

Department of Chemistry
University of Kentucky
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Ninth Annual Symposium on

Chemistry and Molecular Biology

established in memory of
Anna S. Naff

STRUCTURE AND FUNCTION OF CYTOCHROME P-450

Speakers

PROF. I.C. GUNSALUS
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1983 PROGRAM

- 9:00 A.M. Coffee—Chemistry-Physics Room 137
9:30 Welcome and Introduction—
Chemistry-Physics Room 139
9:40 Cytochrome P-450 Structures and
Reactions
—Professor Gunsalus

The P450 heme sulfur proteins of monooxygenase systems encompass a range of synthetic and carbon cycling selectivity, oxygen donor cycles, and product yields. They share unique transient and stable intermediate states, dioxygen cycle, resonance spectra of the iron reporter group and primary sequence of the thiolate axial ligand.

The microsomal heme sulfur-two flavin reductase systems contrast in broad substrate and induction potential, weak substrate binding, low turnover and lipid dependence with the three component systems (P450-redoxin-single FAD flavin reductase) of the mitochondria and microbes which exhibit more restricted substrate and stereo selective oxygen incorporation, increased substrate and inter component affinity under redox modulated asymmetry, higher turnover and coupling in oxygenated product yields. Structure-function comparisons of the three component procaryote hydroxylase models provided by the P450_{cam} (5-methylene) and P450_{lin} (8-methyl and 8-hydroxyl methyl) with monooxygenase varieties from eucaryote organelles are now becoming available. The roles of primary and tertiary structures present a target of general biochemical opportunity for the investigation of substrate and protein component determinants to complement, in precision and detail, the physical probe analyses of static structures and dynamic events.

- 10:30-10:40 Discussion
10:40 Coffee Break
11:00 The Structure and Reactivity of
Intermediates in the Cytochrome
P-450 Reaction Cycle
—Professor Dolphin

Model and enzymatic studies have suggested structures for the coordination sphere around the heme iron for each of the enzymatically important intermediates of Cytochrome P-450. Using ruthenium porphyrins, an analog for the Fe (iv) oxy π -cation radical has been characterized. The role of this intermediate in P-450 function and its relationships to enzymic intermediates in catalases, peroxidases, and cytochrome oxidase will be considered.

- 11:50-12:00 Discussion
1:30 P.M. Synthetic Models of Reactive
Intermediates in the Catalytic
Cycle of Cytochrome P-450
—Professor Groves

High valence iron-porphyrin species are suspected to be responsible for hydrocarbon oxidation in the catalytic cycle of cytochrome P-450. The preparation, characterization and reaction of synthetic models of these reactive intermediates will be described. Comparisons will be made between the reactions of these synthetic compounds and those of liver microsomal cytochrome P-450.

- 2:20 Discussion
2:30 Coffee Break
2:50 Structure and Function of
Isozymes of Cytochrome P-450
—Professor Coon

Cytochrome P-450, the most versatile biological catalyst known, occurs widely in nature, being membrane-bound in animal tissues and apparently cytosolic in microorganisms. Some of the most puzzling properties of P-450 in liver microsomes, including the remarkably broad substrate specificity and the ability to carry out both oxygen activation and peroxide activation, could not be explained until the enzyme system was resolved into its components (phospholipid, reductase, and isozymes of P-450) and these were obtained in purified form. Seven distinct isozymes have now been obtained in an electrophoretically homogeneous state from rabbit liver microsomes and characterized. They have a number of similar properties but differ significantly in spectra, peptide maps, N- and C-terminal amino acid sequences, patterns of induction, and activity toward selected substrates, whether naturally occurring lipids or foreign compounds including drugs, and carcinogens. We have recently identified a highly conserved cysteine-containing tetradecapeptide which may provide the sulfur ligand to the heme iron atom and have shown that the rabbit phenobarbital-inducible isozyme has 80% homology in primary structure with the corresponding rat protein. The purified isozymes exhibit individual preferences for particular substrates but are all apparently capable of binding a variety of hydrophobic substrates. As a result, the disposition of foreign compounds and the metabolism of physiologically occurring substances such as fatty acids, prostaglandins, and steroids are closely interrelated.

- 3:40 Discussion
3:50-4:30 Meeting with Graduate Students
and Faculty—C-P Room 137