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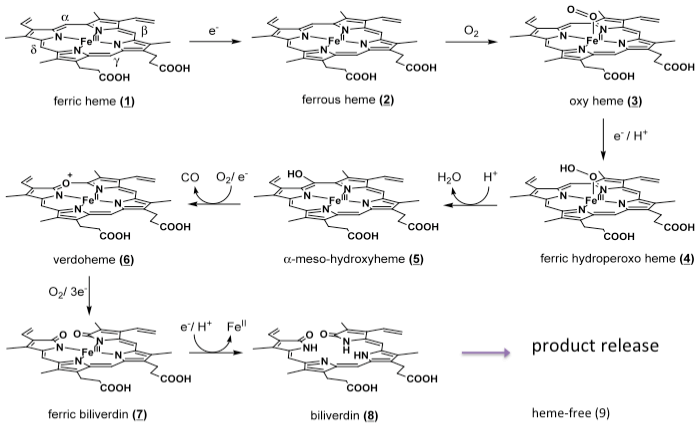
I E C B

Two Distinct Biological Heme Degradation.

Masao IKEDA-SAITO

Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, Sendai, JAPAN

Heme oxygenase (HO), a central enzyme in heme catabolism, converts heme to biliverdin, CO, and a Fe ion through three monooxygenase reactions (right figure). The electronic states, reactivities, and crystal structures of eight catalytic intermediates have been examined with a help of cryo-reduction and annealing to trap unstable, such as (**4**) and (**5**). HO is not a heme protein *per se* but forms a heme complex with heme which serves both as the substrate and the active center. The O2 binds to the ferrous heme iron with an acute Fe–O–O angle of ~110˚ with its terminal oxygen atom close to the α-*meso*-carbon. An extended distal pocket hydrogen bonding network functions as a conduit for transferring protons required for the formation of hydroperoxo, generated by one-electron reduction of the oxy form, and also for the activation of hydroperoxo, leading to the hydroxylation of the heme α-*meso*-carbon. Hydroperoxo cannot be formed upon loss of the nearby H2O, indicating a critical role of this H2O in the HO catalysis. Ferrous verdoheme formation proceeds by reaction of the ferrous porphyrin neutral radical of ferric α-*meso*-hydroxyheme with O2 and one electron. Conversion of verdoheme to biliverdin is realized in a manner very similar to that for the hydroxylation of the heme α-*meso*-carbon, first step of oxygenation step.



HO catalytic intermediates

The recent discovery of the bacterial IsdG-like heme degrading proteins of *S. aureus* and *M. tuberculosis* has expanded the reaction manifold of heme degradation. The *S. aureus* IsdG reaction products are novel chromophores termed staphylobilins, where the *meso*-carbon is released as formaldehyde. The structurally related MhuD cleaves heme to a product mycobilin that retains the *meso*-carbon as an aldehyde. A highly ruffled heme group, a unique feature of the IsdG-like proteins, appears to be responsible for the novel heme degradation reaction.

[1] Matsui, T.; Unno, M.; Ikeda-Saito, M. (2010) *Acc. Chem. Res.* **43**, 240-247
[2] Nambu, S.; Matsui, T.; Goulding, C. W.; Takahashi, S.; Ikeda-Saito, M. (2013) *J. Biol. Chem.* **288**, 10101-10109
[3] Matsui, T.; Nambu, S.; Ono, Y.; Goulding, C. W.; Tsumoto, K.; Ikeda-Saito, M. (2013) *Biochemistry* **52,** 3025-3027

Institut Européen de Chimie et Biologie
2, rue Robert Escarpit - 33607 Pessac, France
Tél. : +33(0)5 40 00 30 38 - Fax. : +33(0)5 40 00 22 15
www.iecb.u-bordeaux.fr