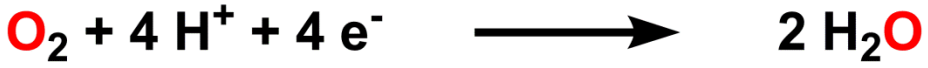
5 Slides About:

Dioxygen Activation in Non-Heme Iron Enzymes

Gerard Rowe
University of South Carolina - Aiken

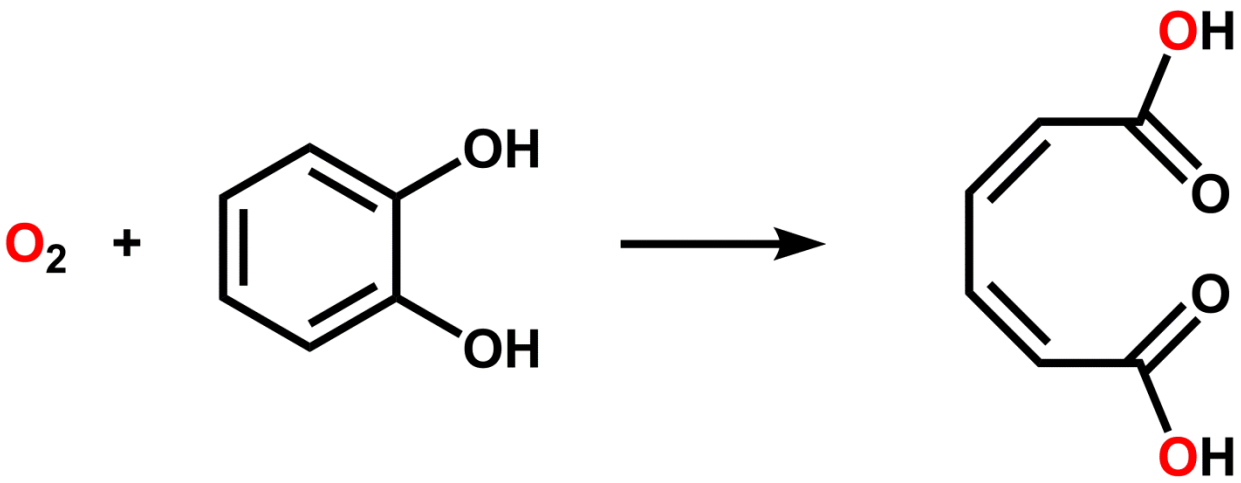
Dioxygen Activation

In general, the biological utilization of dioxygen is a 4-electron process



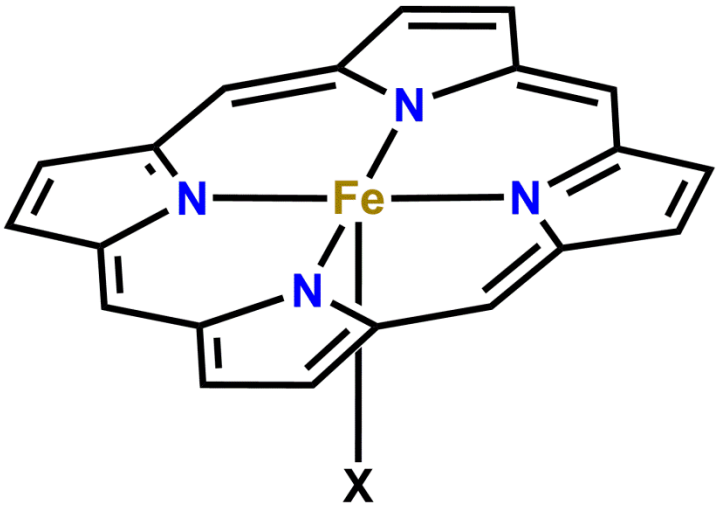
Metabolic Utilization
(Cytochrome c oxidase)

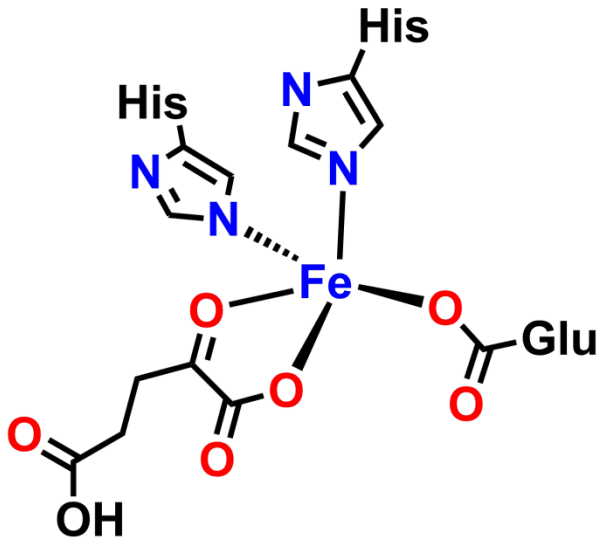
Monooxygenase Activity
(Methane Monooxygenase)



Dioxygenase Activity
(Intradiol Ring Cleaving
Dioxygenase)

Heme vs. Non-Heme Oxidases





General Heme Protein Environment

X = $S_{Met/Cys}$, N_{His}, O_{Tyr}

Porphyrin ligand is redox active

Usually **nonspecific** oxidases

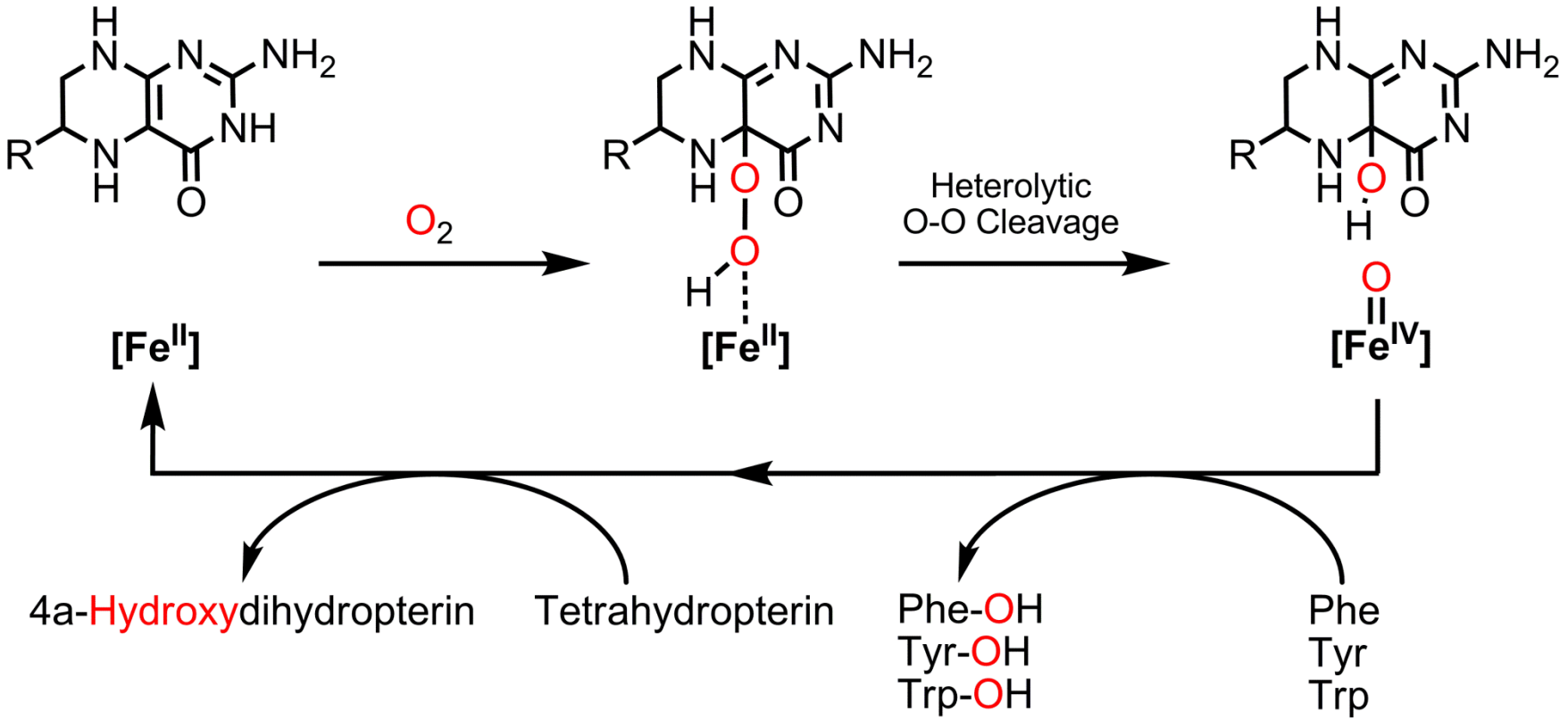
Taurine α-Ketoglutarate Dioxygenase

Utilizes an α-ketoacid cofactor as a source of electrons

Usually **tailored** to one substrate

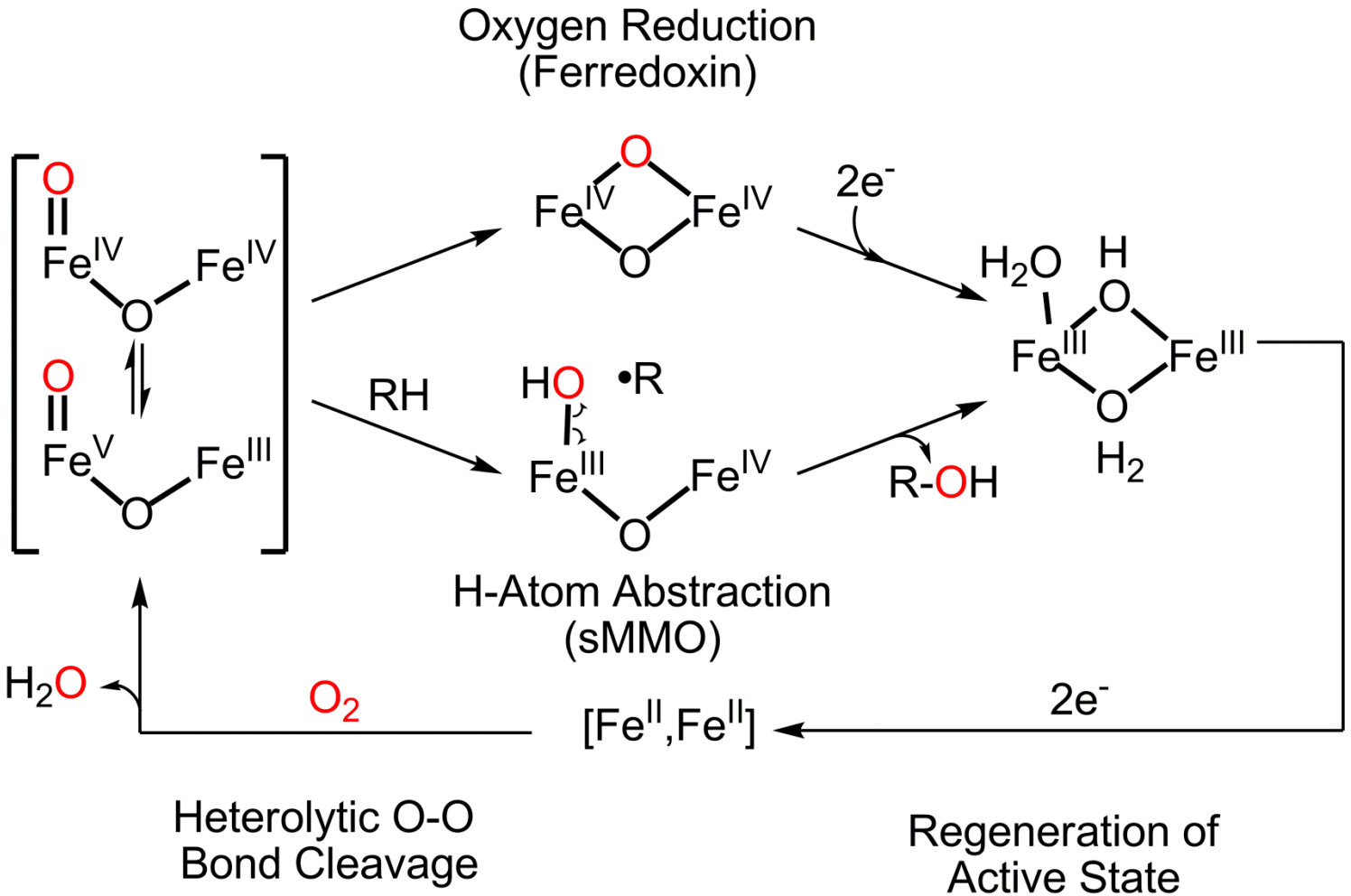
Mononuclear Non-Heme O_2 Activation

Aromatic Amino Acid Hydroxylases Use a Pterin Cofactor that Provides Two Reducing Equivalents

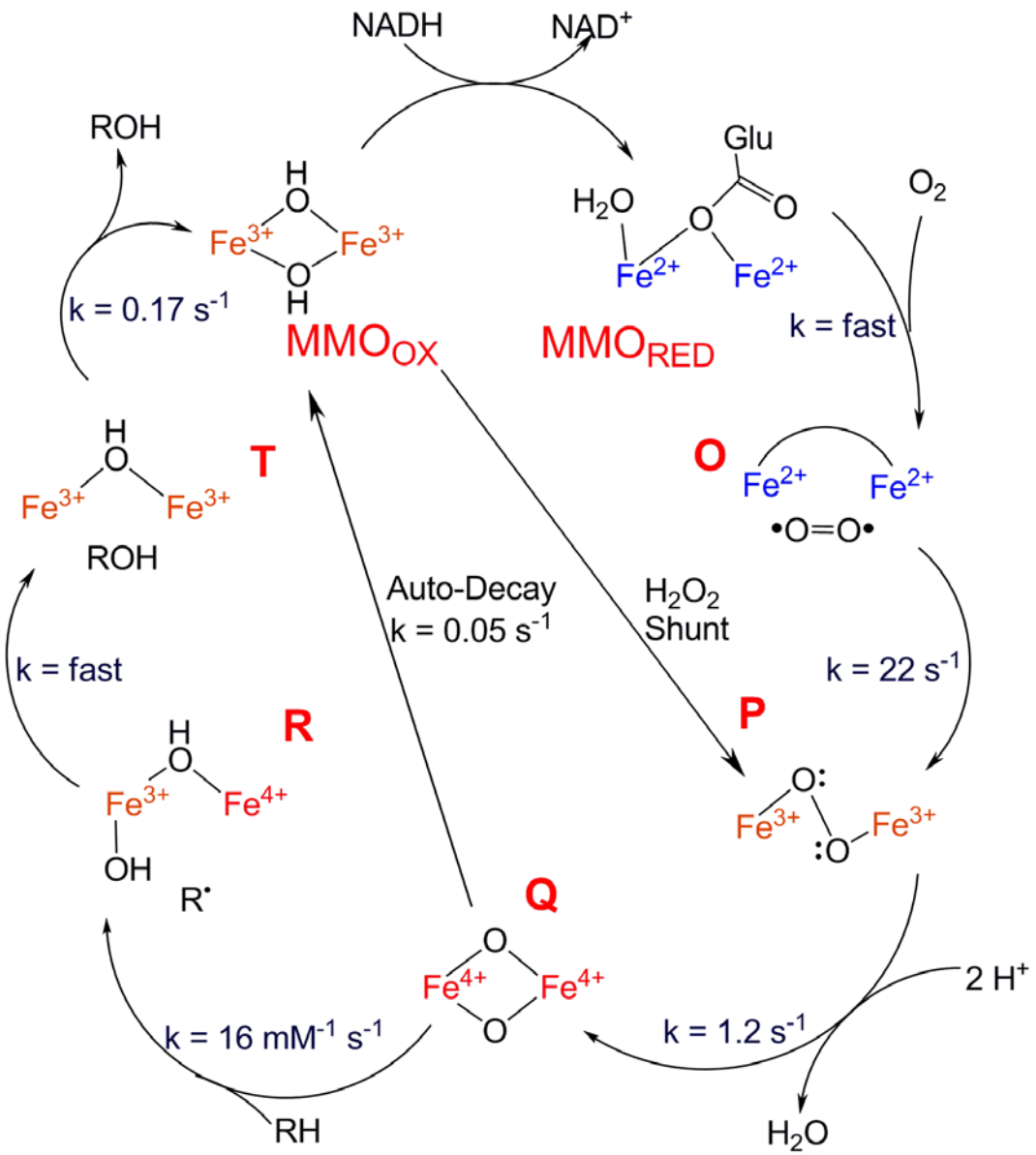


Binuclear Non-Heme O_2 Activation

Binuclear iron enzymes generally do not utilize a cofactor, receiving their electrons from a reductase subunit, instead.



Detailed Look at Activation Mechanism



Addition of O_2 to MMO_{Red} results in an unobserved, but kinetically implicated species **O**

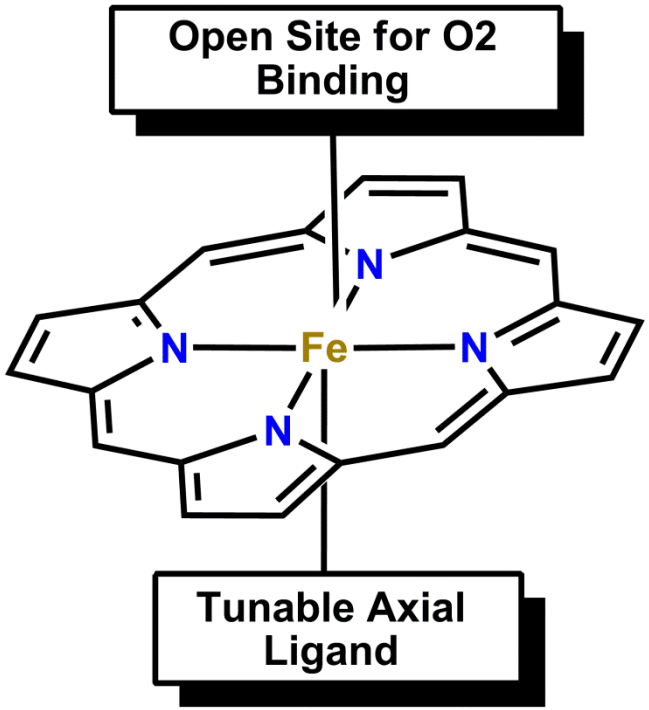
Heterolytic Cleavage of peroxo bond (P → Q) forms a Fe(IV)Fe(IV)-oxo species, termed Q.

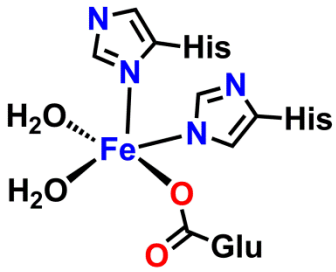
$sMMO_{Ox}$ can directly convert to P by the addition of peroxide.

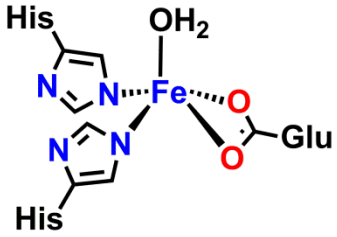
*Rates reported at 4ºC

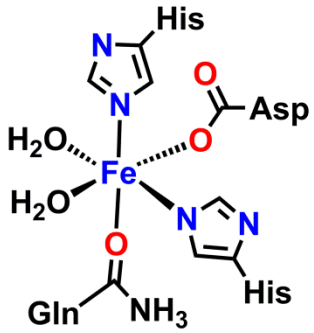
Why Use Non-Heme Oxygenases?

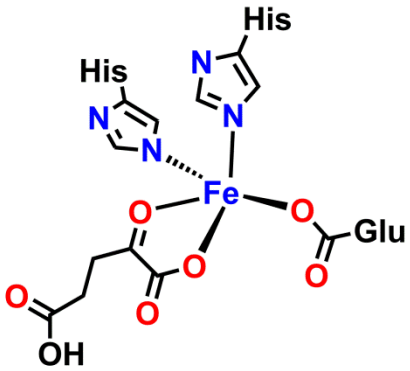
Oxygen is **dangerous**. One misfire of the enzyme can hydroxylate the active site, rendering it useless. Heme oxygenases like P450 can hydoxylate nearly anything, but lack control and tunability. Non-heme oxygenases are **customizable**, and the potency of the intermediate can be reduced.

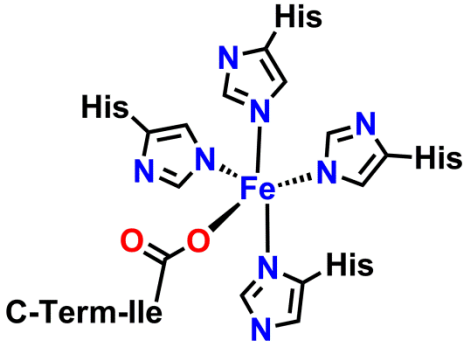












References for Further Study

Mononuclear Enzymes:

Kappock, T. J.; Caradonna, J. P. "Pterin-dependent amino acid hydroxylases." *Chem. Rev.* **1996**, *96*, 2659.

Glickman, M. H.; Klinman, J. P. "Lipoxygenase reaction mechanism: Demonstration that hydrogen abstraction from substrate precedes dioxygen binding during catalytic turnover." *Biochemistry* **1996**, *35*, 12882.

Riggs-Gelasco, P. J.; Price, J. C.; Guyer, R. B.; Brehm, J. H.; Barr, E. W.; Bollinger, J. M.; Krebs, C. "EXAFS spectroscopic evidence for an Fe = O unit in the Fe(IV) intermediate observed during oxygen activation by taurine :alpha-ketoglutarate dioxygenase." *J. Am. Chem. Soc.* **2004**, *126*, 8108.

Bertini, I.; Briganti, F.; Mangani, S.; Nolting, H. F.; Scozzafava, A. "Biophysical investigation of bacterial aromatic extradiol dioxygenases involved in biodegradation processes." *Coord. Chem. Rev.* **1995**, *144*, 321.

Wackett, L. P. "Mechanism and applications of Rieske non-heme iron dioxygenases." *Enzyme Microb. Technol.* **2002**, *31*, 577.

Binuclear Enzymes:

Baik, M. H.; Newcomb, M.; Friesner, R. A.; Lippard, S. J. "Mechanistic studies on the hydroxylation of methane by methane monooxygenase." *Chem. Rev.* **2003**, *103*, 2385.

Wallar, B. J.; Lipscomb, J. D. "Dioxygen activation by enzymes containing binuclear non-heme iron clusters." *Chem. Rev.* **1996**, *96*, 2625.