Molecular Mechanism of Heme Oxygenase Catalysis

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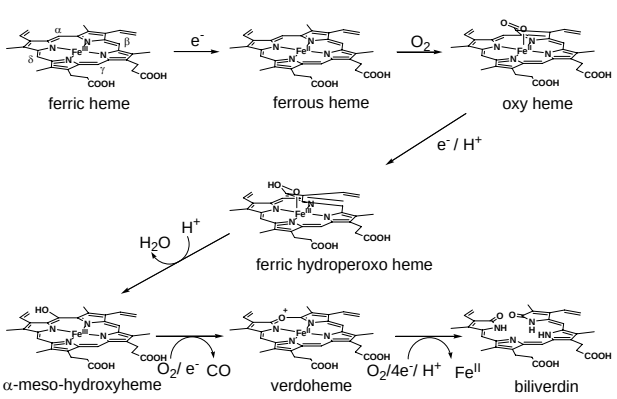

Heme oxygenase (HO) catalyzes O_2-dependent regiospecific conversion of heme to biliverdin, CO and a free Fe, as depicted in the figure. The heme group is tightly sandwiched between the proximal and distal helices with a neutral His axial ligand, the imidazole group of which closely eclipses the porphyrin β and δ meso axis.[1] In the ferrous form, both helices move closer to the heme group, and O_2 binds with an accute Fe-O-O angle of ~110º; the distal helix restricts the O-O bond direction toward the heme α-*meso*-carbon, placing the terminal oxygen atom close to the α-*meso*-carbon.[2] The bound O_2 is stabilized by H-bonds with a distal Gly amide nitrogen and the nearby H_2O, the latter of which is a part of an extended distal pocket H-bond network linked by a conserved distal Asp. The H-bond network functions as a conduit for transferring protons required for the formation of ferric hydroperoxo, which is generated by one-electron reduction of the oxy form, and also for the activation of hydroperoxo, which leads to the selective hydroxylation of the heme α-*meso*-carbon.[3] The ferric hydroperoxo active species could not be formed upon loss of the nearby H_2O by mutation of the Asp, indicating a critical role of this H_2O molecule in the *meso*-carbon hydroxylation. Ferrous verdoheme formation proceeds by reaction of the ferrous porphyrin neutral radical of ferric α-*meso*-hydroxyheme with O_2 and one electron. Ferrous verdoheme iron reacts with O_2 to form a reaction intermediate, reduction of which affords biliverdin. Proton transfer by the distal pocket H-bond network facilitates conversion of verdoheme to biliverdin. HO heme catabolism is realized by the salient HO protein structure that enables conversion of heme, which is rather inert, into reactive hydroxyheme and verdoheme intermediates.

References. 1. Hirotsu *et al. J. Biol. Chem.* **2004**, *279*, 11937-11947. 2. Unno *et al. J. Biol. Chem.* **2004**, *279*, 21055-21061. 3. Davydov *et al. J. Am. Chem. Soc.* **2002,** *124*, 1798-1808; *J. Am. Chem. Soc.* **2003,** *125*, 16208-16209; *J. Am. Chem. Soc.* **2004,** *126*, 15960-15961; Matsui *et al. J. Biol. Chem.* **2005**, *280*, 2981-2989.