinois Institute of

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Technology and stayed there for 9 years. In 1960 he moved to the Department of Chemistry at Northwestern University, where he remained throughout the rest of his career. From 1983 until his death he was a member of the Editorial Board of this Journal.

How does one summarize a lifetime of excellence? To begin with, I might mention that the career of Myron Bender spanned more than 30 years and produced over 200 publications, 18 monographs, and 5 books. He received the Midwest Award of the American Chemical Society, a distinguished Fulbright Fellowship, an Honorary Degree from Purdue University, and membership in the National Academy of Sciences. But information of this sort does not adequately describe the real impact that Myron's research program has had on organic chemistry. It would be far better in this regard to focus specifically on how his work has contributed to the development of chemical thought. This is no easy task in a short presentation. Since Myron's work has always been multifaceted (crossing the boundaries of physical organic chemistry, bioorganic chemistry, enzymology, inorganic chemistry, and colloid chemistry), I must necessarily be selective in delineating below the highlights of his scientific career. In the process of choosing among his accomplishments, I experienced the joy of rereading many of his papers. One cannot help being struck by their uniform clarity and brilliance—no convoluted arguments, no overinterpreted data, no handwaving, no unnecessary complexities to impress the reader—just gems of inductive reasoning. Cited below are a few articles I admire most.

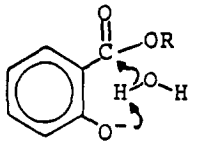
1. M. L. Bender, Oxygen exchange as evidence for the existence of an intermediate in ester hydrolysis. J. Amer. Chem. Soc. ***73,*** 1626 *(1951)*

This paper, the first of a family of papers dealing with ester and amide hydrolyses, showed that an ester labeled with ^{18}O at the carbonyl exchanges its ^{18}O with solvent during hydrolysis; a tetrahedral intermediate is thereby strongly indicated. The "^{18}O" papers launched Myron into national prominence; they also were instrumental in ushering in the era of "aqueous" physical organic chemistry which was to thrive for three decades thereafter. Myron was one of the leading physical organic chemists who did for reactions in water what Winstein and others did for reactions in acetic acid. The mechanistic detail ultimately achieved by Myron was astounding. For example, the ^{18}O exchange work of Bender and Heck in 1967 led to the proposal of a *general base*-catalyzed attack of water on an ester carbonyl forming a tetrahedral intermediate which decomposes *spontaneously* to product, but reverts back to reactants by *acid catalysis* (Eq. [1]). Three steps and three different modes of reactivity! It was also in this paper that Myron proposed that proton transfer within a tetrahedral intermediate could be rate-limiting—an idea far ahead of its time as it turned out.

$$CF_3COSEt + H_2O \underset{k_2(H_3O^+)}{\overset{k_1(H_2O)}{\rightleftharpoons}} [I] \xrightarrow{k_3} CF_3COOH \qquad [1]$$

2. *M. L. Bender, F. J. Kezdy, and B. Zerner, Intramolecular catalysis in the hydrolysis of p-nitrophenyl salicylate. J. Amer. Chem. Soc.* ***85****, 3017 (1963)*

During the time that the West Coast groups were developing the chemistry of "anchimeric assistance" or "neighboring group participation" in acetic acid, the bioorganic component of physical organic chemistry was doing the same with "intramolecular catalysis" in water. Myron was, undoubtedly, a key figure in the development of our present understanding of intramolecularity, one of the most important concepts in organic chemistry. The above paper, providing the first proven case of an intramolecular general base catalysis, illustrates the point. The paper also serves to illustrate a classic piece of physical organic reasoning. Myron was faced with the problem of differentiating between a general base mechanicam (structure **1**) and a kinetically equivalent hydroxide/general acid mechanism (structure **2**). He solved this problem by showing that anionic nucleophiles (e.g., azide ion) do not manifest intramolecular catalysis, thus ruling out mechanism **2** that had a priori been favored by others. This typifies the simple, quiet beauty of Myron's work.



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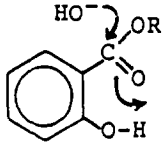

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3. *M. L. Bender, F. J. Kezdy, and C. R. Gunter, The anatomy of an enzymatic catalysis: α-Chymotrypsin. J. Amer. Chem. Soc.* ***86****, 3714 (1964)*

Myron's research over the years was concerned with the mechanism of organic reactions (particularly those of enzyme "models") along with the mechanism of the enzymatic process themselves. There have been others who confined themselves to one aspect or the other, but Myron was deeply involved in both. This probably accounted in large measure for his success, because the riddle of why enzymes react so fast can be solved only by interrelating the physical organic chemistry with the enzymology. The above classic article by Bender and coworkers represents, in the opinion of many, the most penetrating analysis of an enzyme mechanism available at that time. Naturally, Myron drew on the work of the other laboratories in developing the chymotrypsin mechanism which is still valid today. But many of the ideas originated from his own laboratory. Thus, he was the first to provide spectrophotometric evidence for the acyl-enzyme intermediate. He taught the world how to titrate enzymes and thus place enzyme kinetics on a firm, quantitative footing. He synthesized a new enzyme, thiosubtilism, in which a serine hydroxyl at the active site was replaced by a thiol group. Charge relay mechanisms, rate-determining binding, specific binding of water, enzyme dimerization, aging processes, cannibalistic denaturation—all came under his scrutiny. Chymotrypsin, trypsin, papain, elastase, and acetylcholinesterase yielded their secrets to Myron's group. Can there be any doubt that there was something uniquely successful about Myron's approach to the enzyme problem?

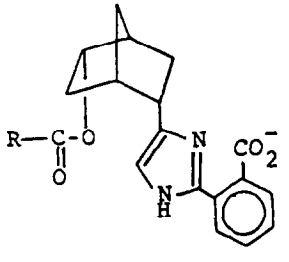
Part of the secret must lie in the fact that he continually applied the principles and rigor of physical organic chemistry to his biological systems.

4. *R. C. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, Accleration of phenyl ester cleavage by cycloamyloses: A model for enzymatic specificity. J. Amer. Chem. Soc.* ***89,*** *3242 (1967)*

Myron was among the very first to recognize that the chemistry of the future would involve complexation (perhaps stereospecific complexation) of reactants prior to the actual reaction. This is, after all, the way enzymes function. In order to mimic such enzymatic behavior, Myron used cyclodextrin systems which complex and then react with small organic substrates. His work in the area is described in a series of articles and a book, of which the above-cited paper is an example. Its import can be appreciated from two sentences taken from the abstract: "The cycloamyloses cause a markedly stereoselective acceleration of phenol release from a variety of substituted phenyl acetates in alkaline solution." "The reaction system constitutes a striking model for the lock and key theory of enzymatic specificity proposed by Emil Fischer." In my opinion, the Bender paper is more than just an interesting enzyme model. It initiated the era of "biomimetic chemistry." It paved the way for others (particularly Breslow, Cram, Lehn, Tabushi, and Murakami) to experiment with preassociative mechanisms. If Myron had accomplished nothing else other than this cyclodextrin work, he would still leave a considerable mark on physical organic chemistry.

5. *I. M. Mallic, V. T. D'Souza, M. Yamaguchi, J. Lee, P. Chalabi, R. C. Gadwood, and M. L. Bender, An organic chemical model of the acyl-α-chymotrypsin intermediate. J. Amer. Chem. Soc.* ***106,*** *7252 (1984)*

Dr. Bender's group reported the synthesis of what is certainly one of the most sophisticated chemical models of the acyl-enzyme to date. It incorporates all three components believed present at the active site of the enzyme: an imidazole ring, a carboxylate, and a hydroxyl (the latter of which becomes acylated during the reaction between the enzyme and an ester substrate). The Bender model (see Scheme 3) has a hydrolysis rate approximately equivalent to the actual acyl-enzyme intermediate and 154,000 times faster than an ordinary ester. Synthetic organic chemistry, physical organic chemistry, and biological relevance are combined here in a magnificent system.



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In subsequent work, the chemistry in the above model was inserted into a cyclodextrin system so that binding processes precede catalysis. Thus, Myron wrote: "Instead of the biochemist isolating and purifying a natural product of evolution that had taken 2 billion years, the bioorganic chemist could go into the lab and synthesize artifical chymotrypsin in about 2 weeks with comparable binding and kinetic properties." The culmination of over 30 years research, including his artificial chymotrypsin, is encapsulated in a recent article: V. T. D'Souza and M. L. Bender, Miniature organic models of enzymes. *Acc. Chem. Res.* **20,** 146 (1987).

Myron Bender's science will not fade away. Obviously, the principles of nature that he uncovered during his career will be incorporated into the chemical literature for a long time to come. But, more than that, I have noticed that Myron's style of science pervades the publications of myself and all the other of his disciples. And I have noticed that *our* students, Myron's scientific "grandchildren," also possess the Bender aura, sometimes without knowing it. The debt here is multigenerational. And now, unfortunately, the chemical community will be unable to express its appreciation when it counts.

Myron had a wonderful wife, Muriel, whose love was apparent whenever they were seen together. This love, I am certain, enabled Myron to cope for many years with the effect of a terrible stroke, and to continue to produce good chemistry despite it, although a similar affliction would have all but destroyed a man not as blessed. One wonders if greatness in science is ever possible without the force of mutual affection. Sadly, Muriel passed away soon after Myron.

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