2007 PROGRAM

8:30 a.m. Registration and Continental Breakfast, Singletary Center for the Arts

9:10 a.m. Welcome by Dr. Charles A. Staben, Associate VP for Research, University of Kentucky - Singletary Center for the Arts, Recital Hall

9:20 a.m. Introductory Remarks - Dr. Steven W. Yates, Chairman, Department of Chemistry, University of Kentucky

9:30 a.m. Dr. John A. Gerlt, University of Illinois at Urbana-Champaign
"Discovering and Predicting New Enzymes in the Enolase Superfamily"

Many members of the mechanistically diverse enolase superfamily have unknown functions. We are using two strategies to assign them: 1) experimental screening of libraries of potential substrates, and 2) *in silico* prediction using homology models and docking of libraries of potential substrates. Using the first strategy, we recently published the assignments of L-fuconate dehydratase and D-tartrate dehydratase functions. We now have discovered that members of another orthologous group catalyze the dehydration of both galactarate and L-talarate as well as their interconversion by epimerization. Using the *in silico* strategy, we predicted that members of a divergent orthologous group would catalyze the racemization of N-succinyl Arg and N-succinyl Lys. We experimentally verified these predictions and solved the structure of this N-succinylamino acid racemase. The predicted and experimental structures of liganded complexes are in excellent agreement. Thus, computational approaches provide a viable strategy for successfully assigning function to members of the enolase superfamiliy as well as other enzymes discovered in genome projects. Supported by GM-71790.

10:40 a.m. Break (Refreshments Available)

11:00 a.m. Poster Session, Room CP-137, Chemistry-Physics Building

12:00 p.m. Buffet Lunch, Alumni House [Please return registration card by April 6, 2007 for reservations]

1:30 p.m. Dr. Vern L. Schramm, Albert Einstein College of Medicine
"Drugs for Cancer and Malaria from Transition State Analysis"

A thermodynamic description of the enzymatic transition state is the bond-vibrational instant of bond breaking. With a lifetime less than a single bond vibration, direct observations of enzymatic transition states are not yet possible. Transition state structure can be probed by kinetic isotope effects coupled to quantum chemical structures of proposed transition states. An accurate transition state structure provides a blueprint for the design of transition state analogues. Chemically stable mimics of enzymatic transition states convert the energy of catalysis into binding energy. Thus, transition state analogues have the potential to bind to target enzymes millions of times more tightly than the substrates. Our drug design program, built around transition state theory, is now producing powerful transition state analogues for several targets with promise for treatment of T-cell leukemia, B-cell leukemia, autoimmune diseases, prostate cancer, head and neck cancer, and malaria. Bacterial antibiotics are also being developed in this program. Two compounds, Immucillin-H and DADMe-Immucillin-H are in clinical trials for leukemia and autoimmune diseases.

2:40 p.m. Break (Refreshments Available)

3:00 p.m. Dr. JoAnne Stubbe, Massachusetts Institute of Technology
"Unnatural Amino Acids: Tools to Investigate Radical Propagation in Class I Ribonucleotide Reductase"

Ribonucleotide reductases (RNRs) catalyze the, thus conversion of nucleotides to deoxynucleotides in all organisms playing an essential role in DNA replication and repair. Class I RNRs are composed of two homodimeric subunits: R1 (α2) and R2(β2). R2 contains the di-iron tyrosyl radical (Y•) cofactor essential for activity. R1 contains the active site where nucleotide reduction occurs. An unresolved mechanistic issue is how the Y• in R2 generates a transient thiyl radical on R1 to initiate the reduction process. This initiation is thought to occur over a 35 Å distance and involve generation of aromatic amino acid radical intermediates. Experiments using unnatural amino acids ($(F)_n$-tyrosines (n = 2, 3, 4), 3-hydroxytyrosine, nitrotyrosine, and benzophenone) in position 356 of R2 have been carried out. These studies provide direct evidence for intermediacy of a Y356• on the propagation pathway. We have recently been able to place unnatural amino acids in the R1 subunit. These studies have demonstrated the importance of Y730 and Y731 within R1 for the radical propagaton process and the substrate/effector conformational gating of this process. Our studies provide direct evidence for hole migration through amino acid radical intermediates over a long distance.

4:10 p.m. Closing Remarks - Dr. Anne-Frances Miller, Department of Chemistry, University of Kentucky

(http://www.chem.uky.edu/seminars/naff/welcome.html)

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Thirty-Third Annual
Naff Symposium on

Chemistry & Molecular Biology

established in the memory of
Anna S. Naff

Enzyme Catalysis and Mechanisms

SPEAKERS

John A. Gerlt
Vern L. Schramm
JoAnne Stubbe

Friday, April 13, 2007

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