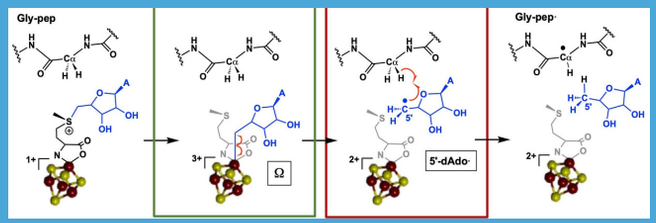
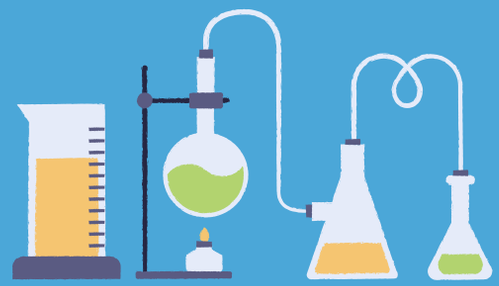
LECTURE ABSTRACT

Enzymes of the radical S-adenosyl-l-methionine (radical SAM, RS) superfamily, the largest in nature, use a [4Fe-4S] cluster and SAM to catalyze remarkably diverse radical reactions. RS enzymes that act on protein or peptide substrates include the glycyl radical enzyme activating enzymes (GRE-AEs) important in anaerobic metabolism, and enzymes that catalyze epimerizations, splicing reactions, and cross-linking reactions during maturation of ribosomally-encoded, post-translationally modified peptides (RiPPs). We are using freeze-quench techniques coupled to electron paramagnetic resonance spectroscopy to gain insights into mechanistic steps and reaction intermediates in these types of reactions. We examine the reaction of the GRE-AE pyruvate formate-lyase activating enzyme (PFL-AE) with peptide substrate mimics such as RVSG”734"YAV, a model for the site of glycyl radical formation on the native substrate pyruvate formate-lyase, as well as RVS(Dha)YAV, which has a dehydroalanine in place of glycine and results in a change in reactivity from H-atom abstraction to adenosylation of the double bond of the Dha residue.



Time-resolved freeze-quench electron paramagnetic resonance spectroscopy shows that at short mixing times for both substrates result in formation of the central organometallic intermediate, Ω, in which the adenosyl 5′C is covalently bound to the unique iron of the [4Fe-4S] cluster. Freeze-trapping the reactions at longer times reveals the formation of subsequent intermediate/product radicals dependent on identity of the substrate. Of central importance, freeze-quenching at intermediate times reveal the conversion of Ω to the nominally ‘free’ 5′-dAdo• radical, which can be observed to convert to a peptide-based radical upon cryo-annealing. These observations reveal the 5′-dAdo• radical to be a well-defined intermediate, caught in the act of subsequent chemistry, providing new insights into the mechanistic steps of radical initiation by radical SAM enzymes.



Questions and comments about the Dawson Lecture can be directed to *chemistry@uky.edu*

Established in memory of Lyle Ramsay Dawson Distinguished Professor and Former Head of the Department of Chemistry

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College of Arts and Sciences
Department of Chemistry

26TH ANNUAL LYLE RAMSAY DAWSON

LECTURE

“Probing Radical SAM Reactivity via Time-Resolved Freeze Quench EPR: A Step-Wise Walk-Through the Radical Menagerie”

Dr. Joan B. Broderick

Department Head
Chemistry & Biochemistry
Montana State University

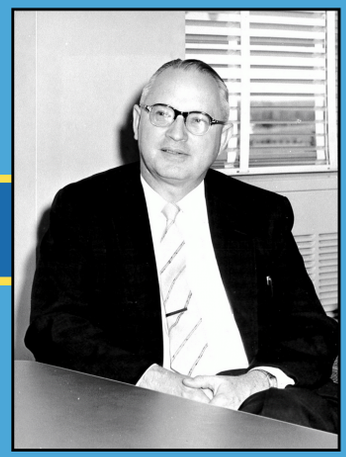
November 10, 2023
3:00 PM
Jacobs Science Building 321
Reception to follow in JSB 361M

College of Arts and Sciences
Department of Chemistry

DR. JOAN B. BRODERICK

Joan B. Broderick is Professor and the Department Head of the Chemistry and Biochemistry Department at Montana State University. She is a bio-inorganic chemist who studies how iron-sulfur clusters and S-adenosylmethionine (commonly known as SAM) are used by nature to initiate radical reactions essential to life. Other research interests include the biological assembly of complex metal clusters, and the trafficking, storage, and utilization of iron and sulfur in biology. Broderick graduated from a small all-girls high school in Bellevue, Washington, where she first became intrigued by the interface of chemistry and biology. Broderick has an undergraduate degree from Washington State University (1987), where she worked in both biochemistry and inorganic chemistry labs. She earned an M.S. and a Ph.D. (1992) from Northwestern University with Tom O'Halloran, where she was a National Science Foundation Graduate Fellow studying mechanistic aspects of the non-heme iron enzyme chlorocatechol dioxygenase. She was an American Cancer Society Postdoctoral Fellow with JoAnne Stubbe at Massachusetts Institute of Technology where she focused on mechanism of the coenzyme B12-dependent ribonucleotide reductase. Broderick was an assistant professor at Amherst College (1993 – 1998), where she began her work on radical SAM enzymes with undergraduate research students. She moved to Michigan State University in 1998, where she was assistant, associate, and full professor before moving to Montana State University in 2005.

Lyle Ramsay Dawson was a native of Illinois and received his undergraduate degree from the University of Illinois in 1932. He received his Ph.D. degree in 1935 from the University of Iowa



Dr. Dawson served in several academic positions in Illinois, Wisconsin, Nebraska and Louisiana and also worked on the Manhattan Project as a Research Chemist and Group Leader in the Metallurgical Laboratory at the University of Chicago. In 1946, he was awarded the War Department's Certificate of Merit and a U.S. Patent for his efforts on the Manhattan Project, which led to the discovery of a fundamental process for the extraction and purification of the elements plutonium and neptunium. He was a member of the committee that organized the Oak Ridge Institute of Nuclear Studies and was a council member of the Institute.

Professor Dawson came to the University of Kentucky in 1945 as Head of the Department of Chemistry. He provided key leadership in initiating and building the doctoral program in chemistry at the university. For example, in his first decade in the department, he individually obtained the major portion of extramural research support. During his twenty-five years with the department, he held contracts for fundamental chemical research with the U.S. Army, the National Science Foundation and the Atomic Energy Commission.

He directed or co-directed seventeen Ph.D. dissertations and nine M.S. theses. He was a talented research director and had a special ability to imbue his students with a concise, clear and complete scientific writing style. He published more than fifty research papers dealing with the chemistry of nonaqueous solutions and coauthored a reference book on the subject.

LYLE RAMSAY DAWSON

Dr. Dawson was a master teacher both in the classroom and in less formal conferences and discussions. His leadership and mentoring led many graduate teaching assistants and junior faculty members to become more effective teachers. His uncompromising devotion to high achievement standards in coursework, research, education and training set the tone for our department for years to come.

Another significant contribution to the department was Professor Dawson's indefatigable advocacy for a new chemistry building. His leadership in soliciting and designing a replacement for the former chemistry building, Kastle Hall, culminated in the opening of the current Chemistry-Physics Building in 1963. He also served the campus community in other ways. Dr. Dawson was elected a Distinguished Professor in the College of Arts and Sciences in 1954—1955 and was appointed to the rank of Distinguished Professor in the field of Physical Chemistry by the University of Kentucky Board of Trustees in 1956. He served as Acting Dean of the Graduate School in 1954—1955, 1956 and 1960—1961.

Dr. Dawson's contributions outside the university were well recognized. He was a Fellow of both the American Institute of Chemists and the American Association for the Advancement of Science. He was a member of the American Chemical Society, Electrochemical Society, Sigma Xi, Omicron Delta Kappa, Alpha Chi Sigma and Kappa Delta Pi, serving leadership roles in each of these organizations. He served several times as a Tour Lecturer and Visiting Scientist under the sponsorship of the American Chemical Society. He was also active in a variety of other nonacademic organizations.

Dr. Dawson's twenty-five years in the department represent a truly outstanding combination and balance of administrative leadership, teaching, research and service. Although Dr. Dawson passed away in 1976, his impact on the department continues to this day. The endowment of the Lyle Ramsay Dawson Lecture Series by his beloved daughter, Venita Dawson Curry, permits us to rejoice in this legacy and to continue our tradition of world-class chemical research.