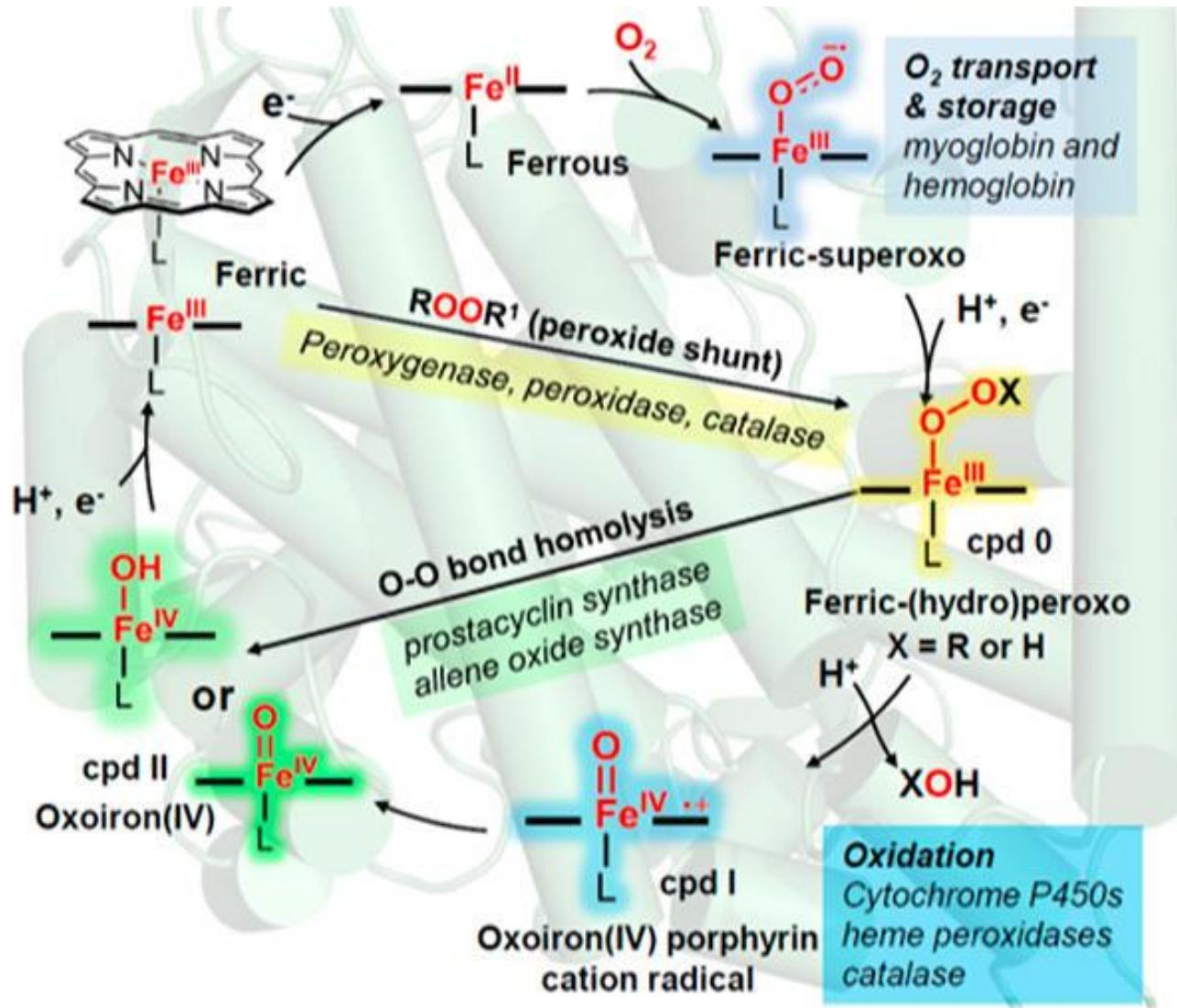


# What can we learn from mother nature?



# Material

Book: *Shriver and Atkins Inorganic Chemistry*

“Oxygen Activation and Radical Transformations in Heme Proteins and Metalloporphyrins”

X. Huang, J. T. Groves, *Chem. Rev.* **2018**, *118*, 2491–2553.

“Dioxygen Activation by Nonheme Diiiron Enzymes: Diverse Dioxygen Adducts, High-Valent Intermediates, and Related Model Complexes”

Andrew J. Jasniewski and Lawrence Que, Jr., *Chem. Rev.* **2018**, *118*, 2554–2592.

“Versatility of biological non-heme Fe(II) centers in oxygen activation reactions”

E. G Kovaleva, J. D. Lipscomb, *Nat. Chem. Bio.* **2008**, *4*, 186-193.

“Copper Active Sites in Biology”

E. I. Solomon, D. E. Heppner, E. M. Johnston, J. W. Ginsbach, J. Cirera, M. Qayyum, M. T. Kieber-Emmons, C. H. Kjaergaard, R. G. Hadt, L. Tian, *Chem. Rev.* **2014**, *114*, 3659–3853.

“Heme and Nonheme High-Valent Iron and Manganese Oxo Cores in Biological and Abiological Oxidation Reactions”

M. Guo, T. Corona, K. Ray, W. Nam, *ACS Cent. Sci.* **2019**, *5*, 13–28.

# Challenge

Petroleum-based fuels

Non-renewable

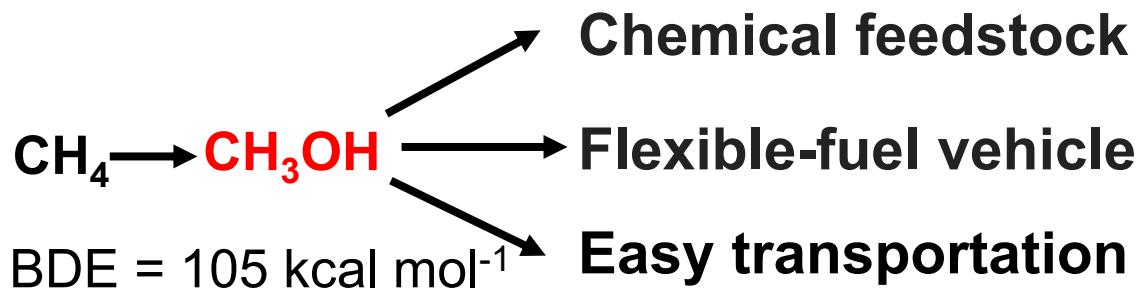
Emit CO<sub>2</sub>

Global Warming



<https://www.thoughtco.com/advantages-and-disadvantages-of-global-warming-1434937>

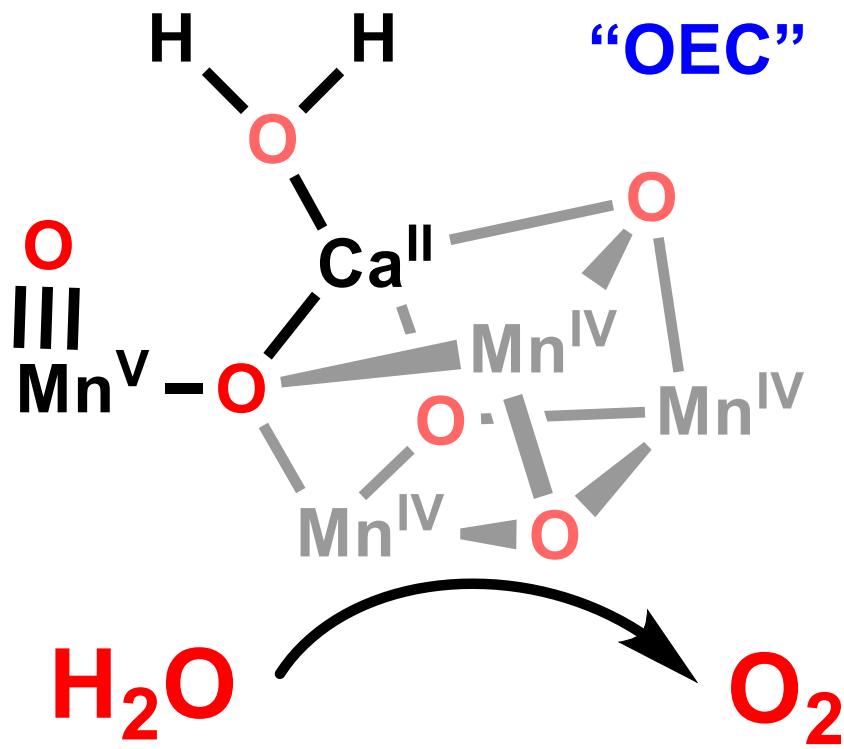
160 billion cubic meters  
natural gas flared



*Energies 2016, 9, 14.*

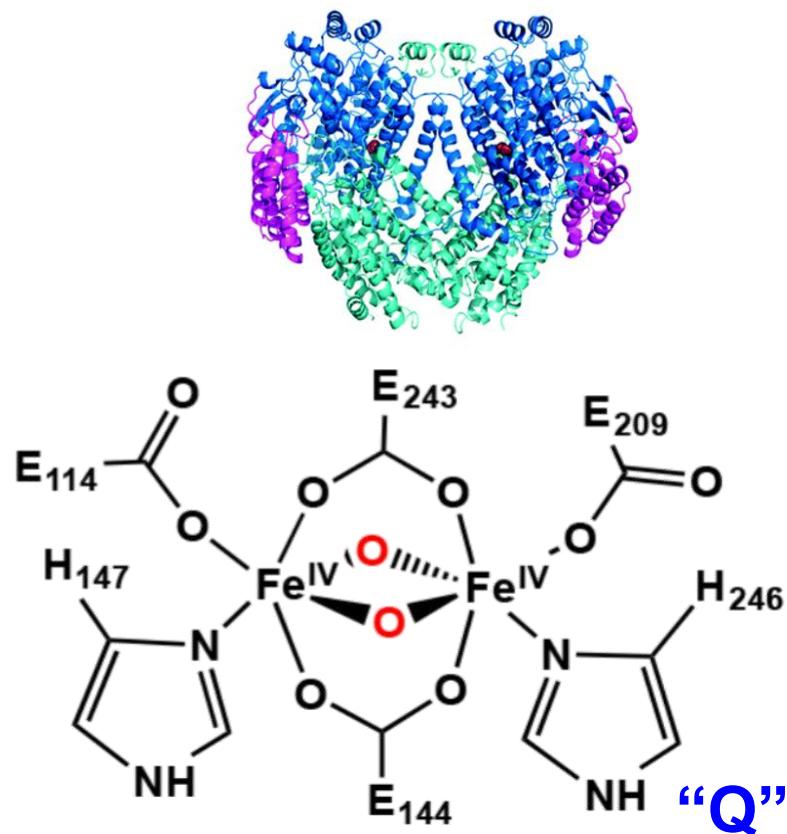
# Inspiration from nature

## Photosystem II



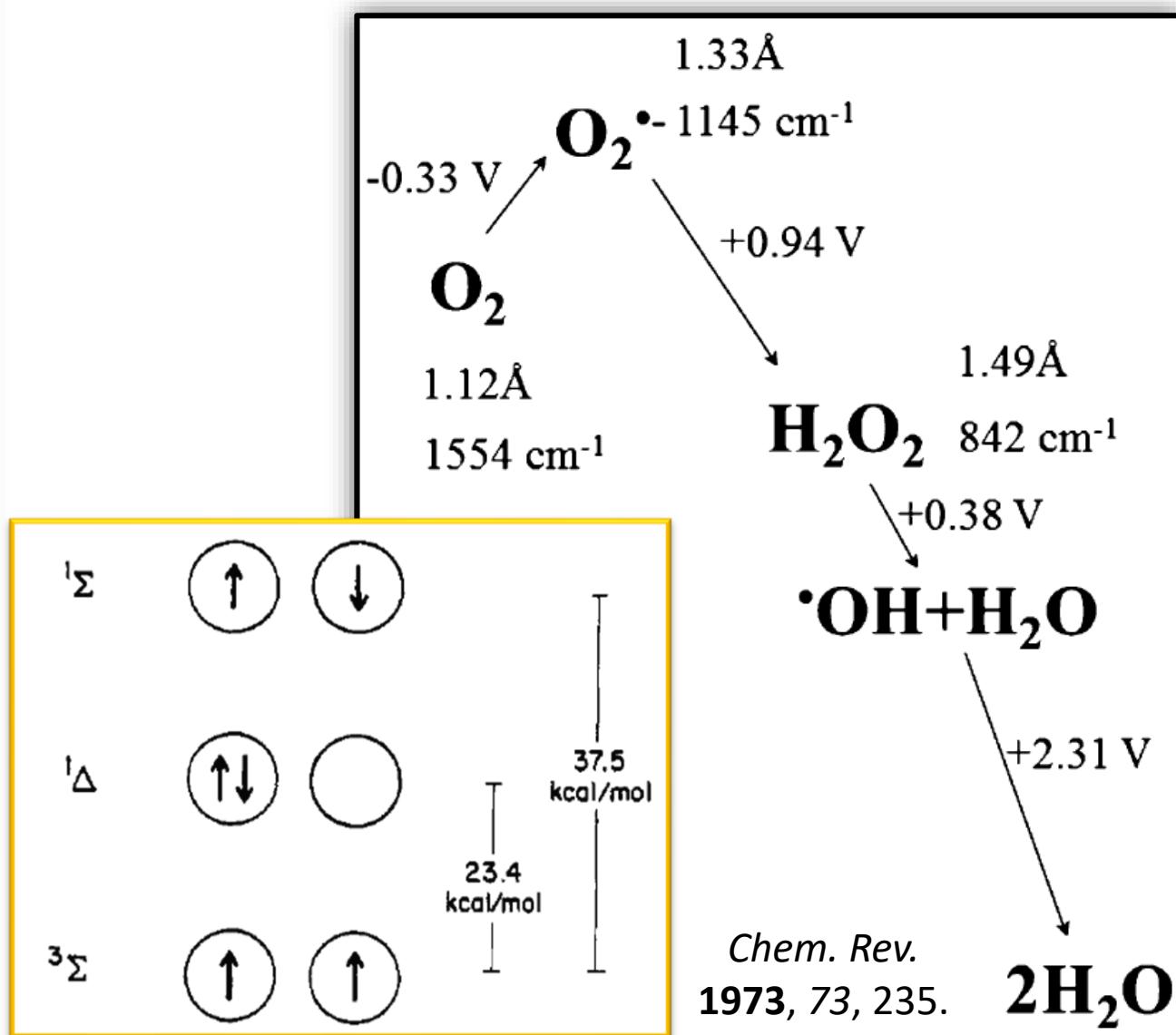
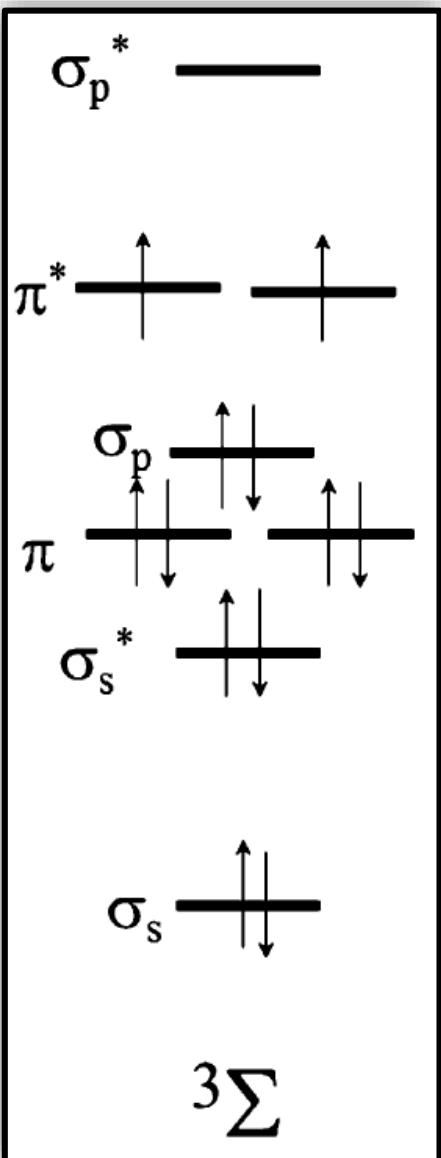
Science 2006, 314, 821

## Methane Monooxygenase



Chem. Rev. 2018, 118, 2554

# The Magic of Dioxygen

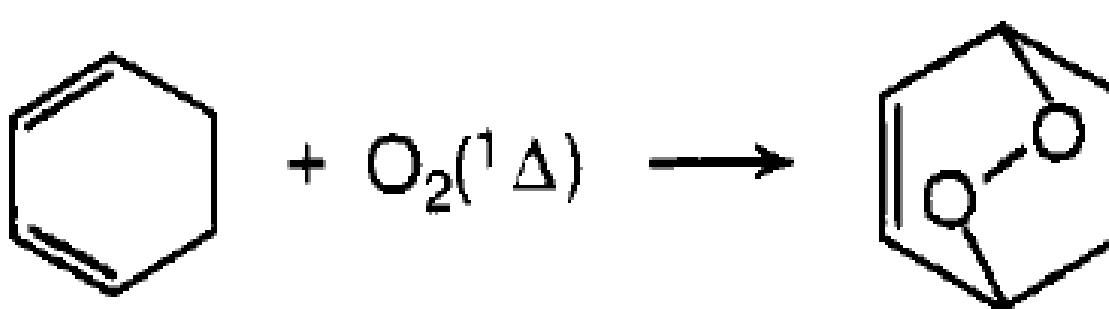


Properties of dioxygen and its reduced species superoxide ( $O_2^{\bullet-}$ ),  $H_2O_2$ , hydroxyl radical ( $\cdot OH$ ), and water. Redox potentials (V) are reported against the NHE (pH 7.25)

# The Magic of Dioxygen

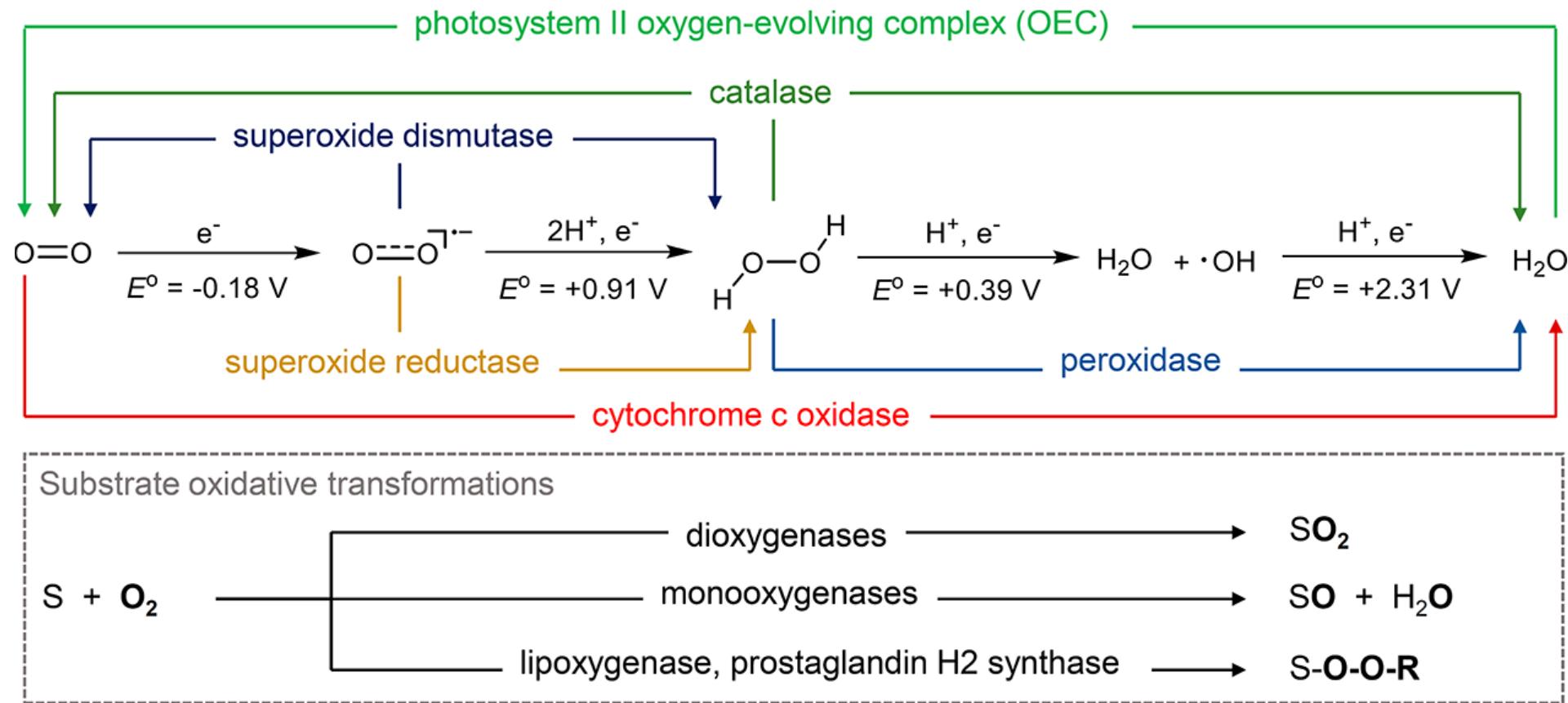
TABLE I. Inorganic Compounds of Dioxygen

	Example compd	O-O, $\text{\AA}^a$	Bond energy, <sup>b</sup> kcal/mol
$\text{O}_2^+$	$\text{O}_2\text{PtF}_6$	1.12	
$\text{O}_2$		1.21	118
$\text{O}_2^-$ (superoxide)	$\text{KO}_2$	1.28	
$\text{O}_2^{2-}$ (peroxide)	$\text{H}_2\text{O}_2$	1.49	35



How do you detect singlet oxygen?

# The Magic of Dioxygen



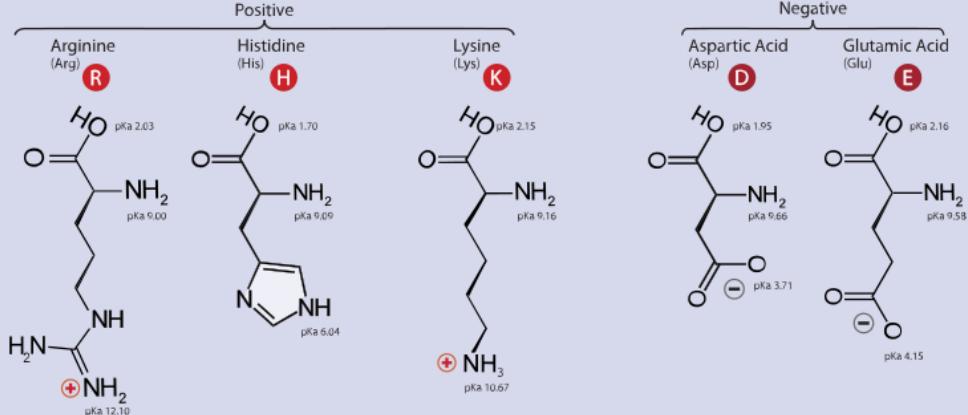
*"The dark side of molecular oxygen encompasses deleterious reactions of species derived from  $O_2$  that can lead to damage of cellular components. These reactive oxygen species (ROS) have historically been perceived almost exclusively as agents of the dark side, but it has more recently become clear that they play beneficial roles as well."*

# Ligands

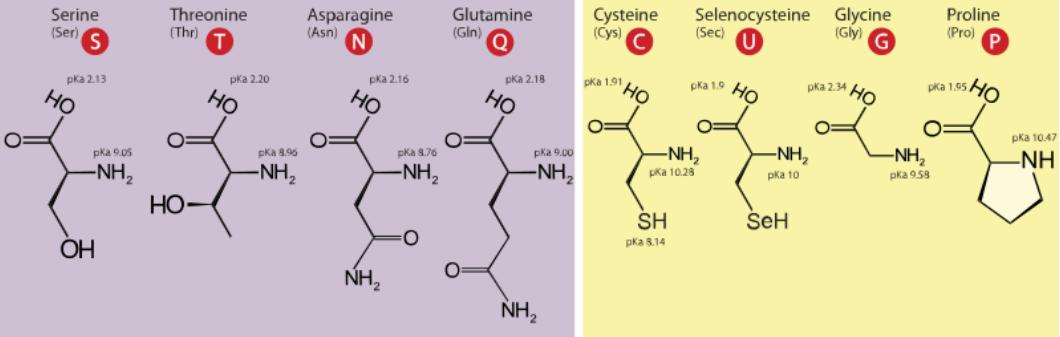
## Twenty-One Amino Acids

⊕ Positive      ⊖ Negative  
• Side chain charge at physiological pH 7.4

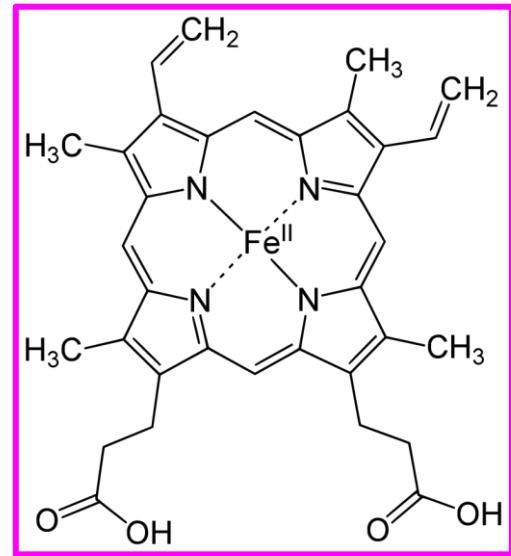
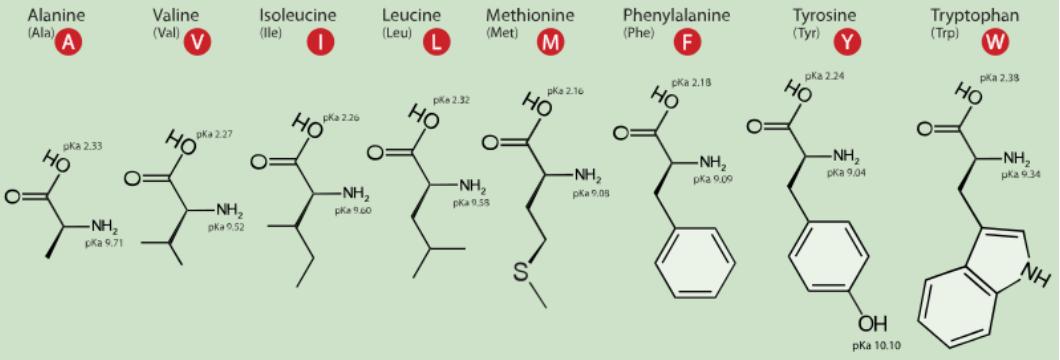
### A. Amino Acids with Electrically Charged Side Chains



### B. Amino Acids with Polar Uncharged Side Chains



### D. Amino Acids with Hydrophobic Side Chain



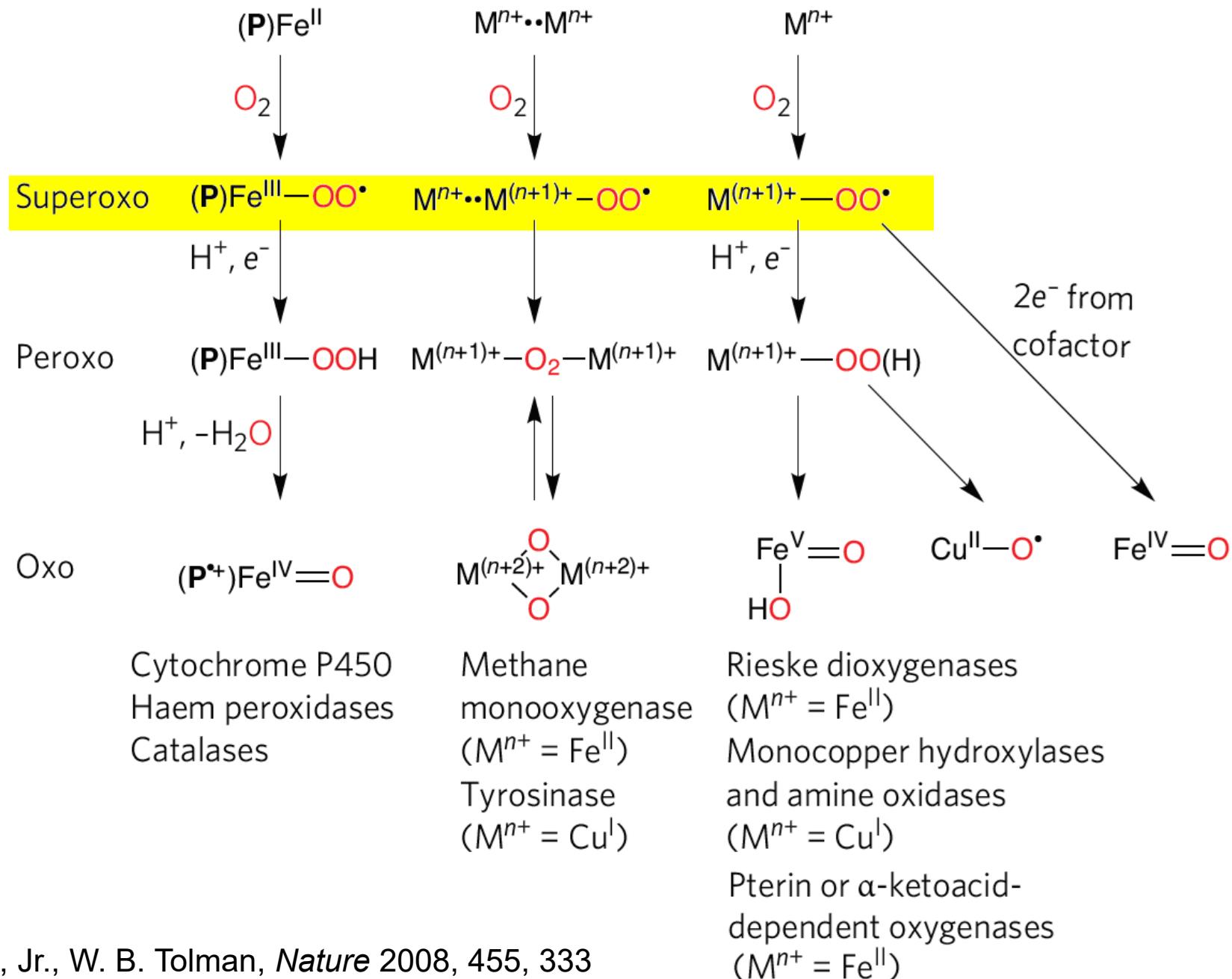
Oxygen based ( $\text{O}_2^{\bullet}$ ,  $\text{O}_2^{2-}$  &  $\text{O}^{2-}$ )

$\text{H}_2\text{O}$ ,  $\text{OH}^-$

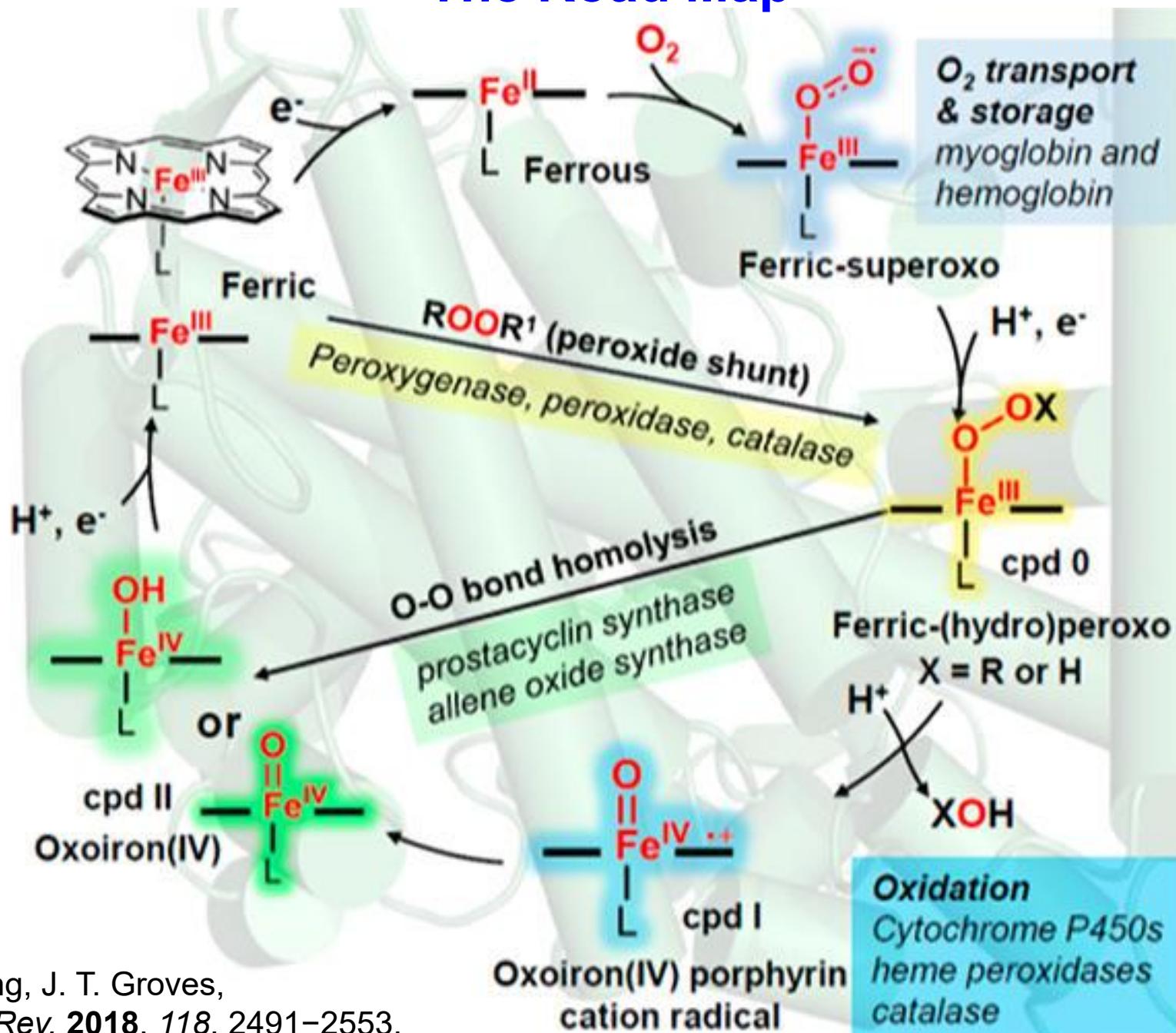
$\text{HCO}_3^-$ ,  $\text{CO}_3^{2-}$

$\text{S}^{2-}$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{NO}$ ,  $\text{CO}$ ,  $\text{CH}_3^-$

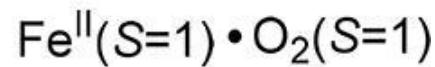
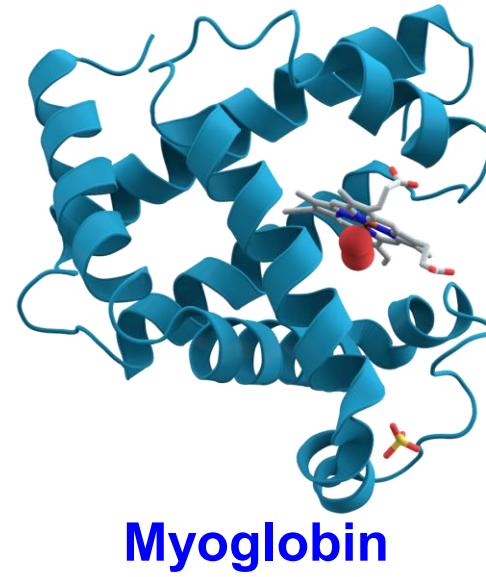
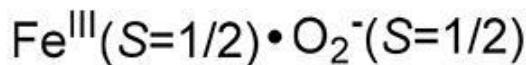
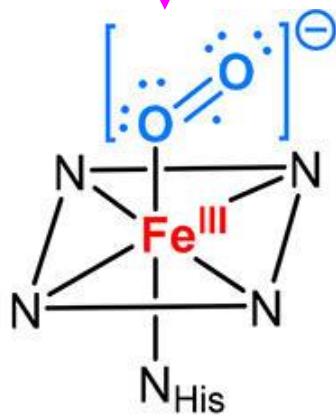
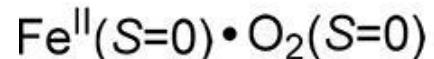
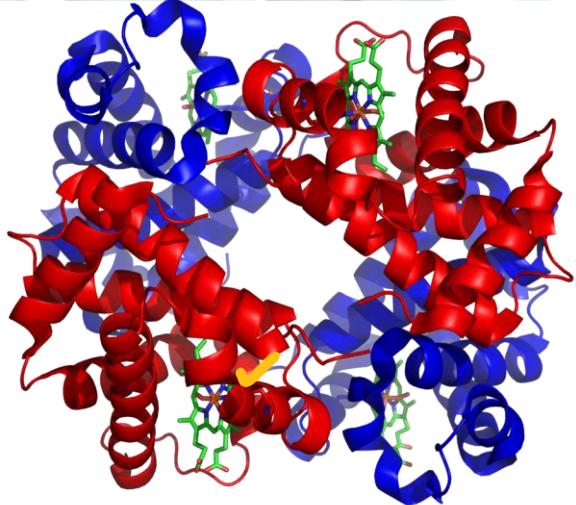
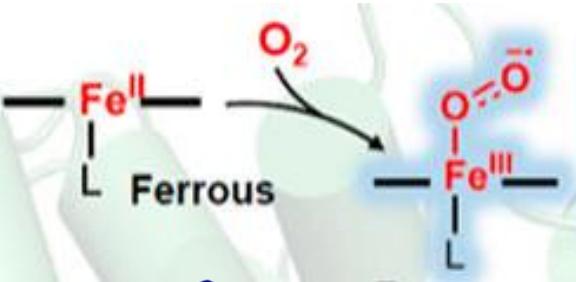
# Metallo-oxygenase mechanisms



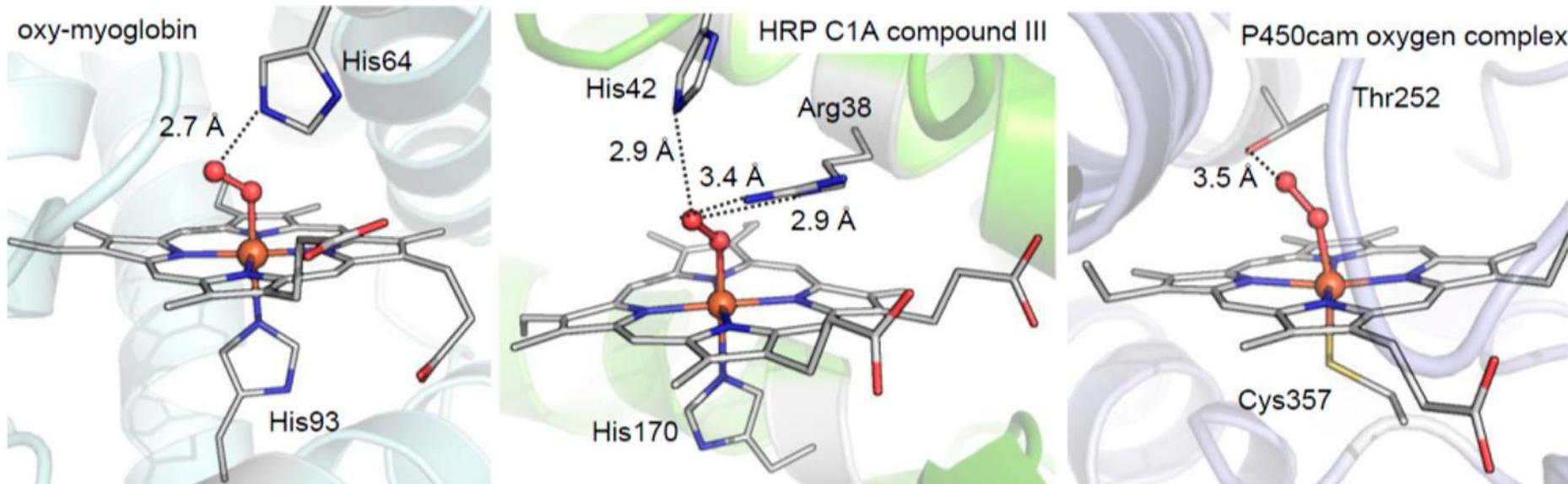
# The Road Map



# Myo/Hemo-globin – Oxygen transporter



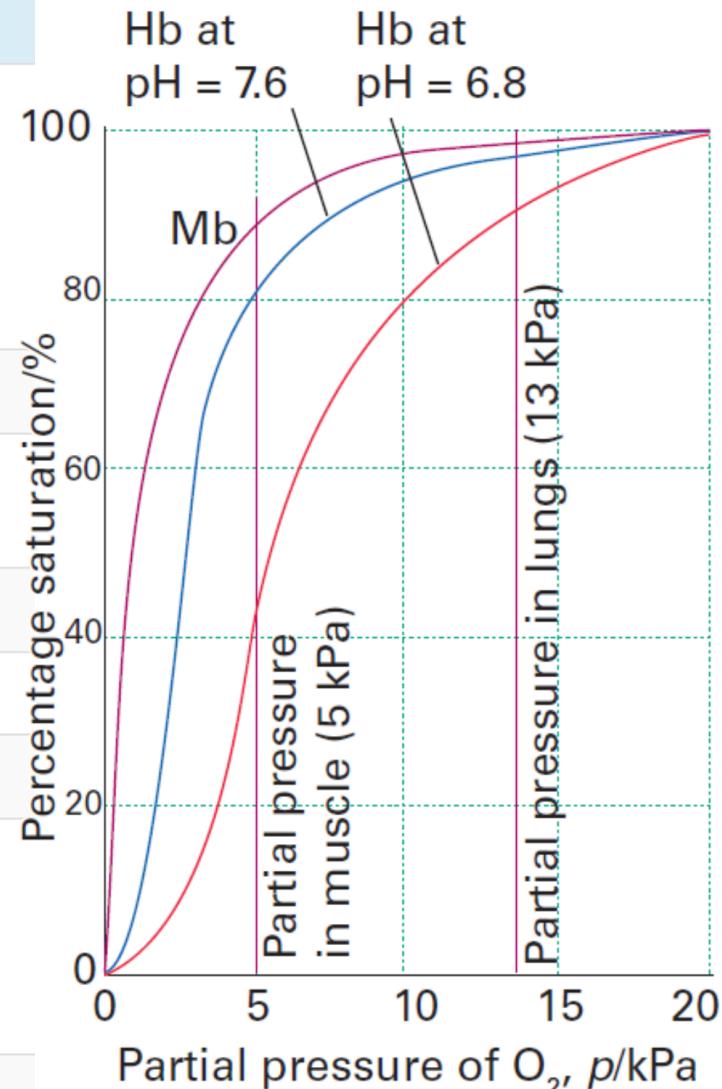
# Myo/Hemo-globin – Oxygen transporter



entry	Fe–O (Å)	O–O (Å)	Fe–O–O (°)	Resolution (Å)	PDB	Ref
Sperm whale myoglobin	1.81(1)	1.24	122(1)	1.0	1A6M	52
Sperm whale myoglobin	1.83(6)	1.22(6)	115(5)	1.6	1MBO	46
Human hemoglobin <sup>a</sup>	1.87(13)	1.24(2)	159(12)	2.1	1HHO	47
P450cam (CYP101)	1.8	1.25	142	1.9	1DZ8	49
P450cam (CYP101)	1.81	1.27	131	2.1	2A1M	50
P450eryF (CYP107A)	1.81	1.29	128	1.7	1Z8O	51
HRP C1A	1.8	1.3	126	1.6	1H57	48

# Myo/Hemo-globin – Oxygen transporter

BASIS FOR COMPARISON	HEMOGLOBIN	MYOGLOBIN
Number of chains	Haemoglobin has 4 chains of two different types- alpha and beta, delta, gamma, or epsilon (depending on the type of hemoglobin).	It contains single polypeptide chains.
Type of structure	A tetramer.	A monomer.
Binds	Binds CO <sub>2</sub> , CO, NO, O <sub>2</sub> and H <sup>+</sup> .	Binds to O <sub>2</sub> , tightly and firmly.
Their presence	Systemically all over the body.	In muscles cells.
Types of curve	Sigmoid binding curve.	Hyperbolic curve.
Also known as	Hb.	Mb.
Role	Haemoglobin is transported along with blood to whole body and carry oxygen.	Myoglobin supplies oxygen to muscles only, which is helpful at the starving time of oxygen.
Concentration in blood	High in RBC.	Low.

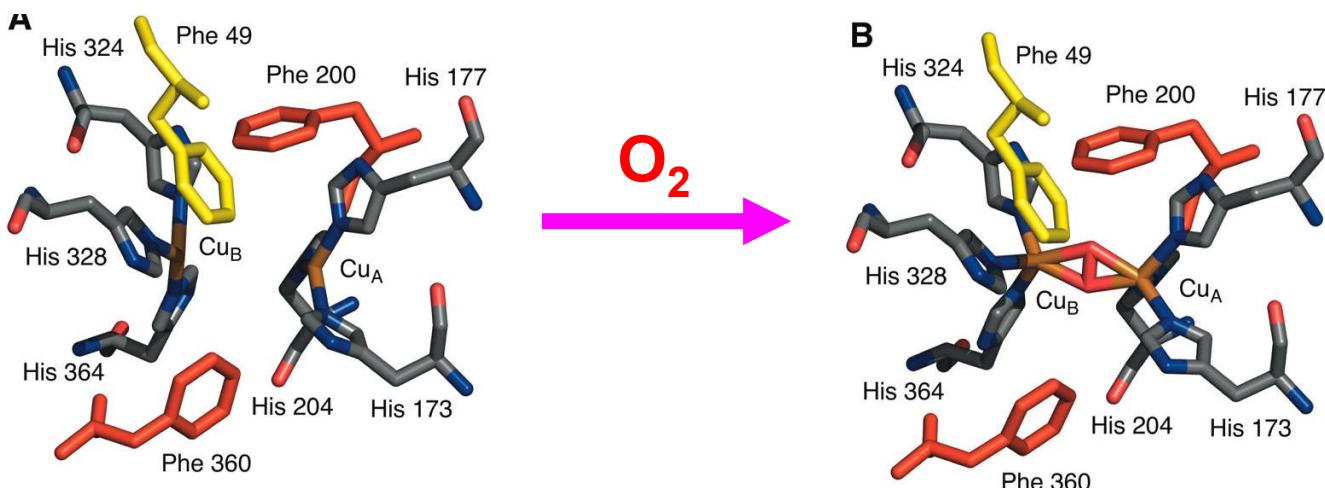


# Why Horseshoe crab blood is blue?



Used for the detection of bacterial endotoxins in medical applications

1 L 11.5 lakhs



Deoxy-Hc (A) and oxy-Hc (B) from *Li. polyphemus* shows a large geometric change at the active site upon oxygen binding (the Cu•••Cu distance decreases by 1.0 Å)

# Why Horseshoe crab blood is blue?

BLOOD COLOR	ANIMAL	WHY THIS COLOR?
Red	Humans	Hemoglobin contains iron that binds to oxygen, making blood appear red.
Blue	Horseshoe crab, octopus, lobster, spider	Hemocyanin contains copper that binds to oxygen, making the blood appear blue.
Green	Earthworm, leeches	Chlorocruorin contains iron that binds to oxygen, making the blood appear green.
Green	Skink (type of lizard), marine worms	Recycling of hemoglobin stuck halfway; biliverdin (green) accumulates in the body.
Violet	Lamp shells	Hemerythrin contains iron that binds to oxygen, making blood appear violet-pink.
Clear	Ice fish	Blood does not contain a respiratory protein.

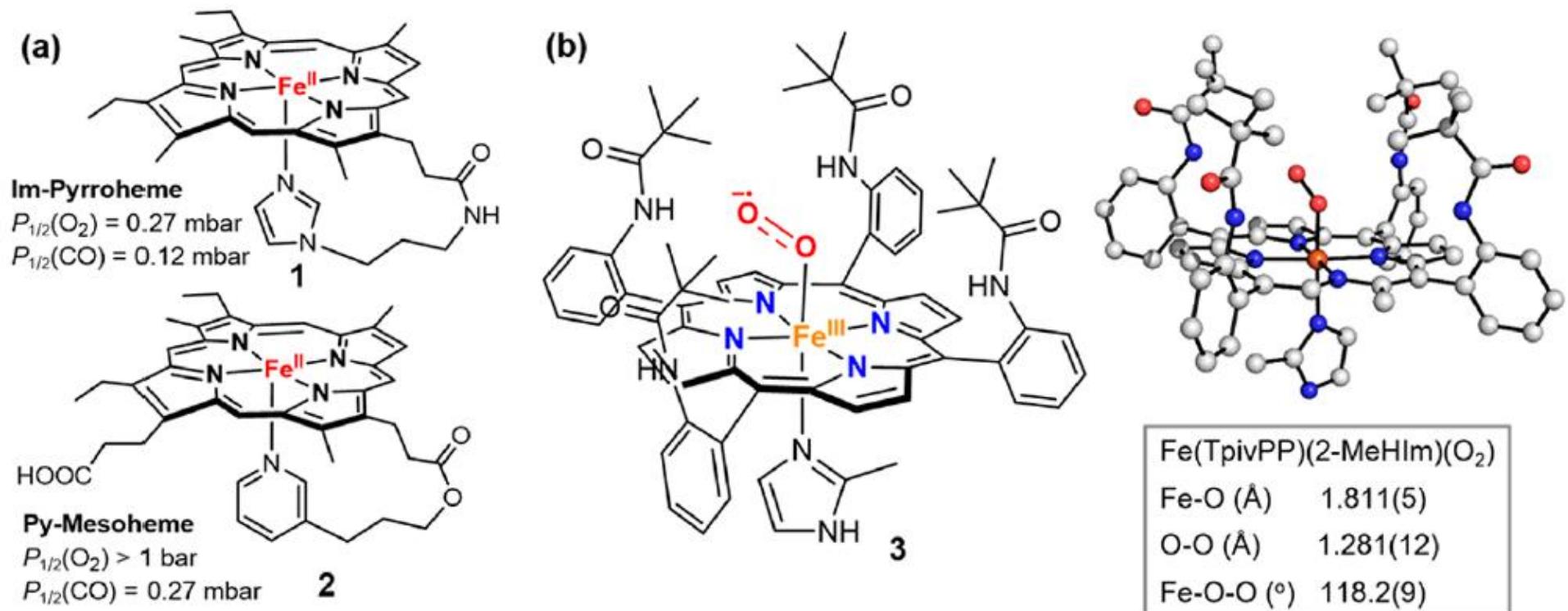
Check this link:

<https://www.acs.org/content/dam/acsorg/education/resources/highschool/chemmatters/issues/best-of-chemmatters/sample-lesson-plan-the-many-colors-of-blood.pdf>

Metalloenzyme	Metal(s)	Main Function(s)
Cytochrome c oxidase	Fe, Cu	Electron transport in mitochondria (final step in cellular respiration)
Carbonic anhydrase	Zn	Conversion of CO <sub>2</sub> and water to bicarbonate and protons (CO <sub>2</sub> , hydration)
Nitrogenase	Fe, Mo	Nitrogen fixation (conversion of N <sub>2</sub> , to ammonia)
Superoxide dismutase	Cu, Zn or Mn	Dismutation of superoxide radicals (antioxidant defense)
Catalase	Fe	Decomposition of hydrogen peroxide to water and oxygen
Alcohol dehydrogenase	Zn	Oxidation of alcohols to aldehydes/ketones
Xanthine oxidase	Mo, Fe	Oxidation of hypoxanthine to xanthine and xanthine to uric acid
Urease	Ni	Hydrolysis of urea into ammonia and carbon dioxide
Glutathione peroxidase	Se	Reduction of hydrogen peroxide and organic hydroperoxides
DNA polymerase	Mg	DNA synthesis during replication and repair
Pyruvate kinase	K, Mg	Glycolysis-conversion of phosphoenolpyruvate to pyruvate
Laccase	Cu	Oxidation of phenols and similar molecules, often in lignin degradation
Methionine synthase	Co (B <sub>12</sub> )	Transfer of methyl groups (important in methionine biosynthesis)
Hydrogenase	Ni, Fe	Catalysis of hydrogen oxidation or production
Carboxypeptidase	Zn	Proteolytic cleavage of peptide bonds (protein digestion)

These metalloenzymes represent essential catalysts for many biological reactions, including energy metabolism, detoxification, DNA replication, electron transport, and nitrogen fixation.

# Fe<sup>III</sup>-superoxo porphyrin complexes

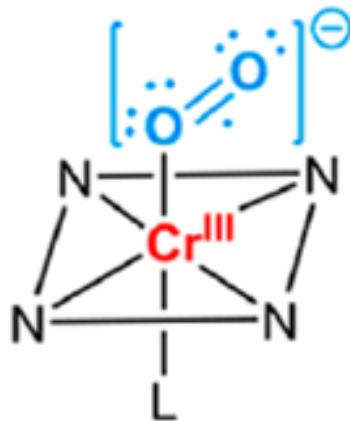


- (a) Structure of Im-pyrroheme and Py-mesoheme and their binding affinities to O<sub>2</sub> & CO.  
(b) Structural parameters of Fe(TpivPP)(2-MeHIm)(O<sub>2</sub>)

# Bonding and electronic properties of various metal-dioxygen porphyrin complexes



$$S_{\text{total}} = 1/2$$



$$S_{\text{total}} = 1$$



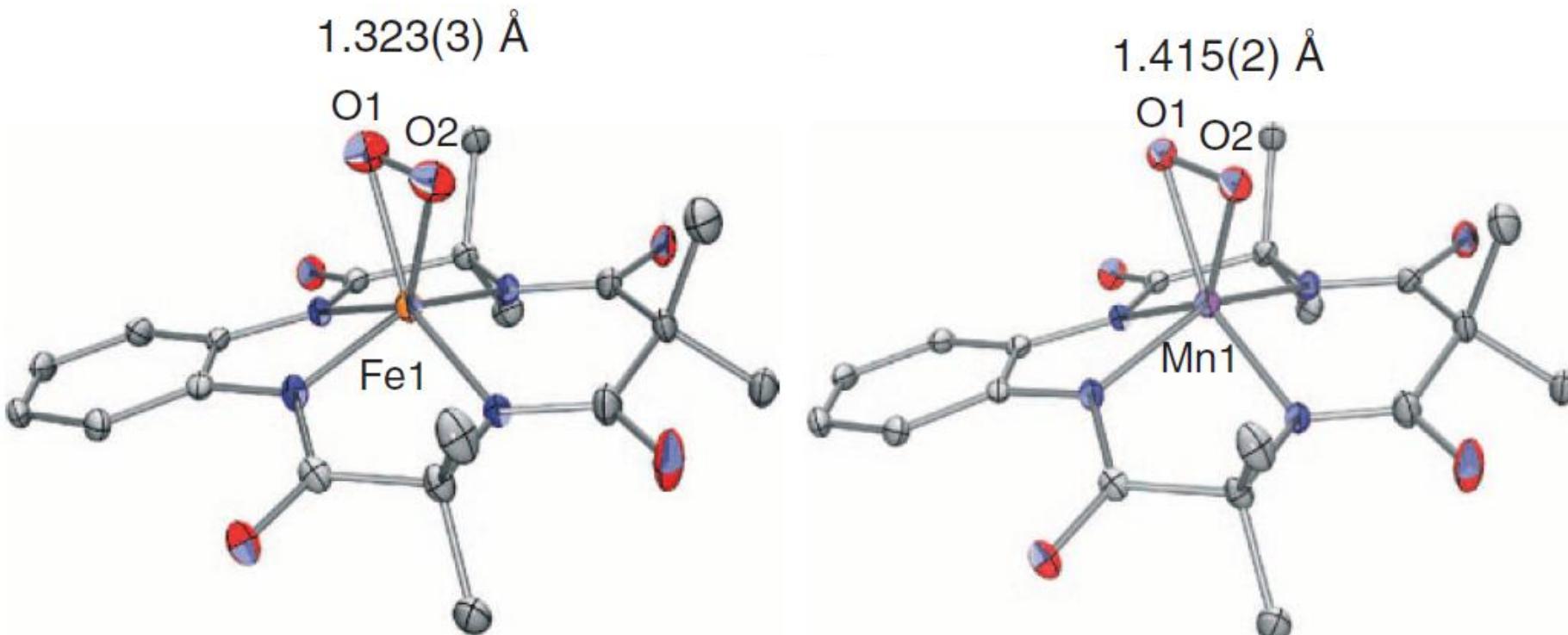
$$S_{\text{total}} = 0$$



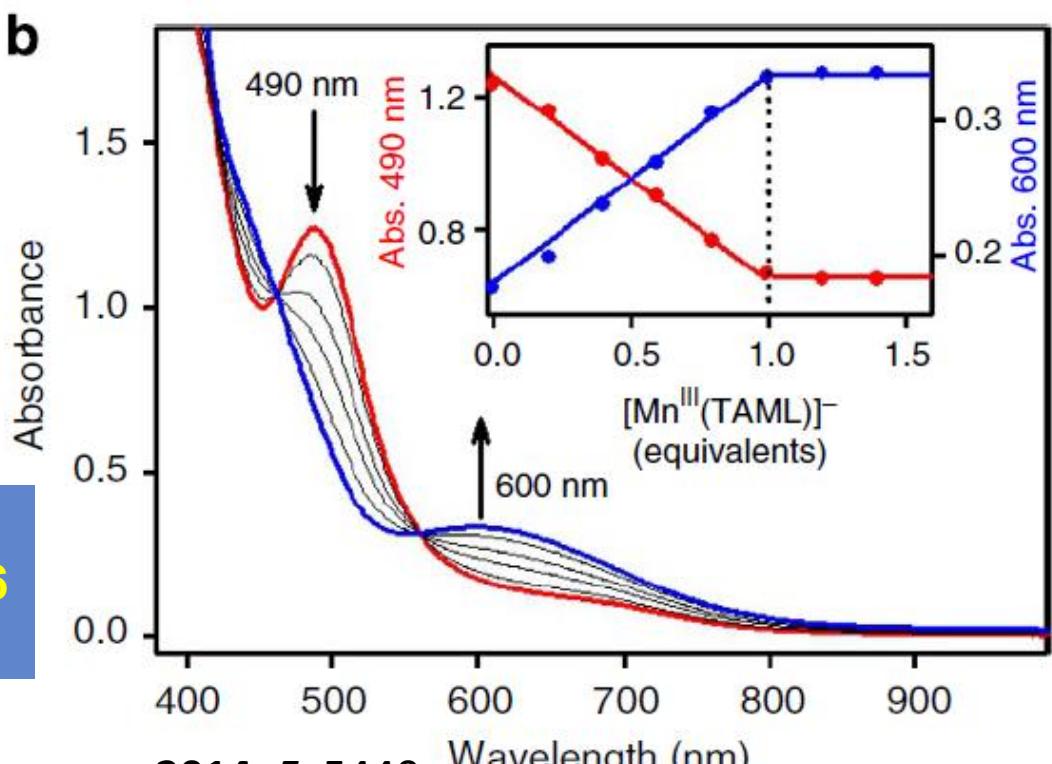
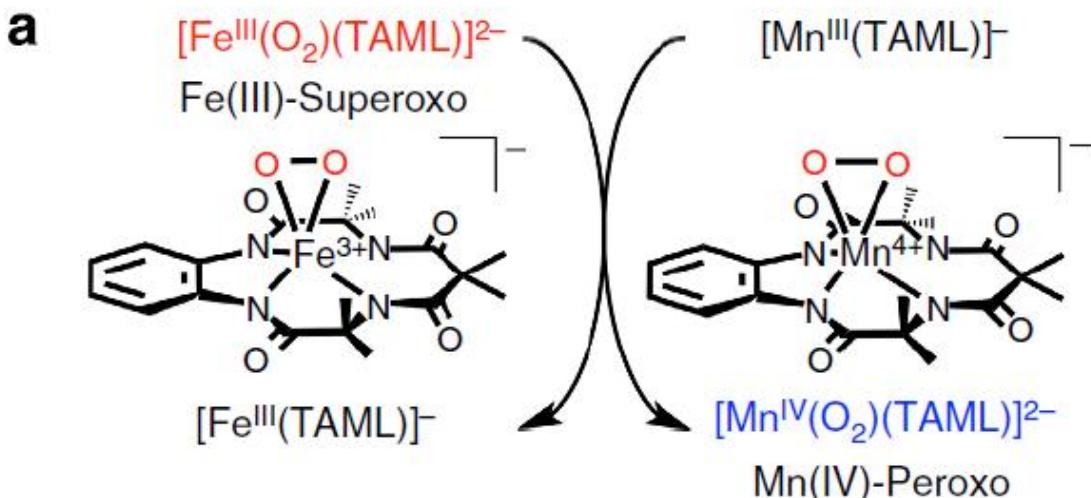
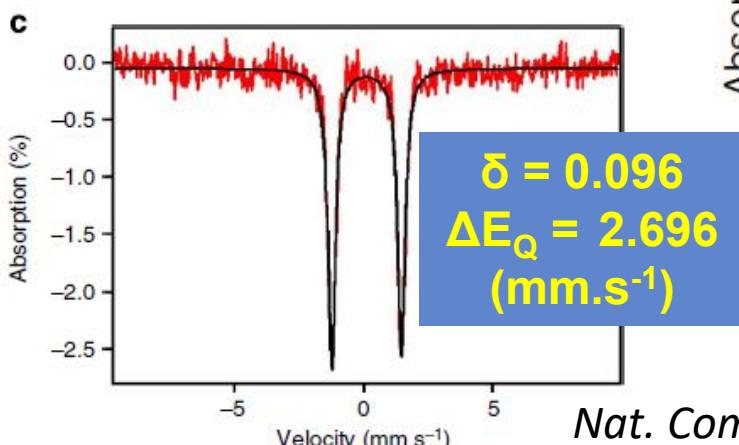
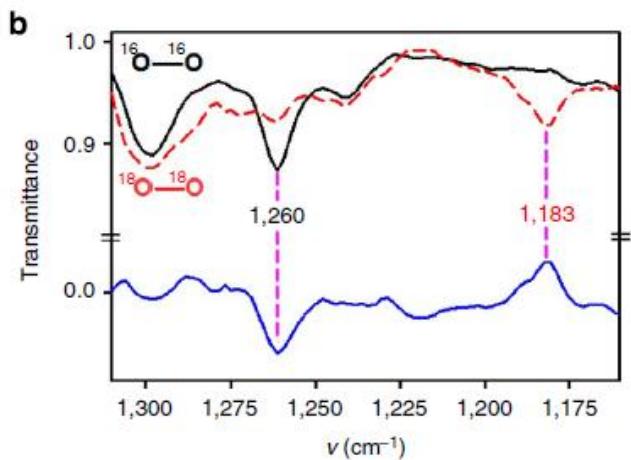
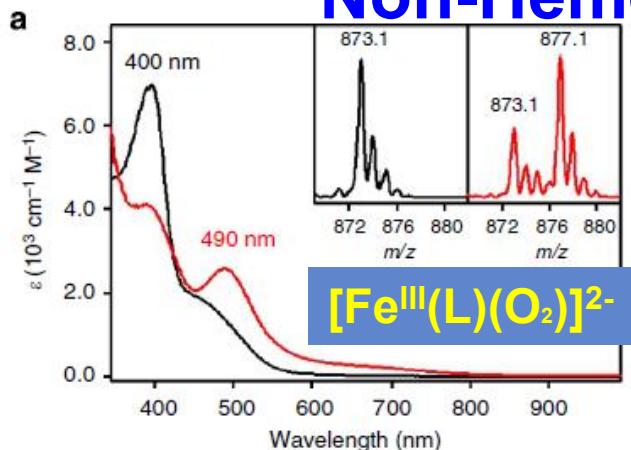
$$S_{\text{total}} = 3/2$$

# Crystallographic and spectroscopic characterization and reactivities of a mononuclear non-haem iron(III)-superoxo complex

Seungwoo Hong<sup>1</sup>, Kyle D. Sutherlin<sup>2</sup>, Jiyoung Park<sup>1</sup>, Eunji Kwon<sup>1</sup>, Maxime A. Siegler<sup>3</sup>, Edward I. Solomon<sup>2,4</sup> & Wonwoo Nam<sup>1</sup>



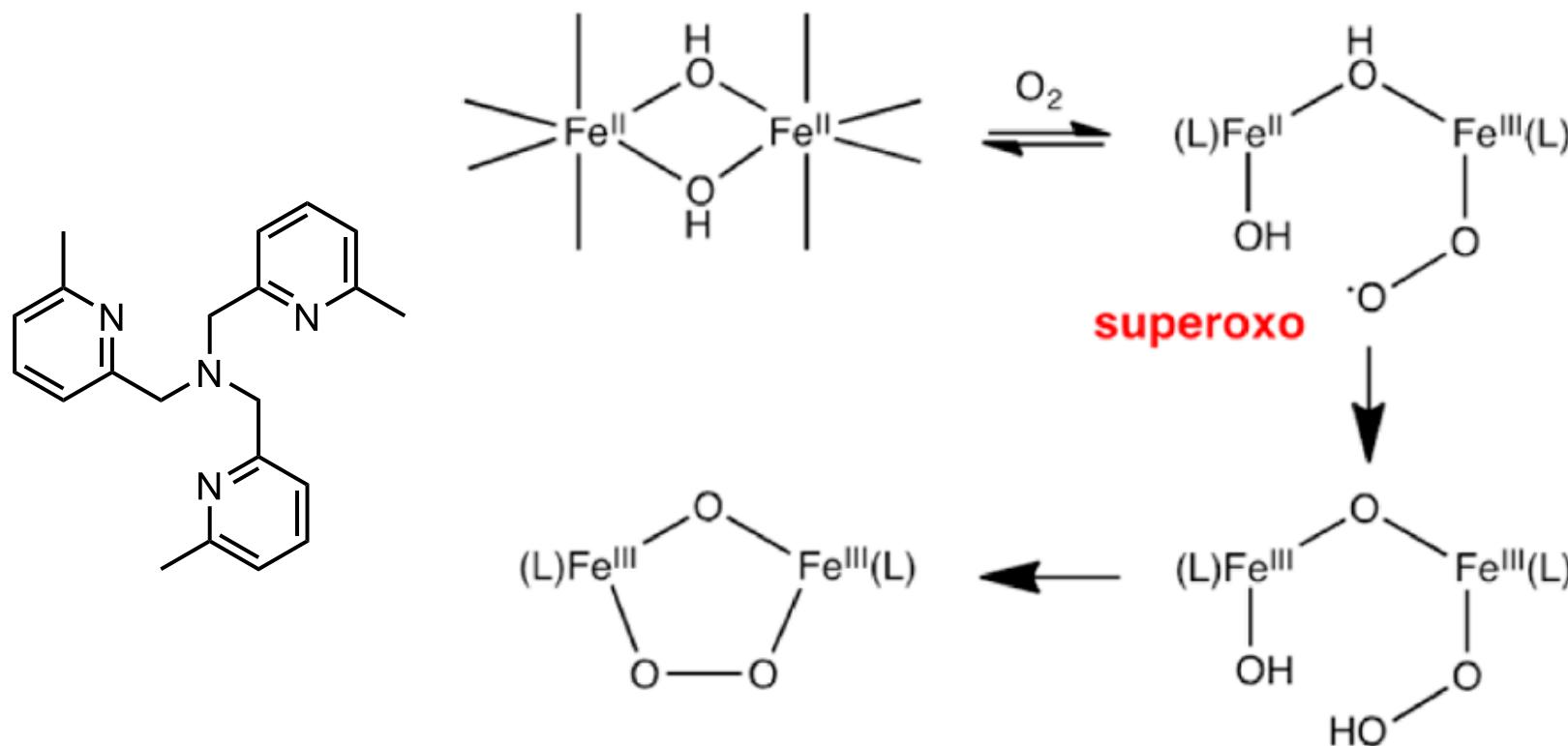
# Non-Heme Fe<sup>III</sup>-superoxo complexes



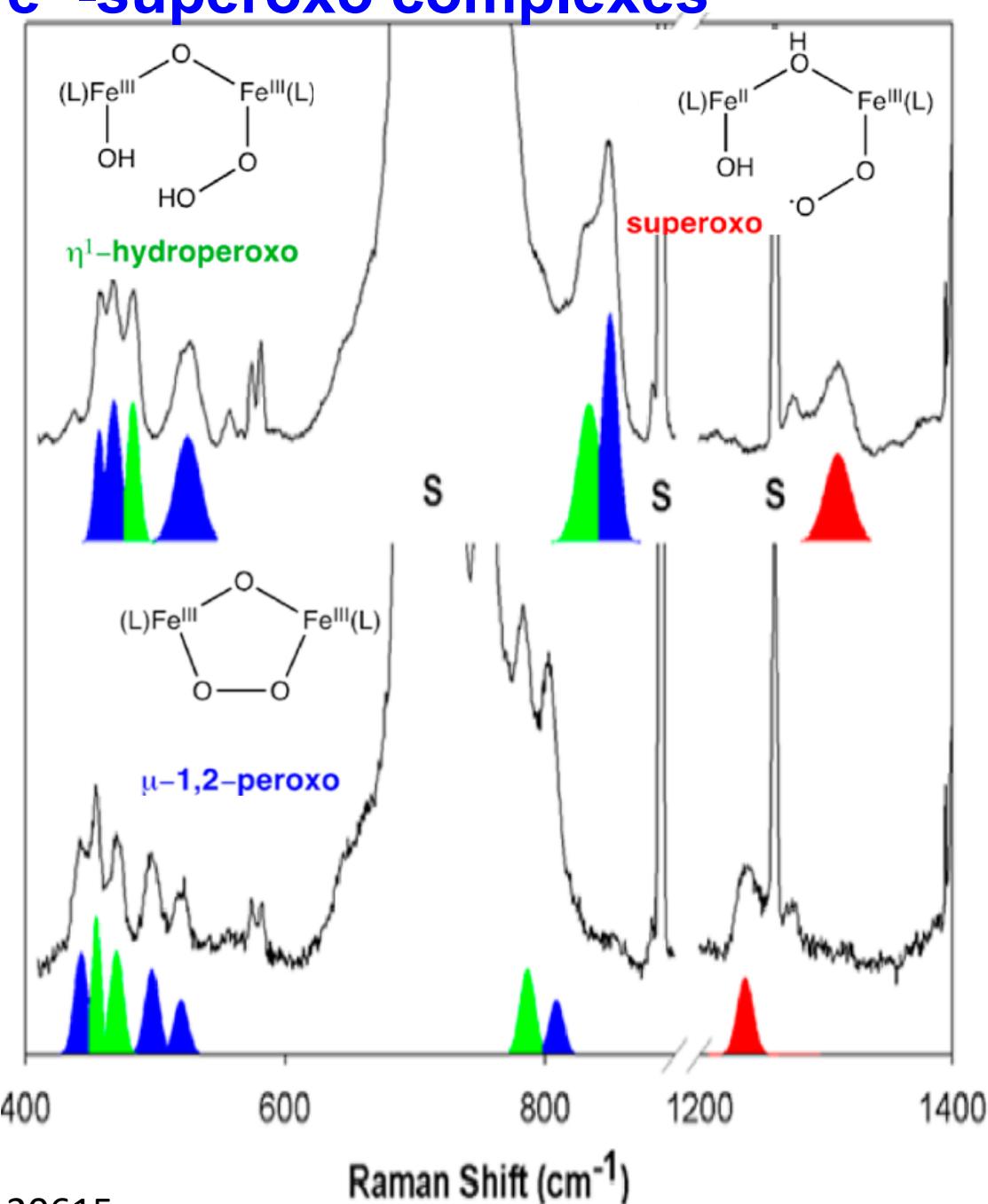
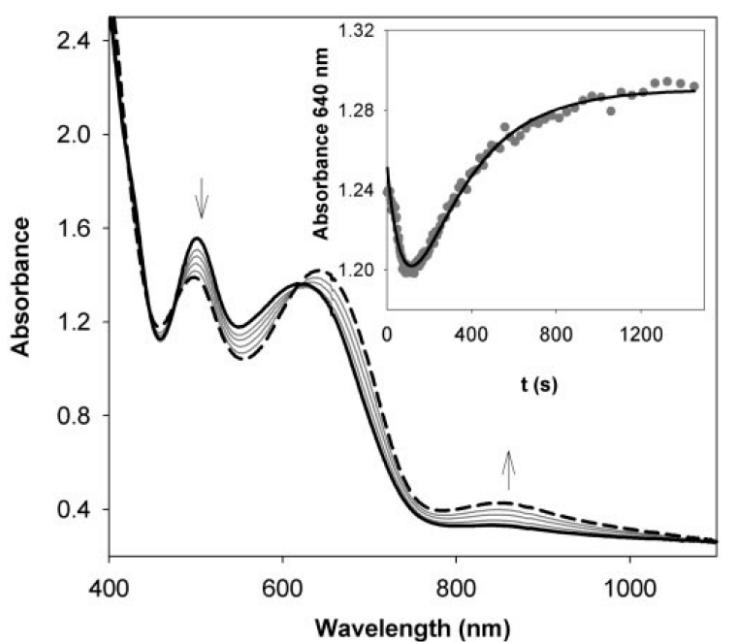
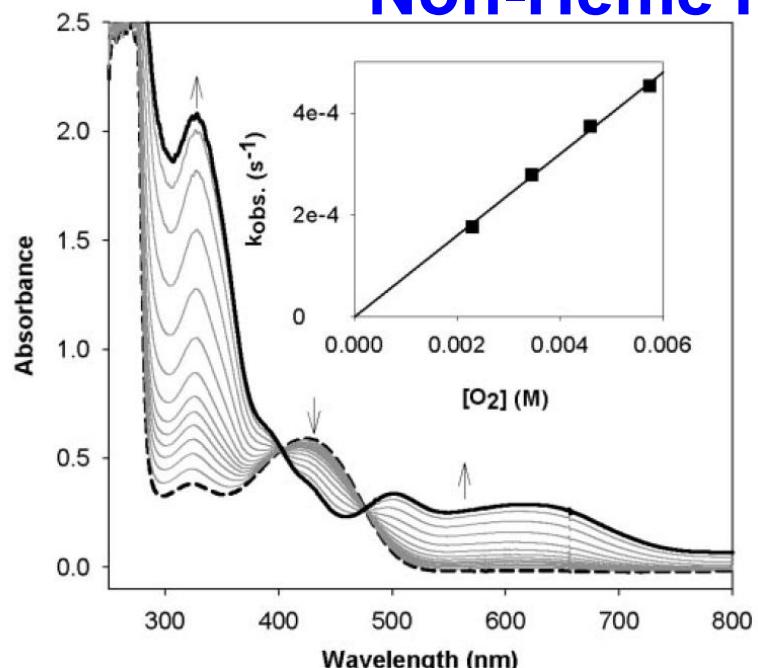
# Intermediates in the oxygenation of a nonheme diiron(II) complex, including the first evidence for a bound superoxo species

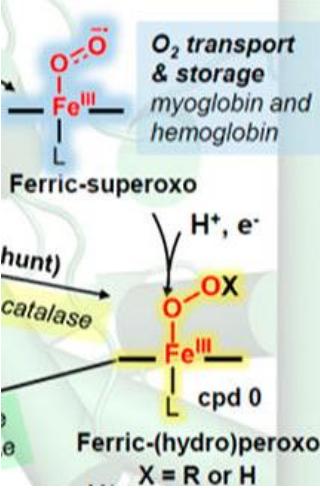
Xiaopeng Shan and Lawrence Que, Jr.\*

Department of Chemistry and Center for Metals in Biocatalysis, University of Minnesota, 207 Pleasant Street Southeast, Minneapolis, MN 55455

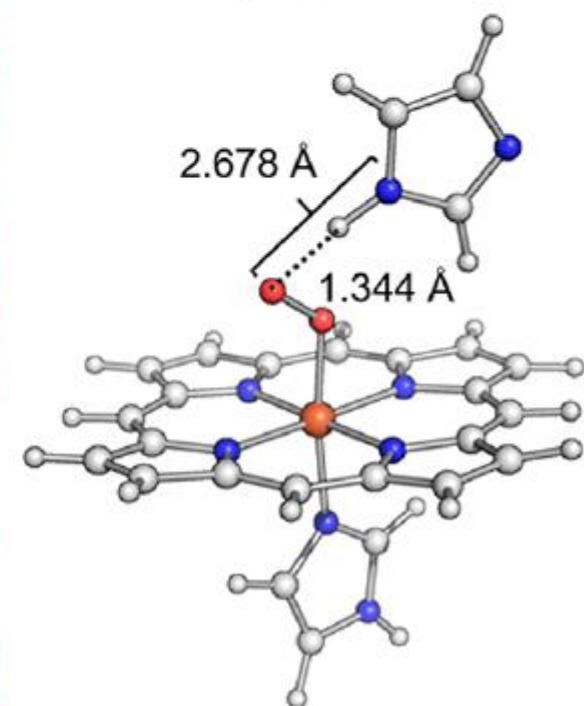
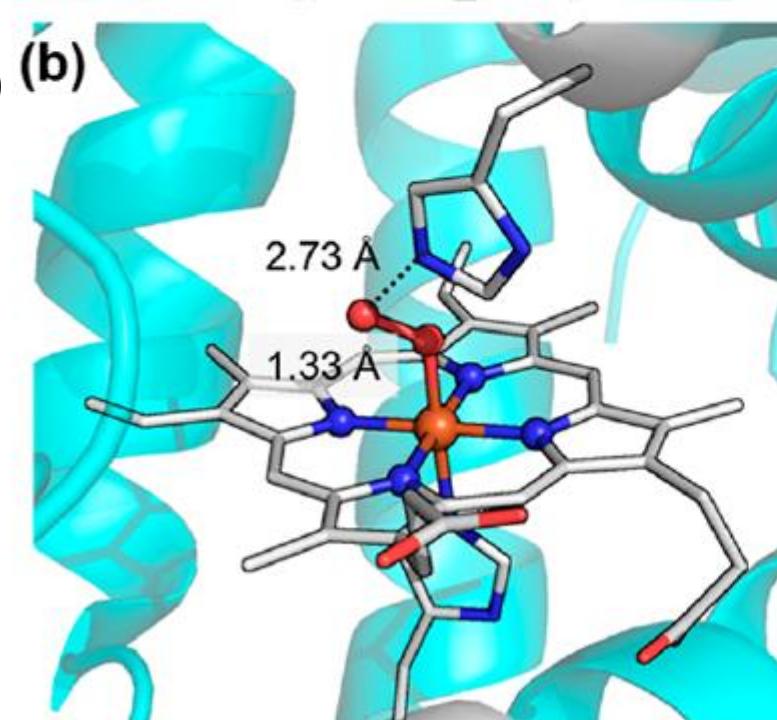
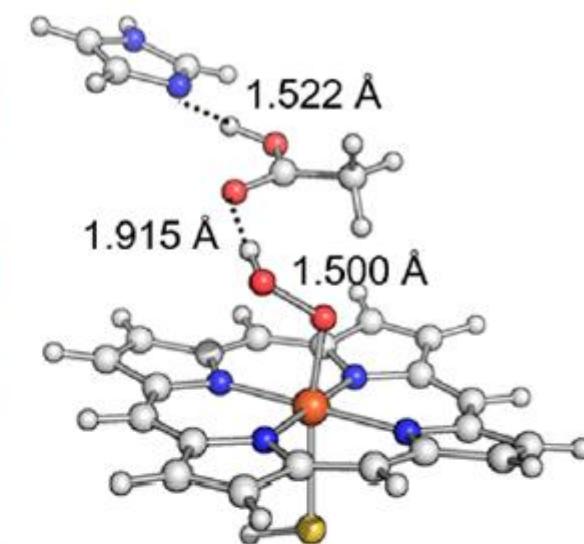
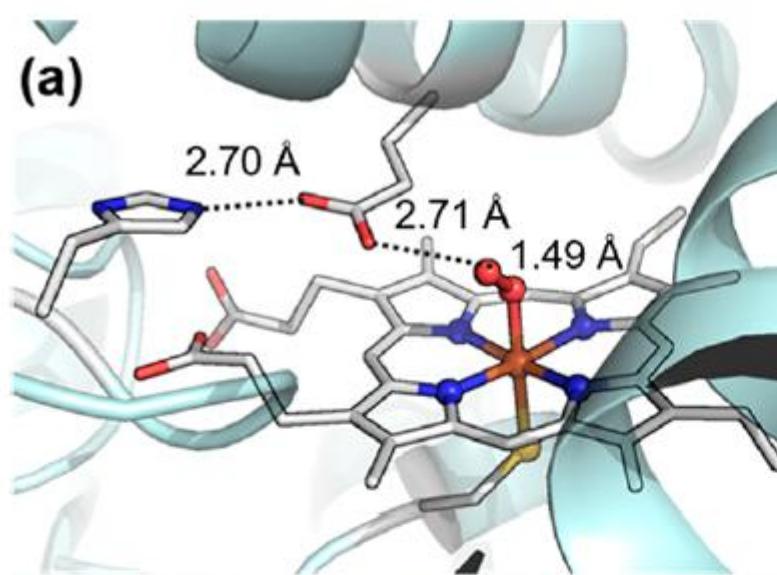


# Non-Heme Fe<sup>III</sup>-superoxo complexes



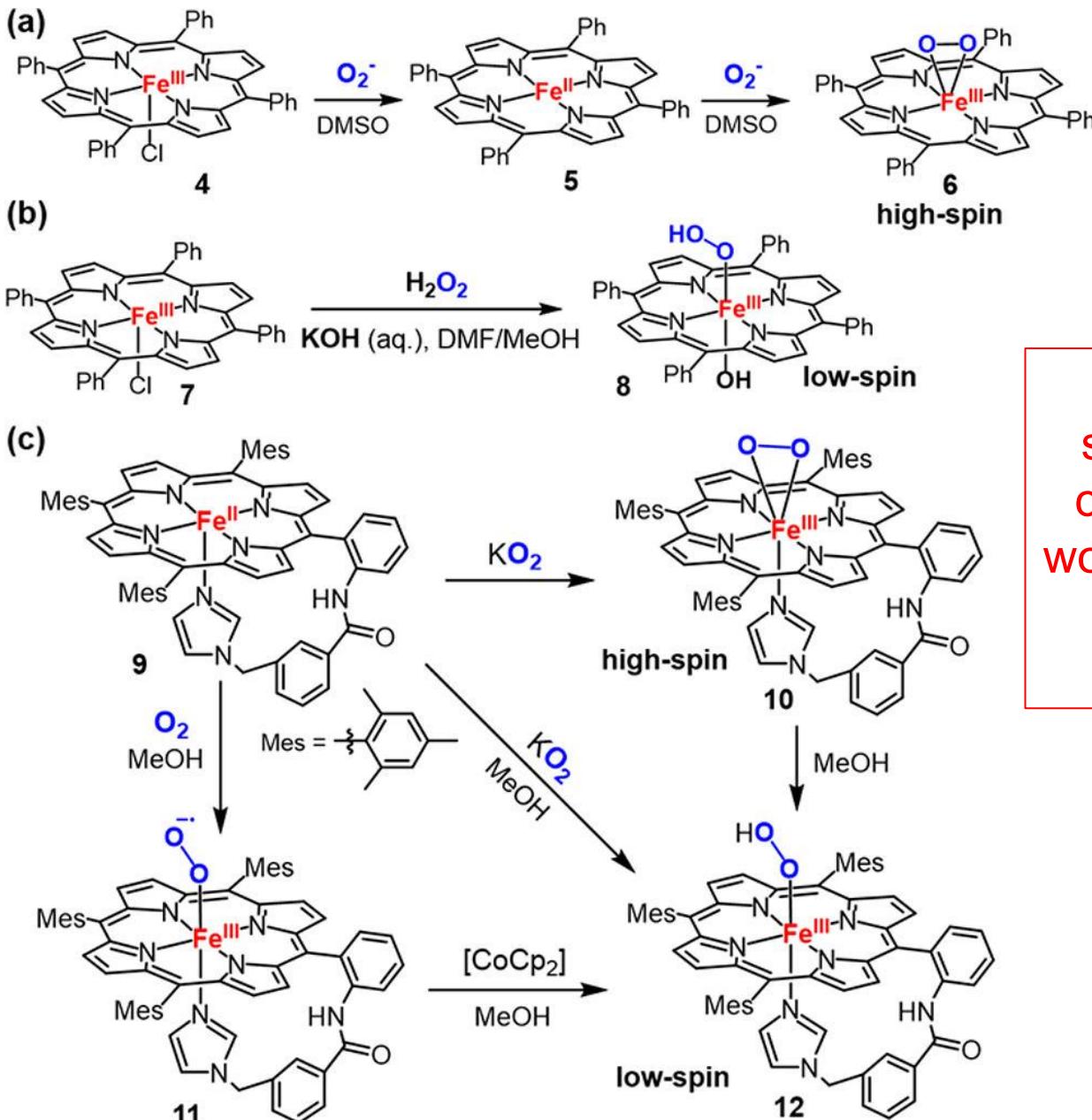


# Ferric-hydroperoxo: Compound-0



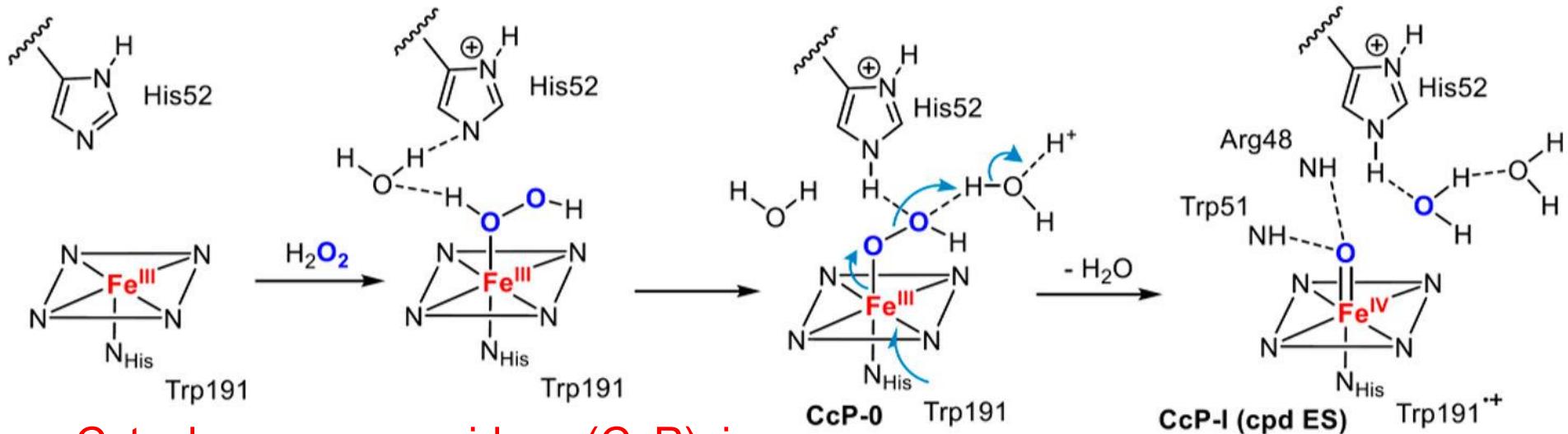
(Left) Crystal structures of (a) CPO-0 (PDB: 2J5M) and (b) the ferric-peroxo intermediate of Mb (PDB: 2Z6T)  
(Right) the corresponding QM/MM optimized structure

# Ferric-hydroperoxy: Compound-0



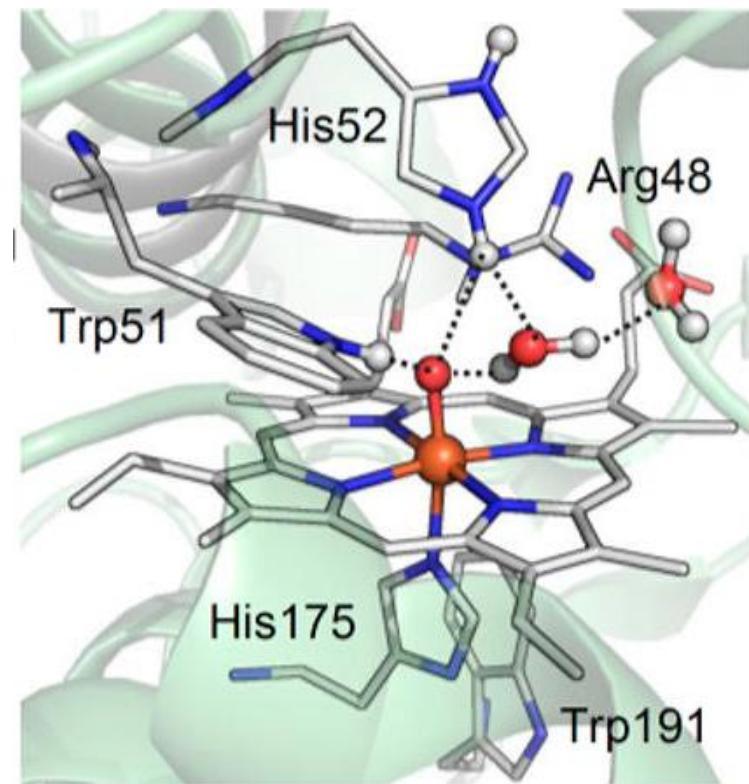
So, what  
spectroscopic  
characteristics  
would you expect  
for these  
molecules?

# High valent Fe-oxo: Compound-I

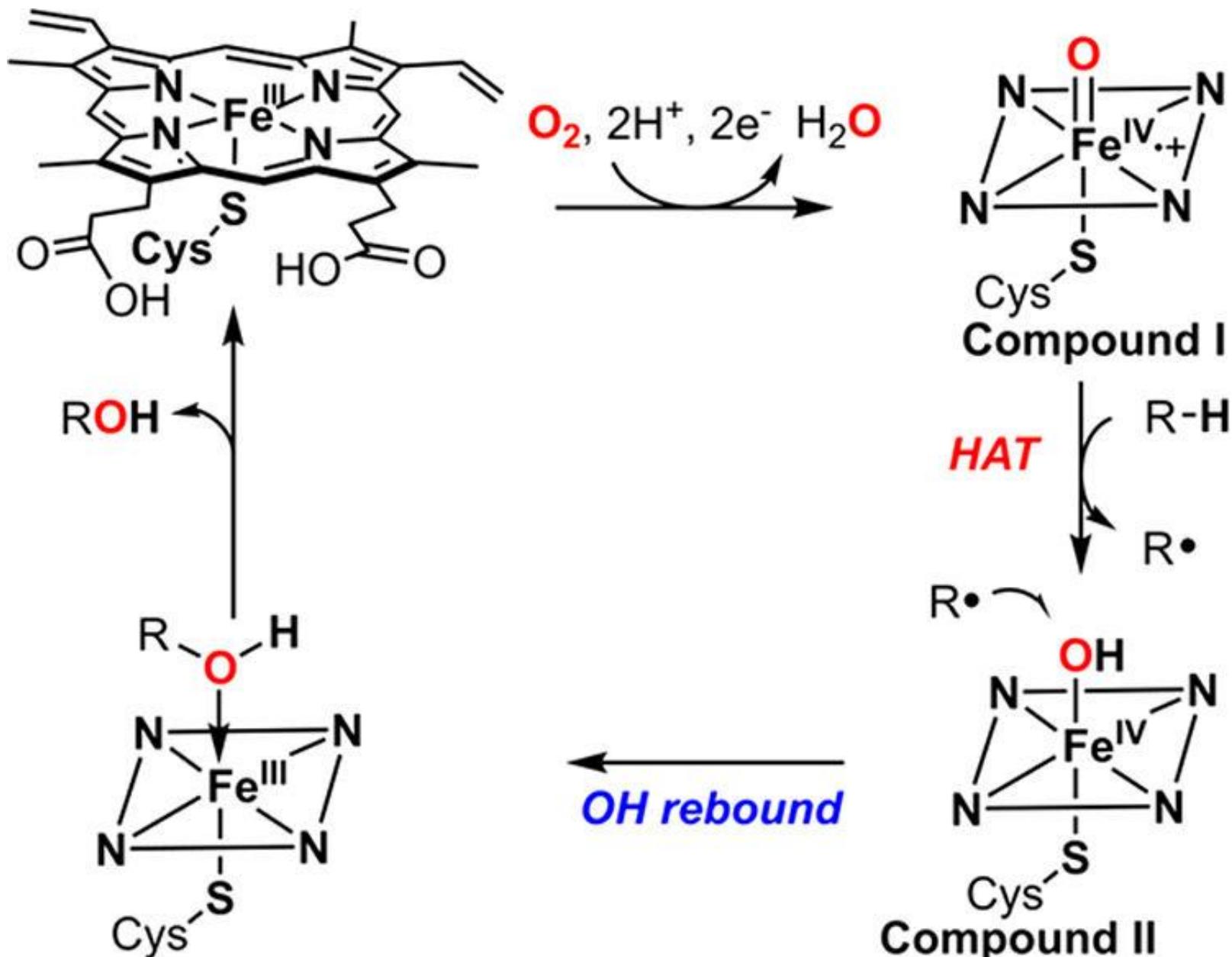


- Cytochrome c peroxidase (CcP), in which a highly conserved histidine/arginine (His52/Arg48) diad in the distal pocket was found to be crucial for Cpd-I generation
- This enzyme uses  $H_2O_2$  as oxidant
- Note the radical is located on to the Trp 191 and not on the porphyrin ring.
- “Push-Pull” mechanism is operative

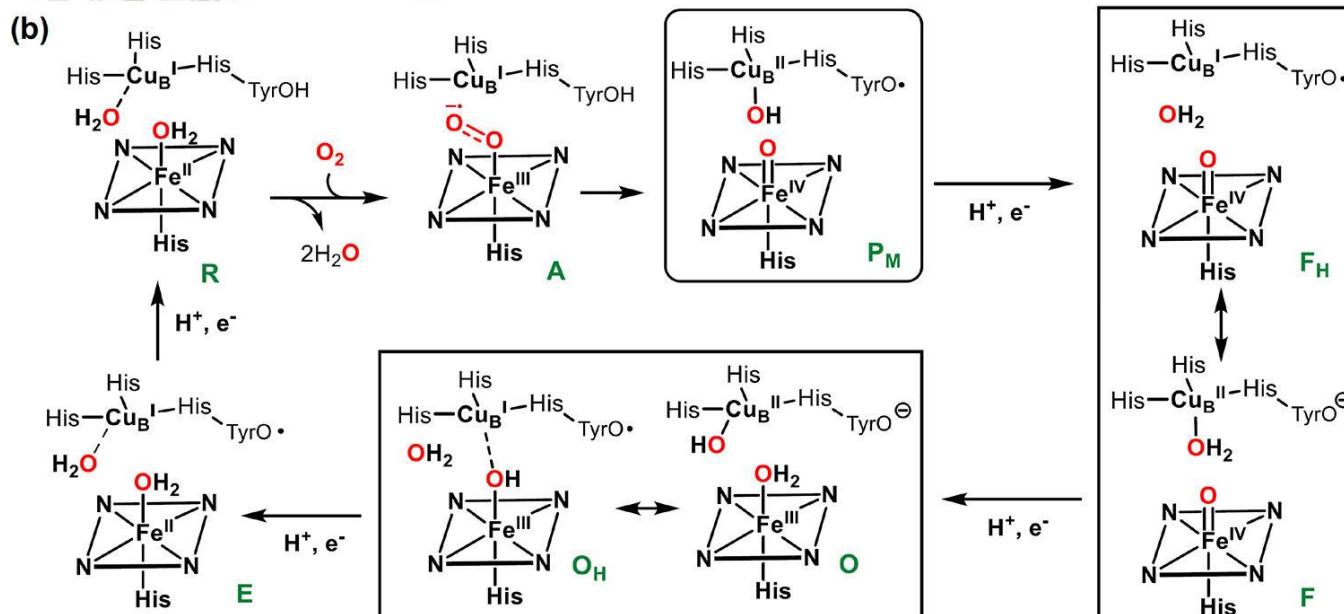
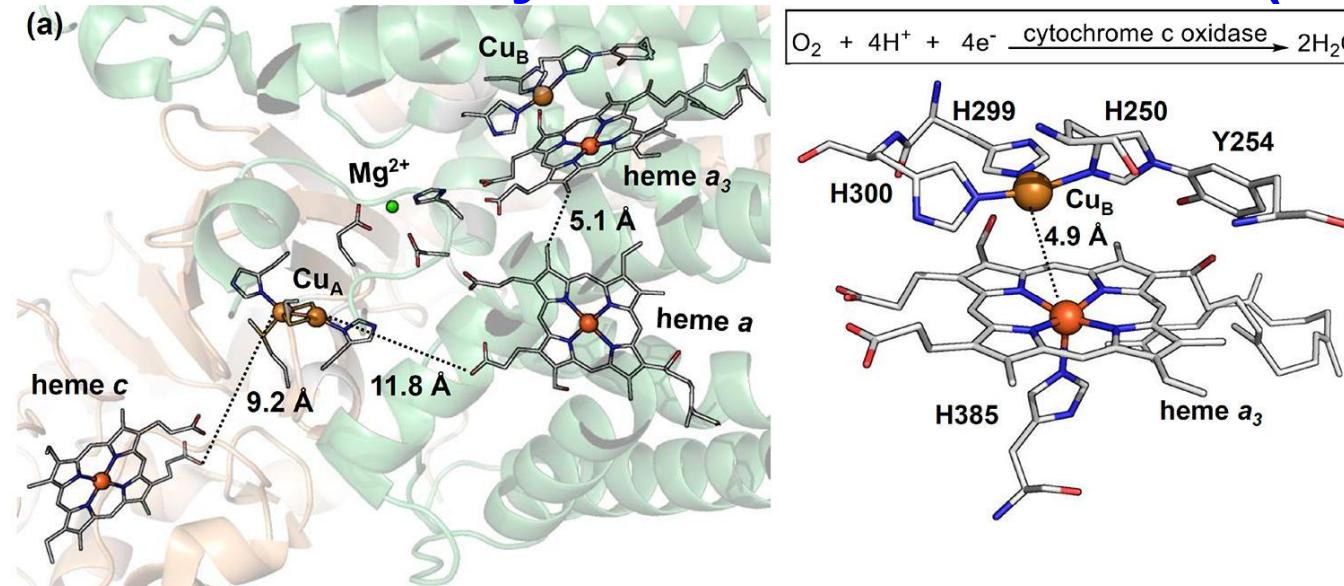
T. H. Yosca et al., Science 342, 825 (2013).



# Compound-I reactivity

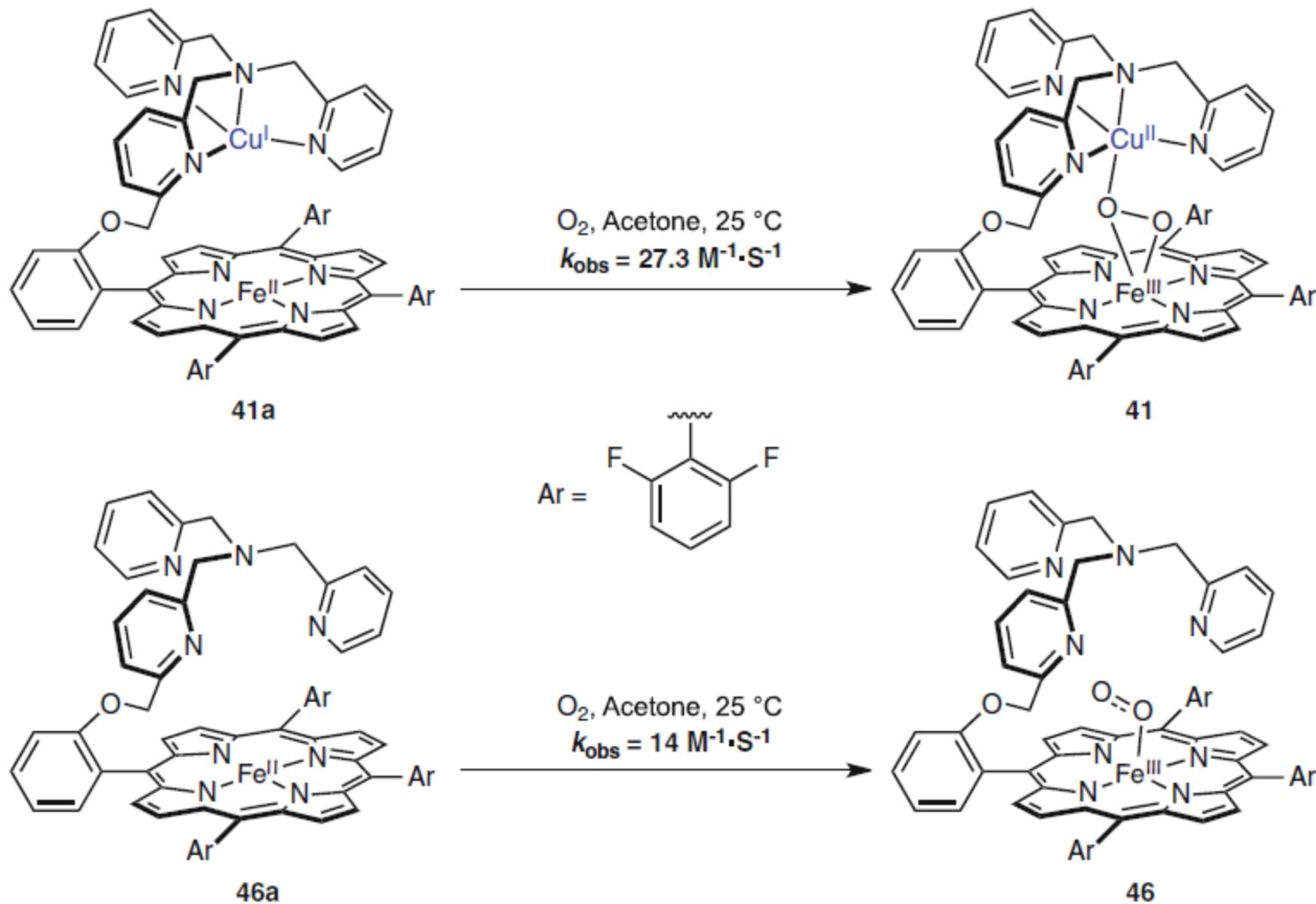


# Special case: Heme/Cu terminal oxidases – cytochrome c oxidases (CcO)

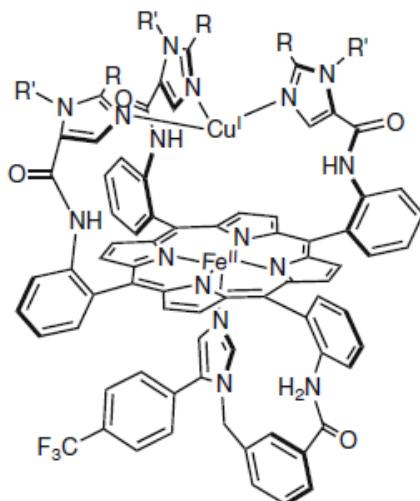


- Fe–Cu separation of around 5 Å
- One of the Histidine is covalently cross-linked to a tyrosine residue
- The Fe(III)–Cu(II) is the resting state (**O**)
- **R** will bind oxygen rapidly ( $\sim 1.4 \times 10^8 M^{-1} s^{-1}$ )
- Formation of putative  $Fe^{III}-O-O-Cu^{II}$  is proposed to involve prior to the formation of **P<sub>M</sub>** state.

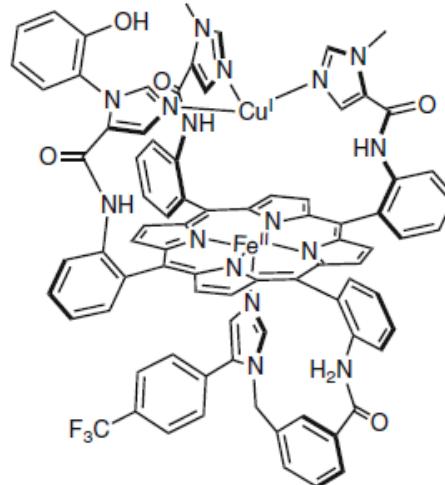
# Models for CcO



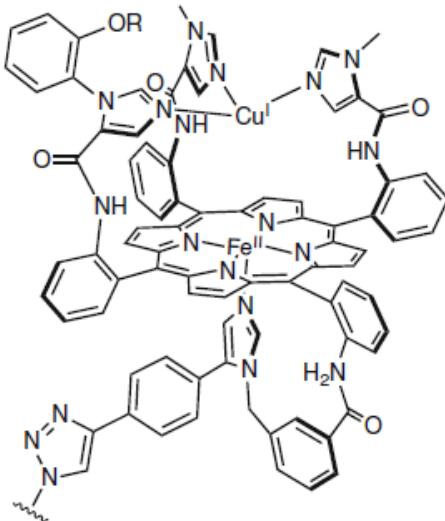
# Models for CcO



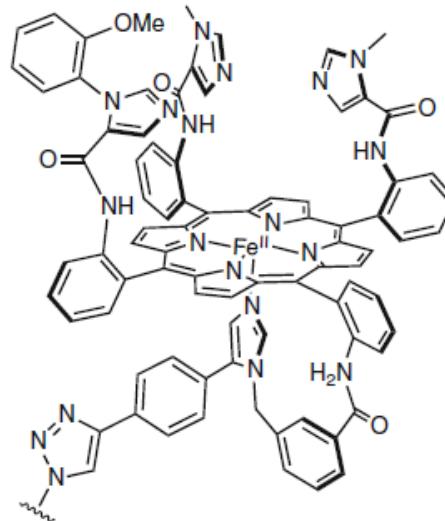
- a: R = H, R' = CH<sub>3</sub>
- b: R = (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, R' = H
- c: R = (CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, R' = CH<sub>3</sub>



48

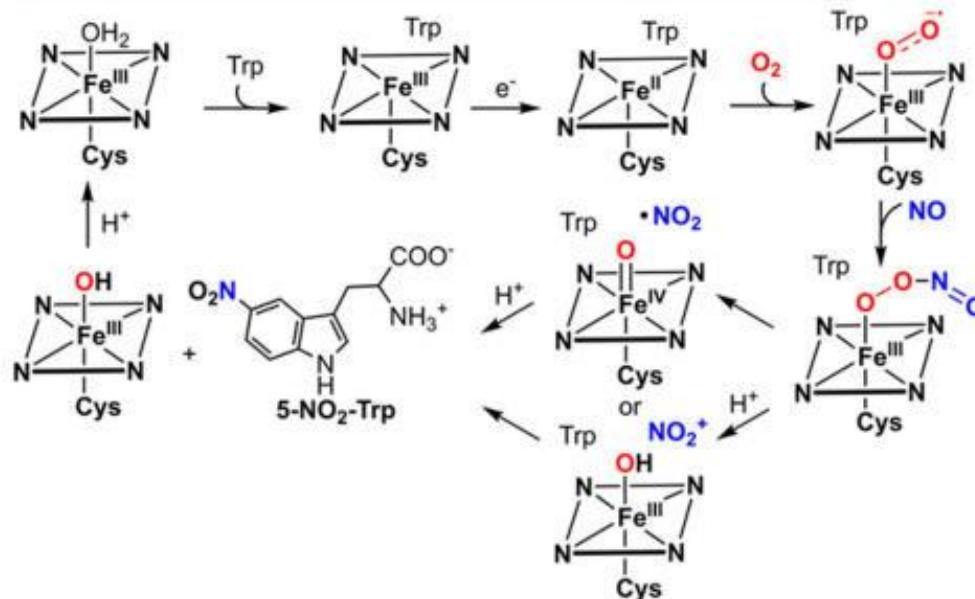
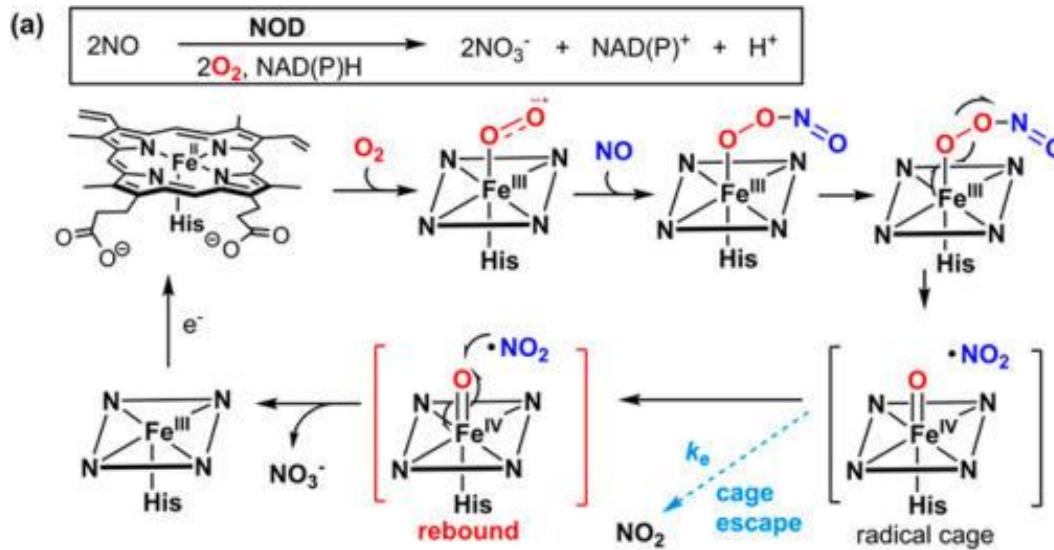


- a: R = H
- b: R = Me



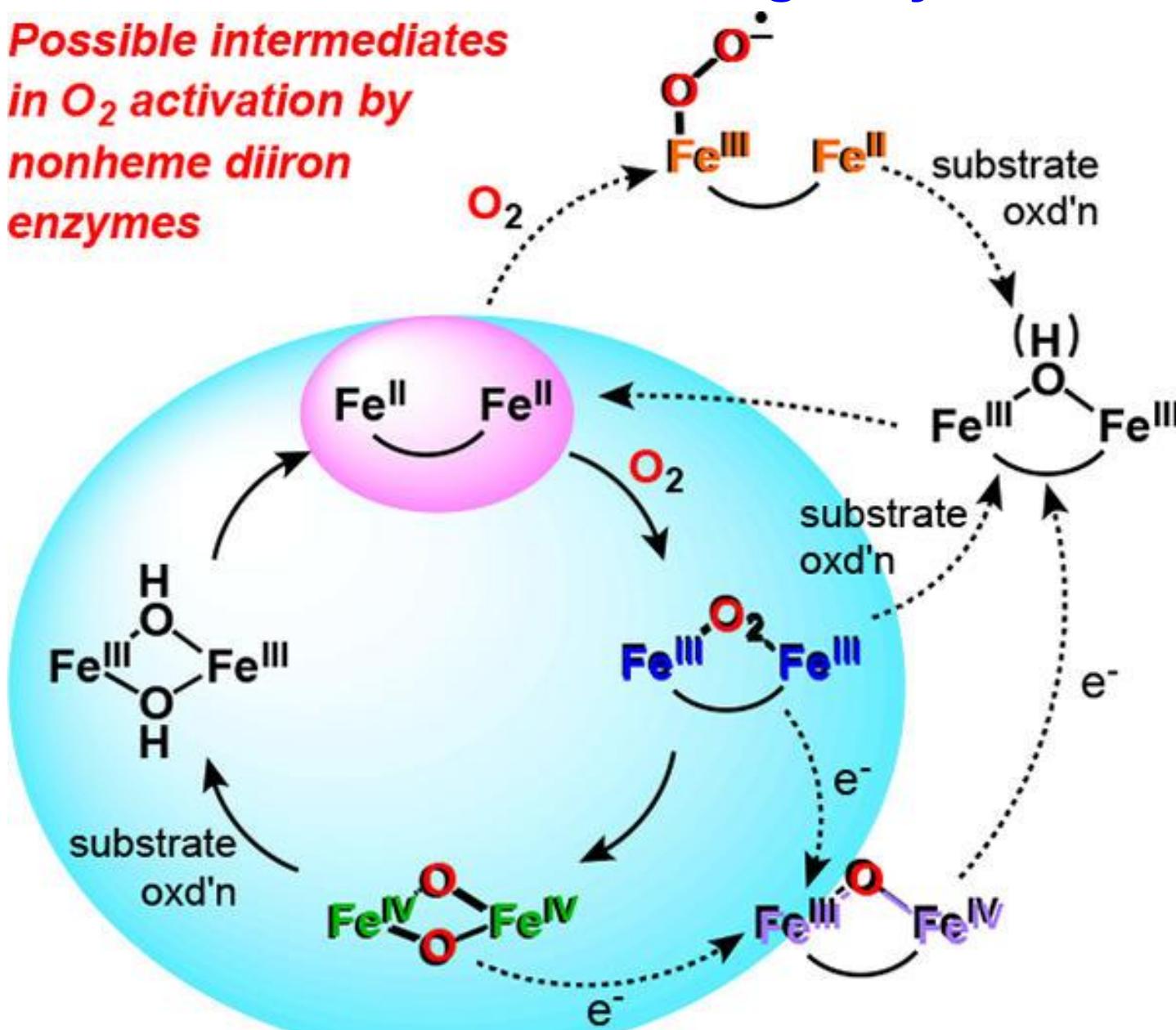
49c

# Metal Peroxynitrites



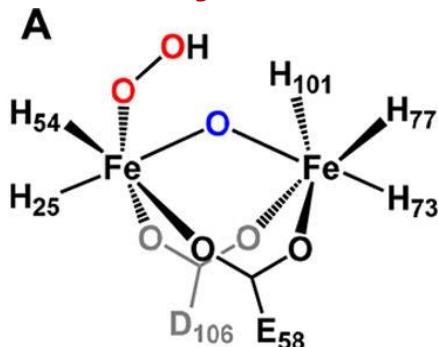
# Non-heme diiron containing enzymes

Possible intermediates  
in  $O_2$  activation by  
nonheme diiron  
enzymes

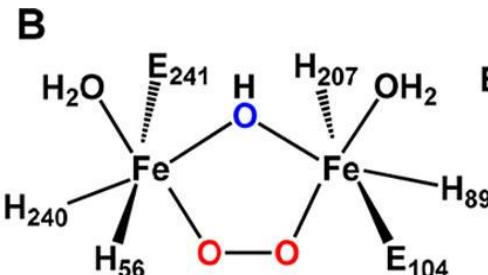


# Representative examples for non-heme diiron enzymes

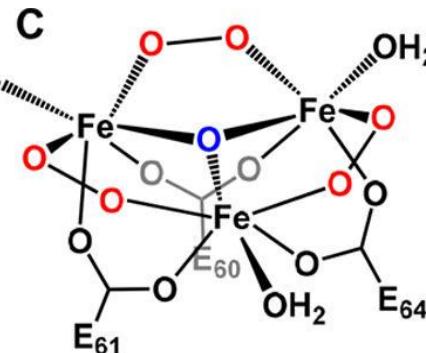
OxyHr



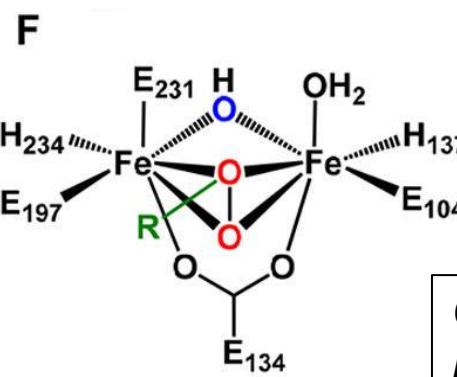
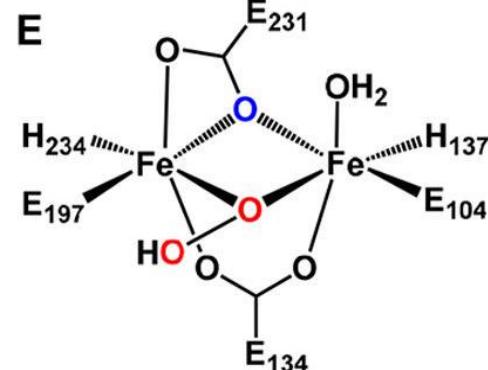
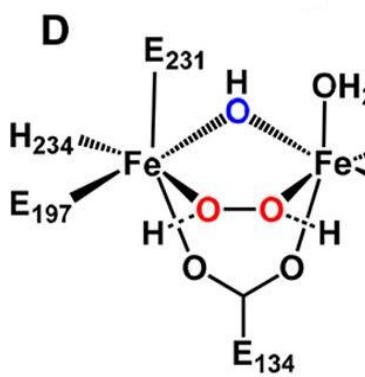
*hDOHH*



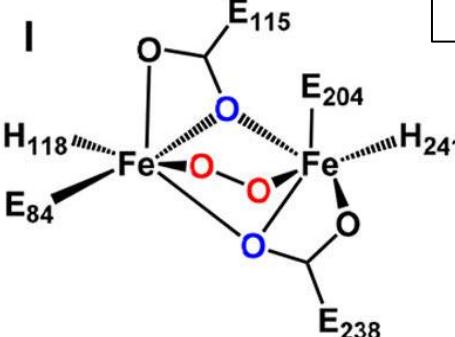
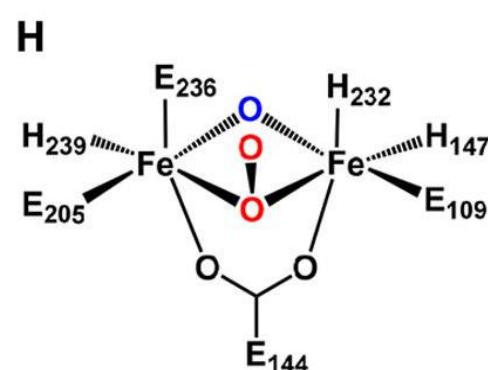
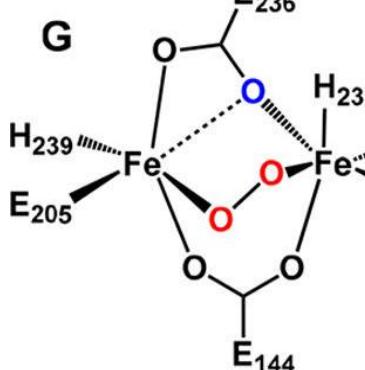
human L ferritin



T4MOH/D  $\mu$ -1,2-peroxy    T4MOH/D  $\mu$ -1,1-(hydro)peroxy    T4MOH/D  $\mu$ - $\eta_2$ : $\eta_2$ -arylperoxy



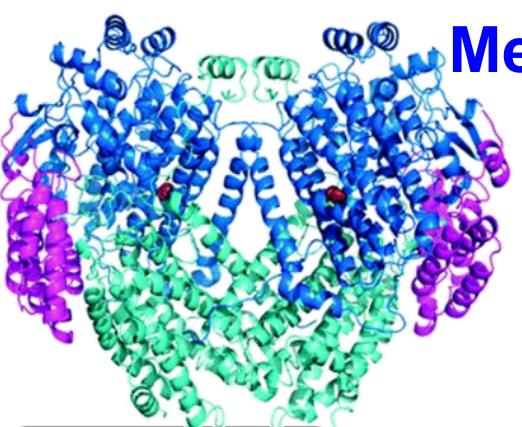
Chem.  
Rev. 2018,  
118, 2554



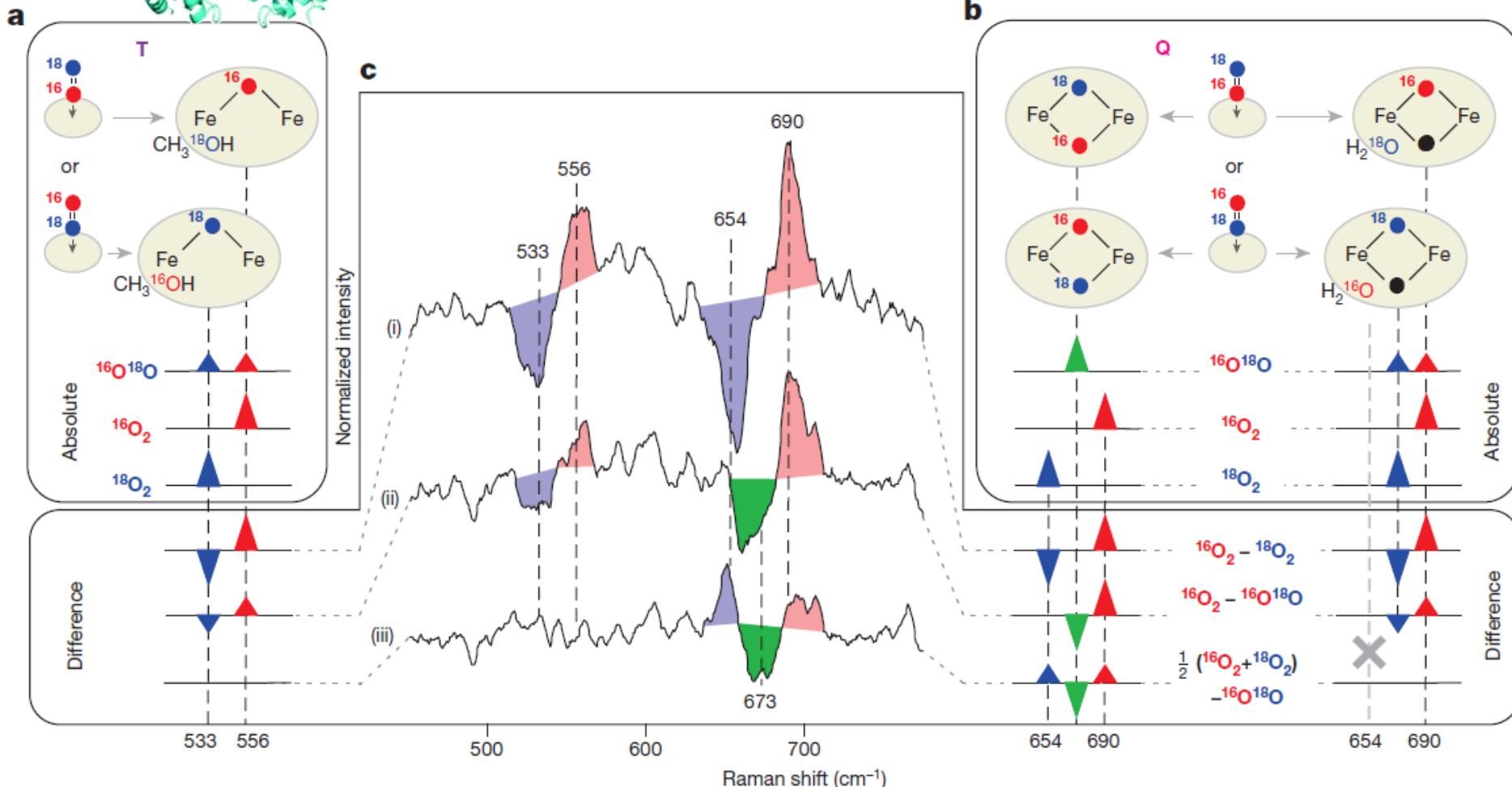
CmII  $\mu$ -1,2-peroxy

CmII  $\mu$ -1,1-peroxy

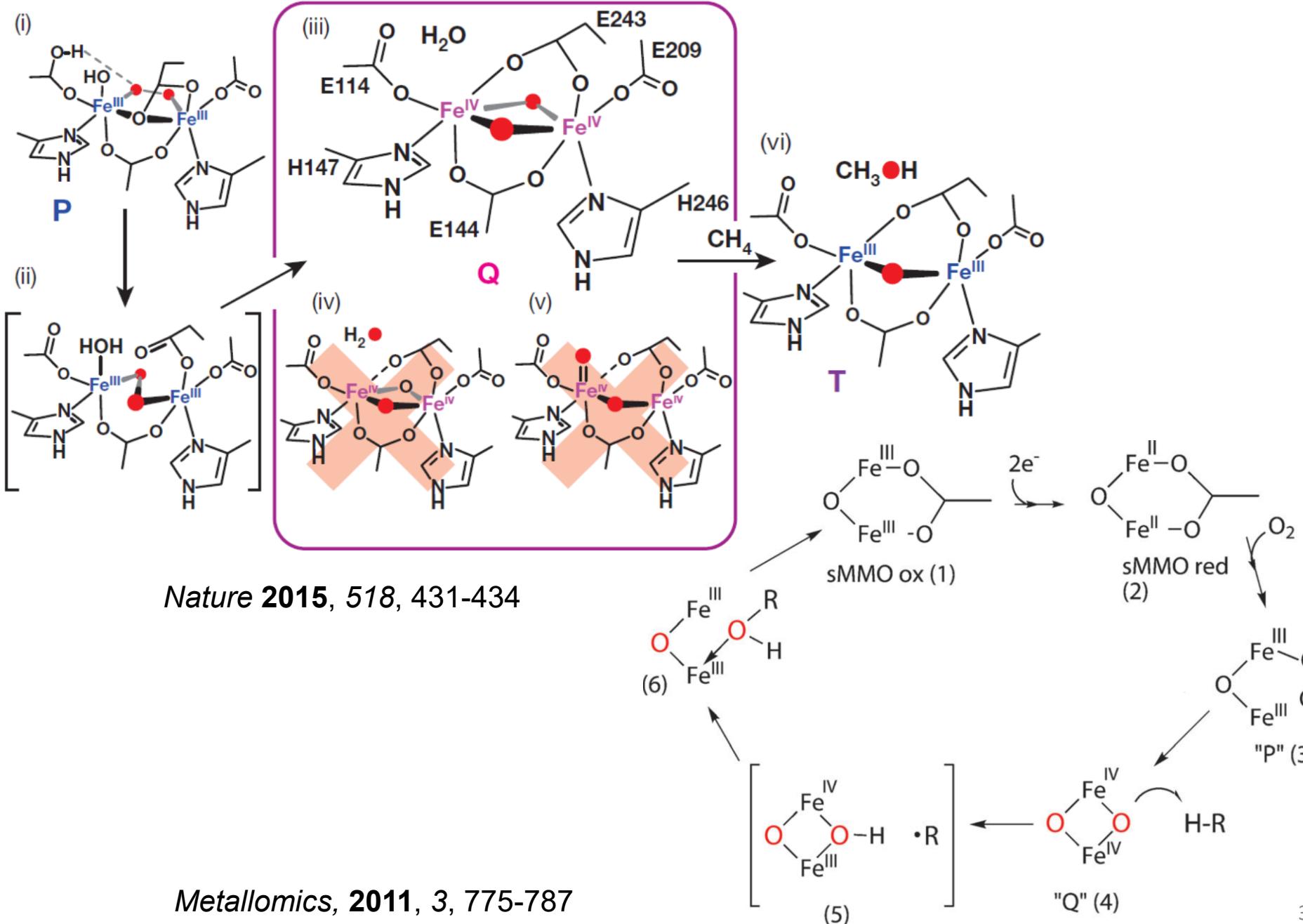
$\mu$ -1,2-peroxy for RNR



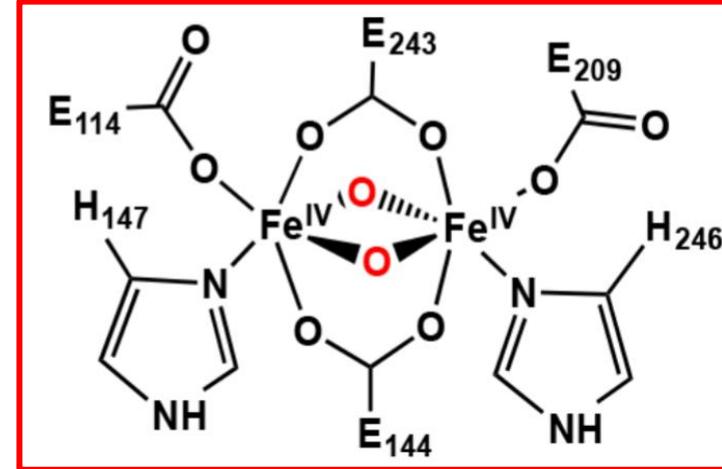
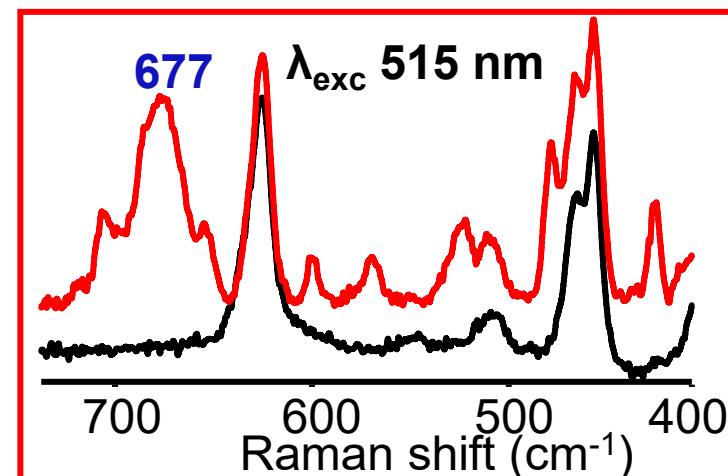
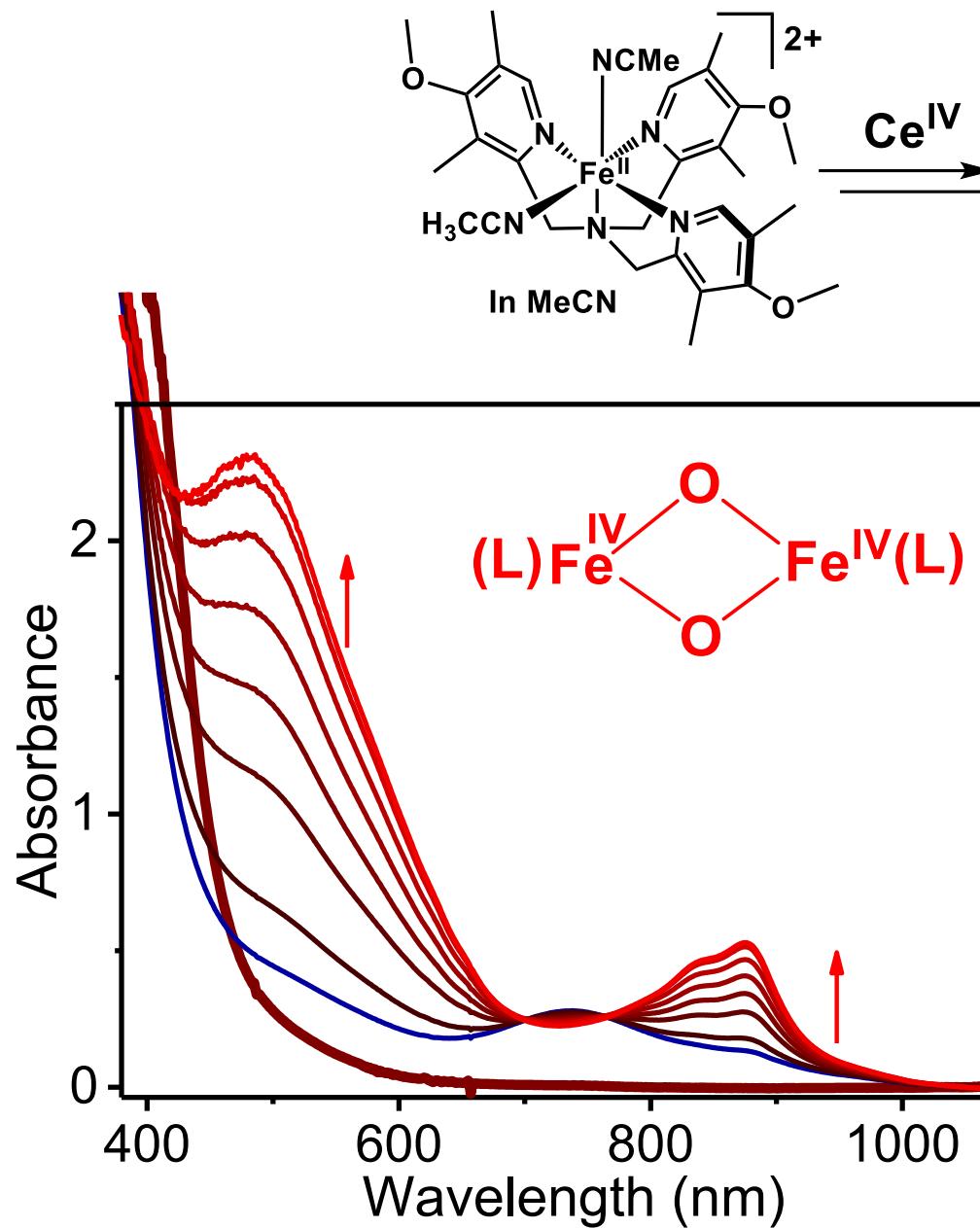
# Methane Monooxygenase - Q



# Methane Monooxygenase - Q

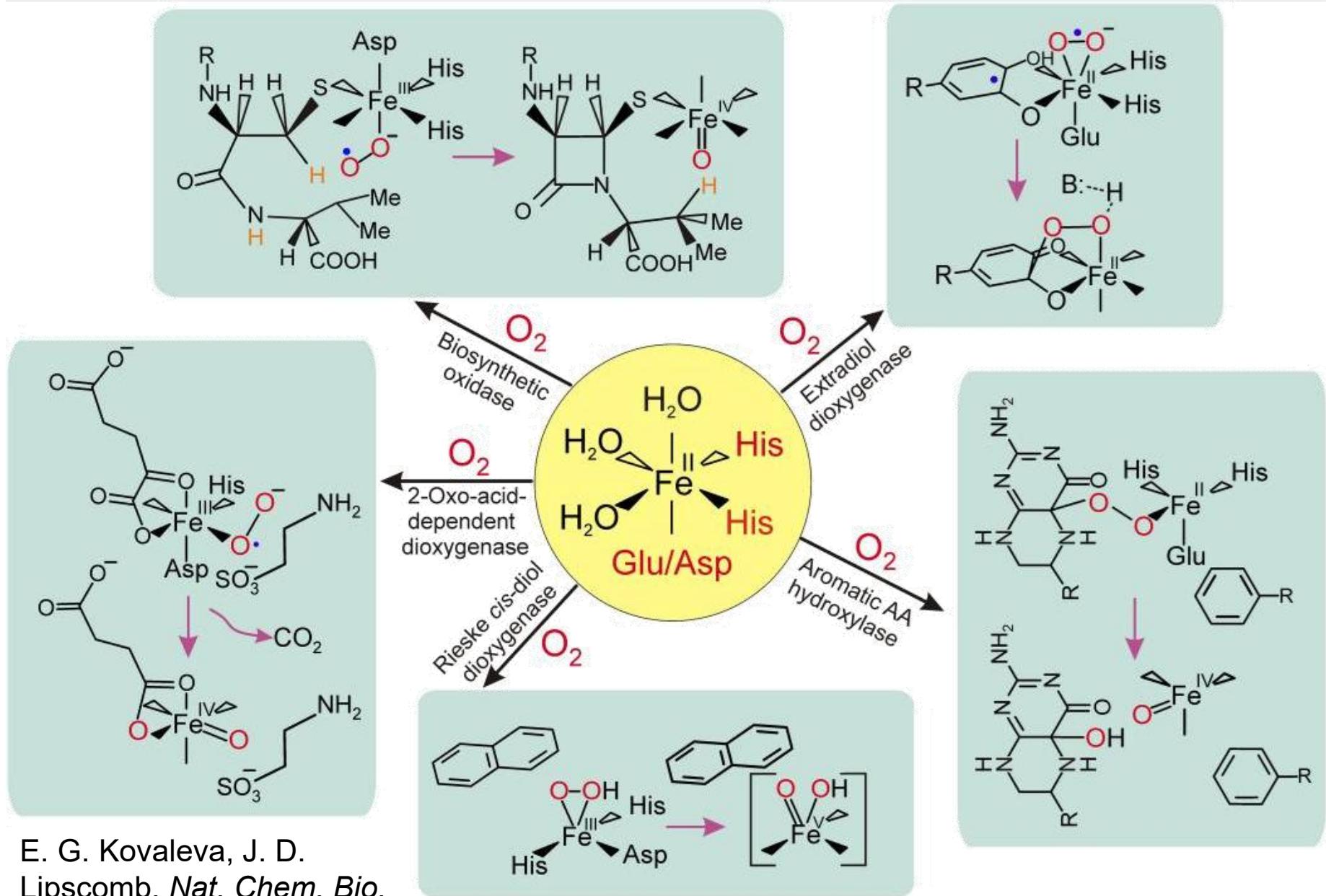


# Spontaneous formation of $\text{Fe}^{\text{IV}}_2\text{O}_2$



**“MMO Q”**

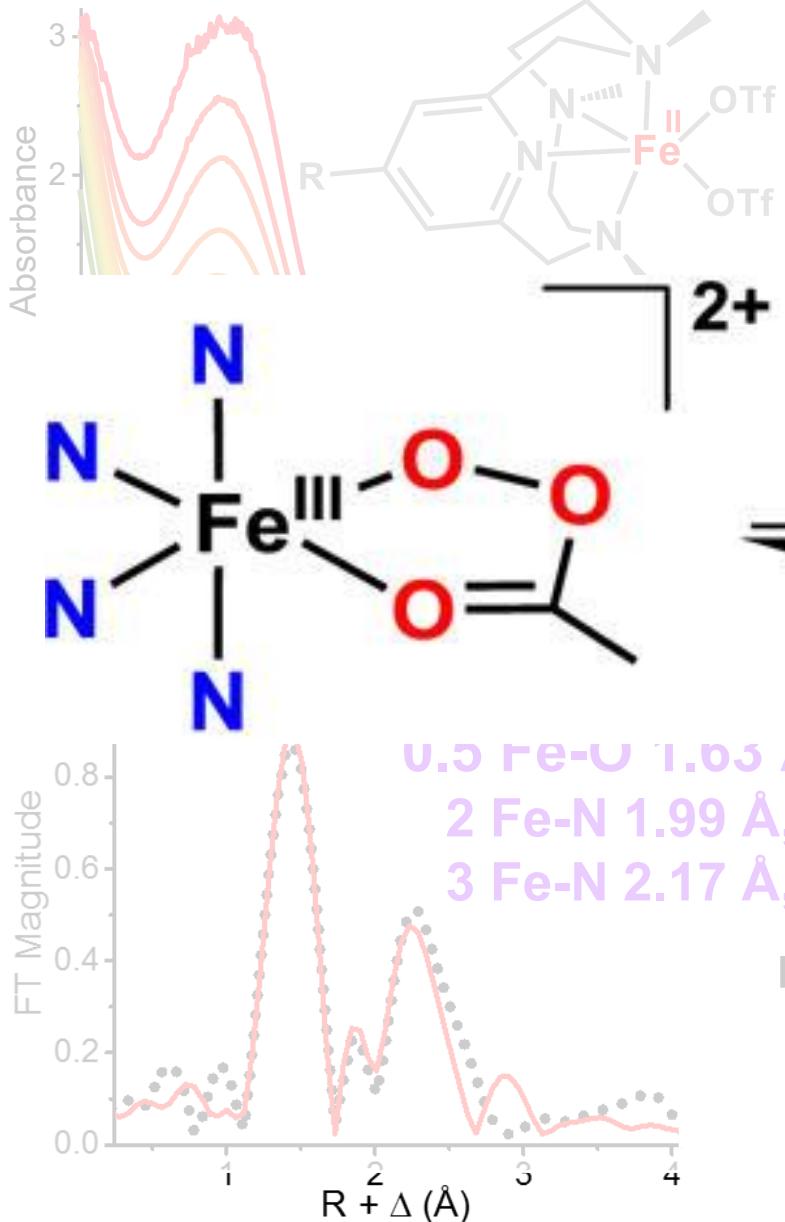
# Representative examples for non-heme mono iron enzymes



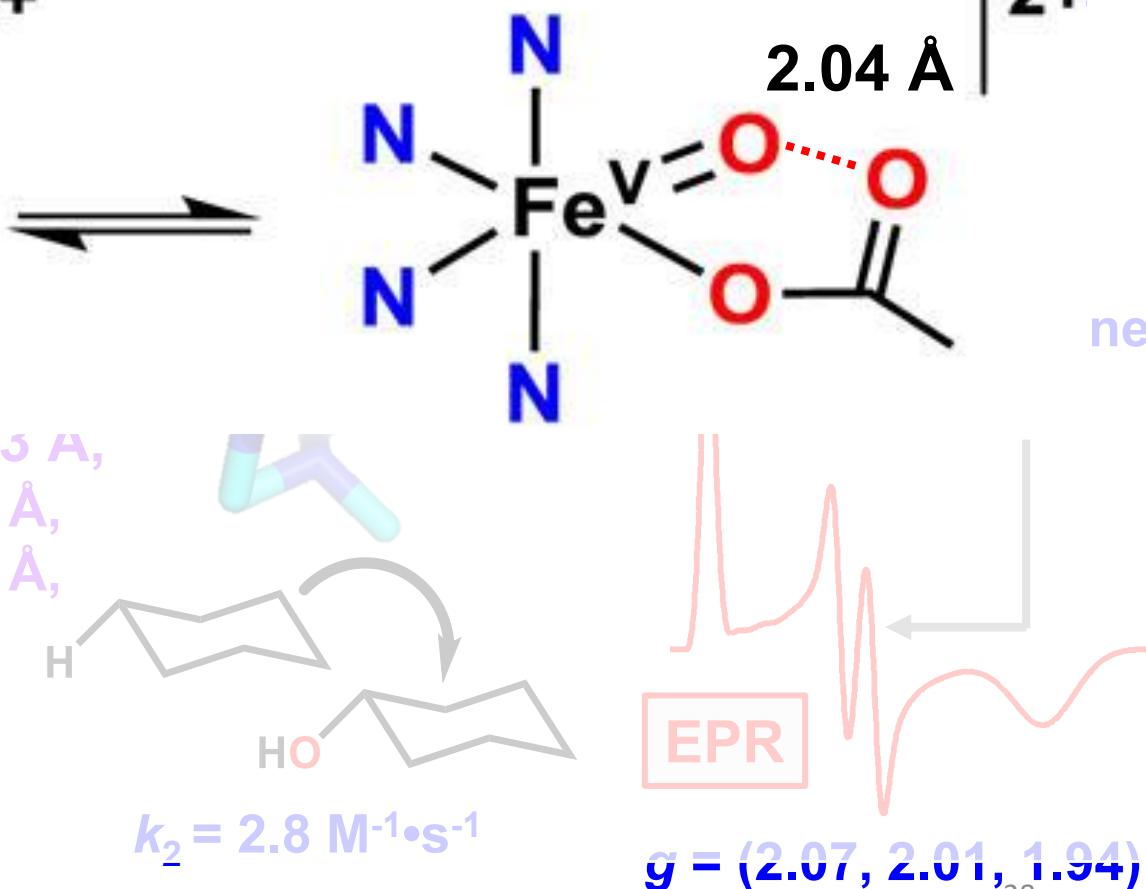
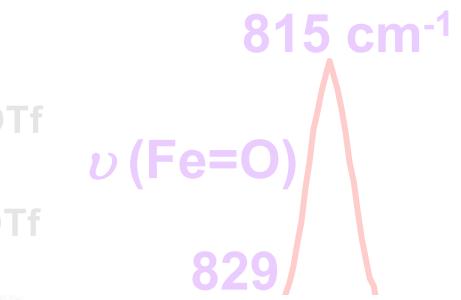
E. G. Kovaleva, J. D.  
Lipscomb, *Nat. Chem. Bio.*  
**2008**, 4, 186-193.

Acc. Chem. Res. 2007, 40, 484-492. 37

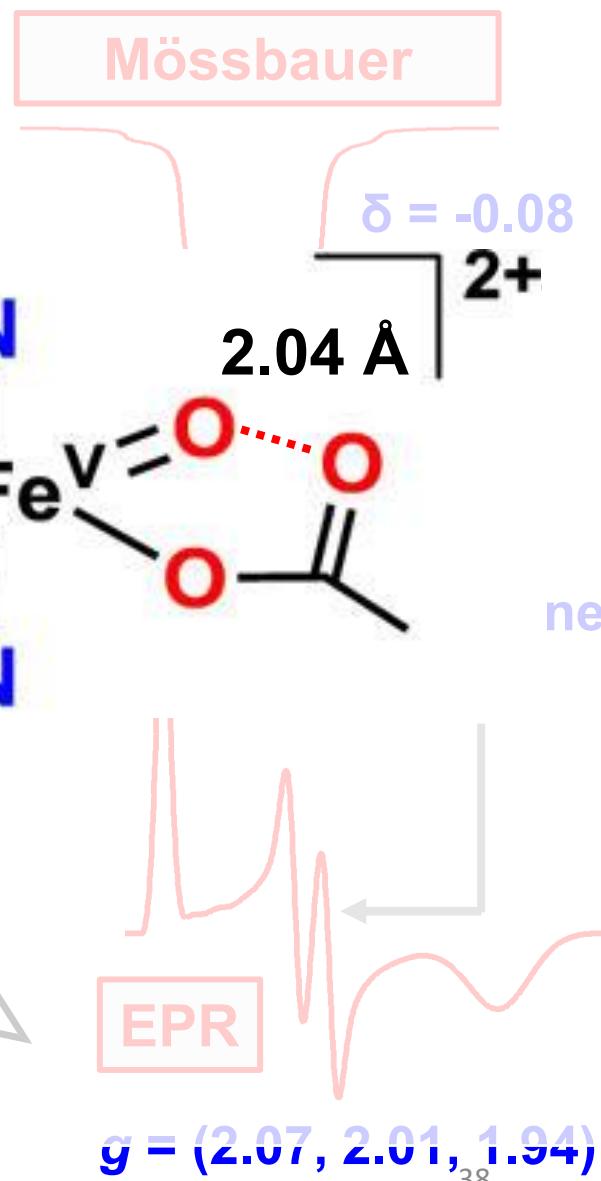
# UV-Vis Absorption



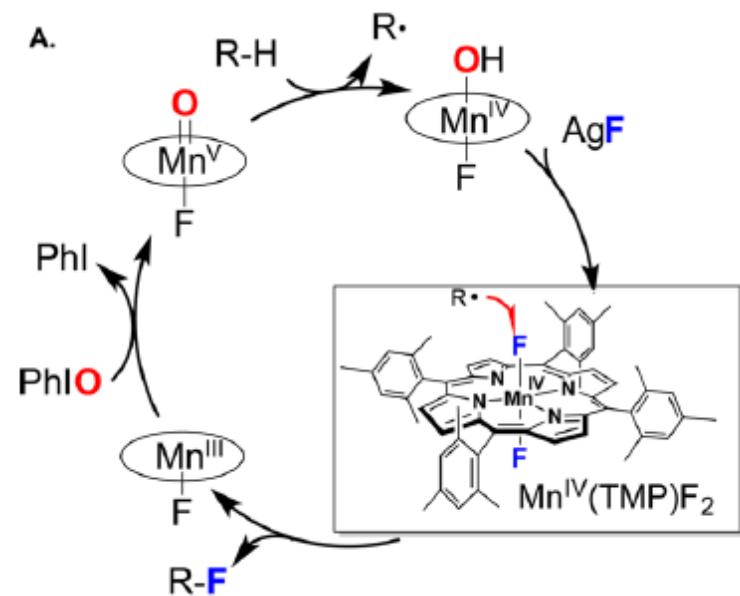
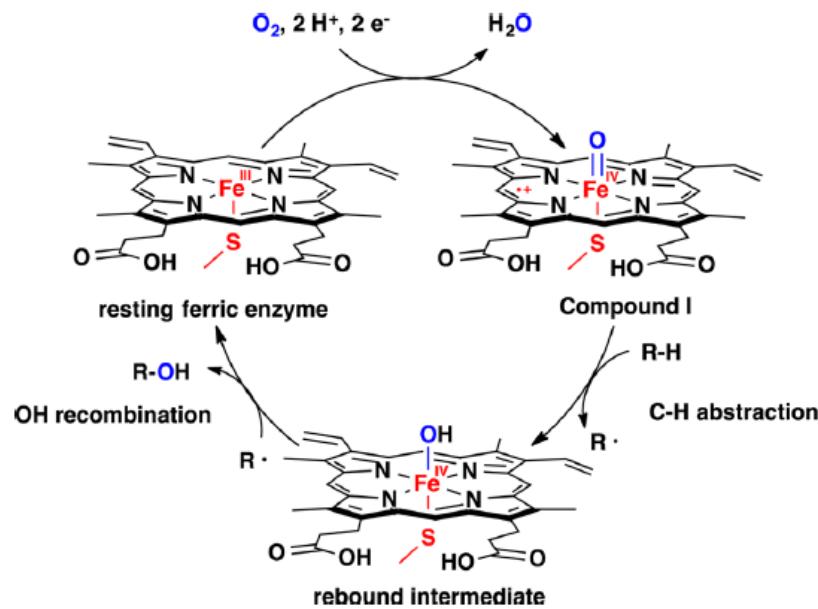
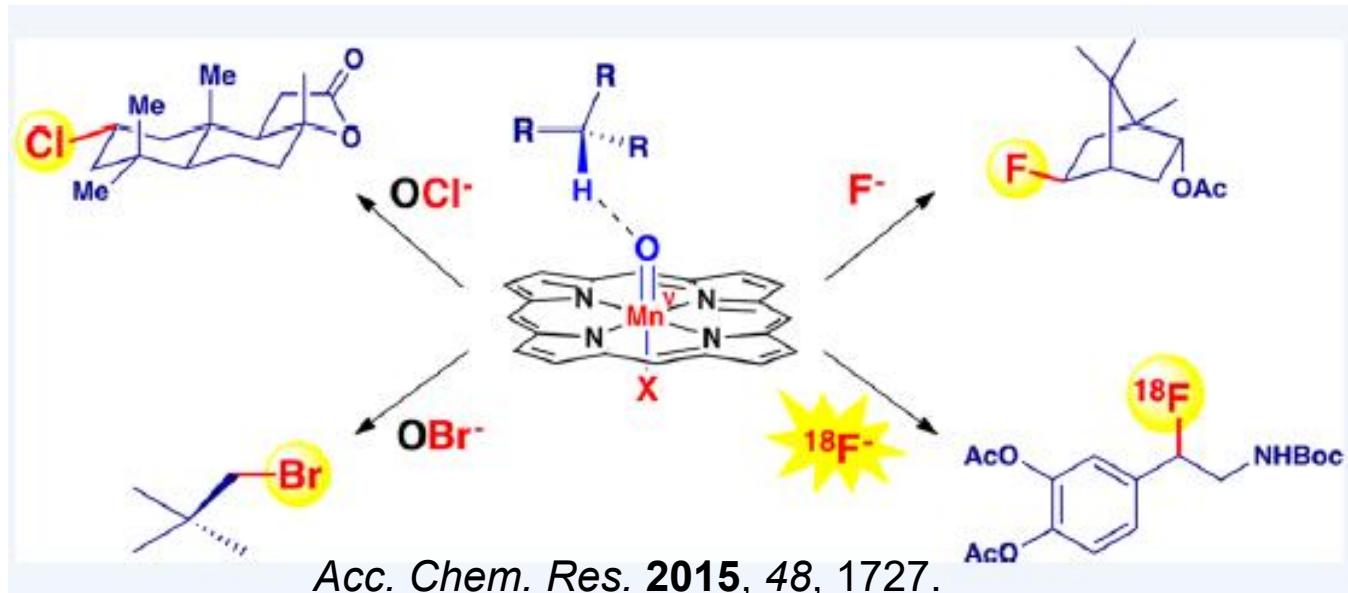
rRaman



# Challenging Fe<sup>V=O</sup>

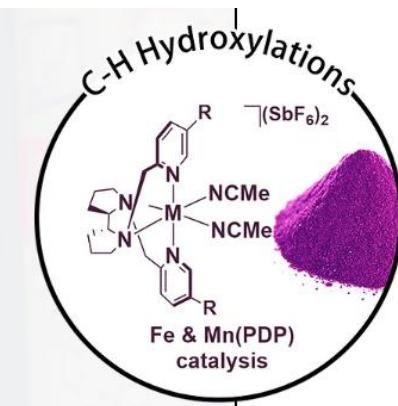


# Manganese Catalyzed C-H Halogenation

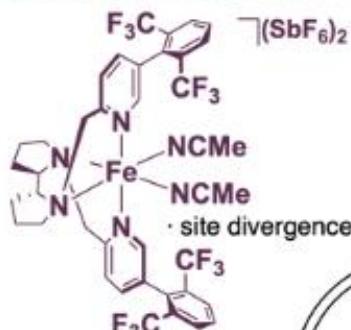


# C-H Hydroxylation

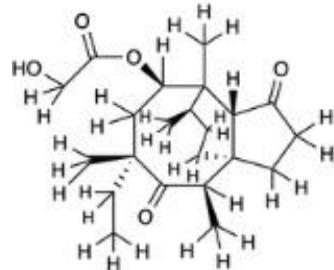
Fe(PDP)  
Science 2007, 2010  
Aldrich, Strem (White-Chen)



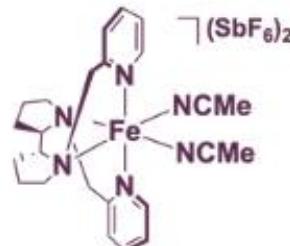
Fe(CF<sub>3</sub>-PDP)  
J. Am. Chem. Soc. 2013



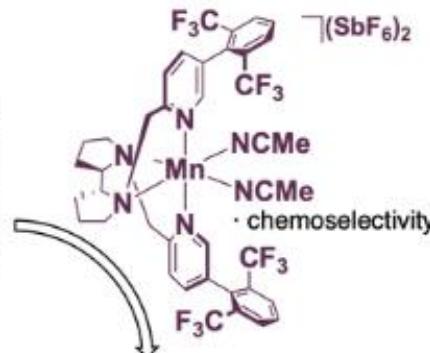
view prior to 2007



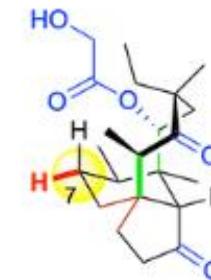
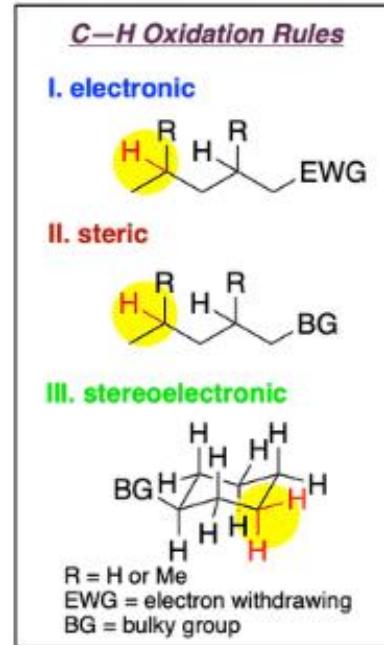
...very little difference in reactivity between the various C—H bonds in alkanes, so targeting a specific C—H bond is difficult." - *Nature* 2007 (446) 391.



Mn(CF<sub>3</sub>-PDP)  
Nature Chem. 2018  
Strem (White-Gormisky-Zhao)



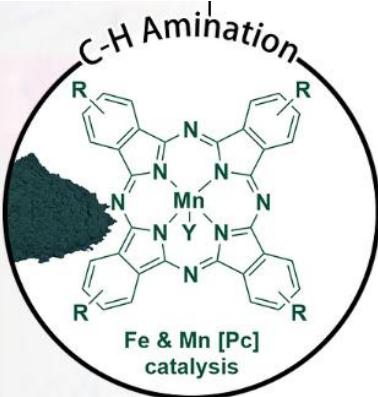
view after 2007



after 2007 rules shown in:  
fluorinations,  
brominations,  
chlorinations,  
azidations,  
alkylations,  
aminations,  
xanthylation

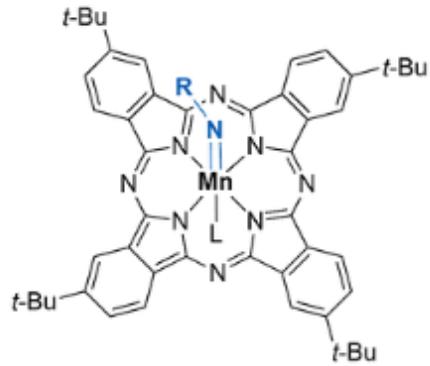
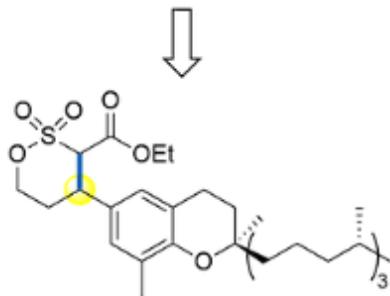
"electron rich C—H bonds cleaved faster than electron-poor C—H... the steric properties of reagent reacting with the C—H bonds can affect the regioselectivity of the C—H functionalization." *ACIE* 2018 (57) 4234.

# C-H Amination

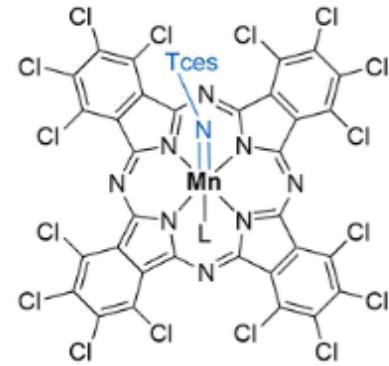
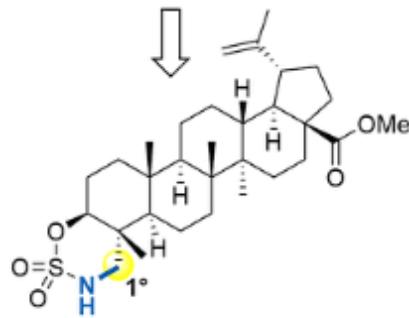


X = N, C  
R = EWG  
[FePc]•X

first iron catalyst for intramolecular  
allylic C—H amination (2012), and  
for catalytic C—H alkylation (2017)

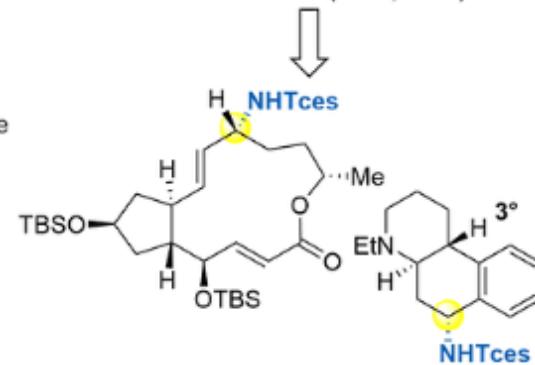


R = EWG  
[Mn(t-Bu)<sub>4</sub>Pc]•SbF<sub>6</sub>  
**Paradine-White catalyst (Aldrich)**  
first catalyst for intramolecular  
amination of all C(sp<sub>3</sub>)-H  
bond types (2015)



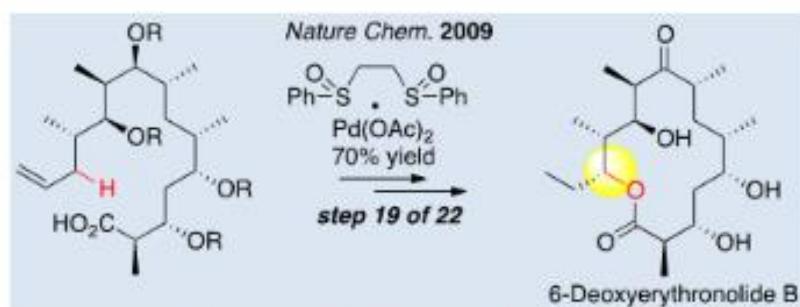
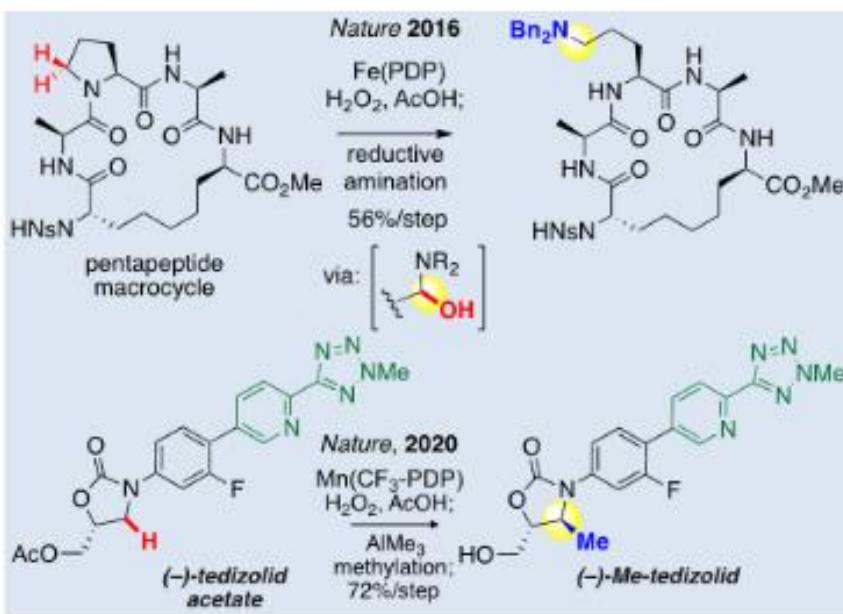
Tces = SO<sub>3</sub>CH<sub>2</sub>CCl<sub>3</sub>  
[MnClPc]•SbF<sub>6</sub>  
**Clark-White catalyst (Aldrich)**

Base metal catalyst for intermolecular,  
selective, late-stage benzylic and allylic  
C—H amination (2018, 2021)

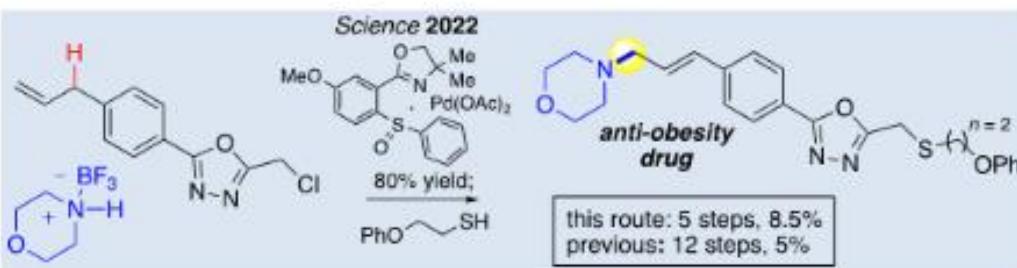


# Late-Stage Functionalization

drug and natural product diversification

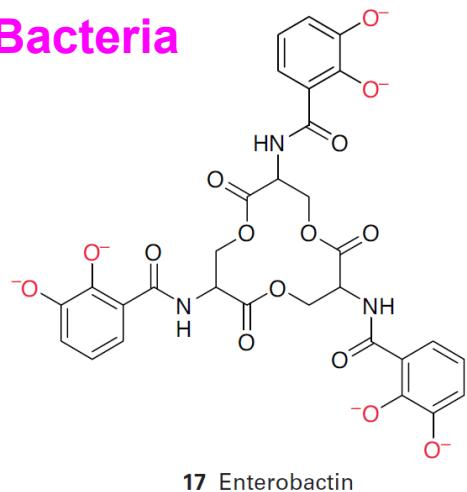


The Advent of Late-Stage Functionalization



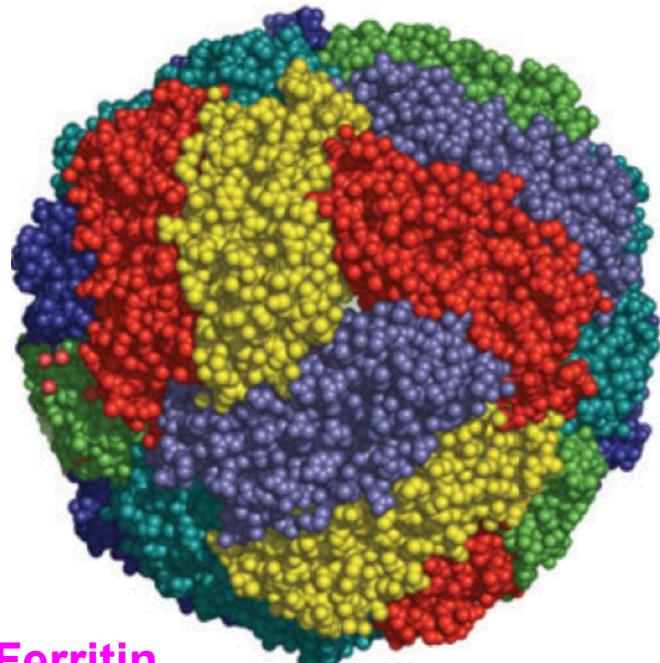
# Transport and storage of iron

Bacteria



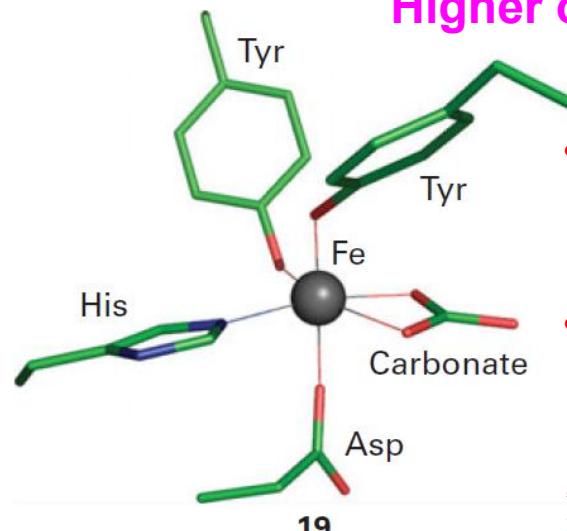
17 Enterobactin

Association constant for Fe(III) is  $10^{52}$

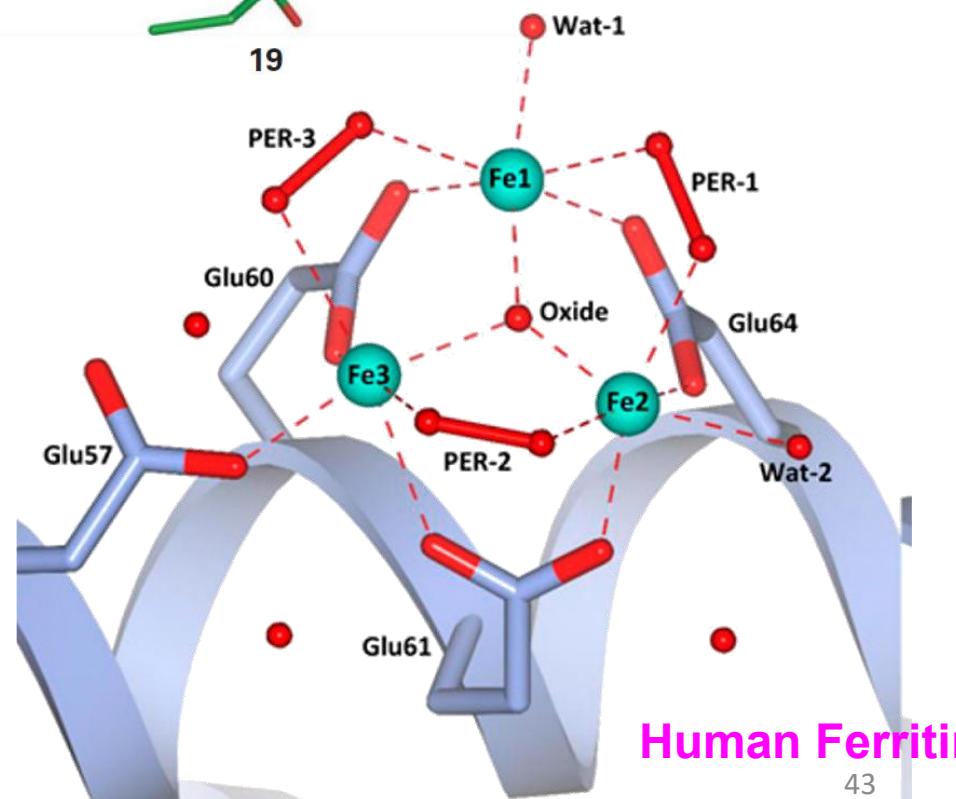


Ferritin

Higher organisms (human)



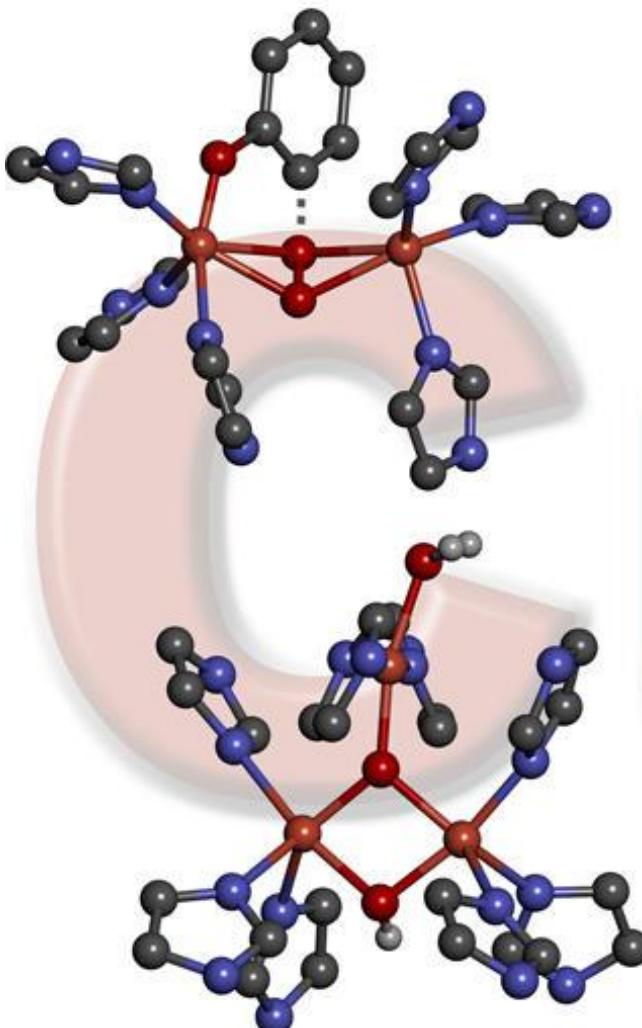
- Under physiological conditions  $10^{22-26}$
- Carbonate binding is pH dependent



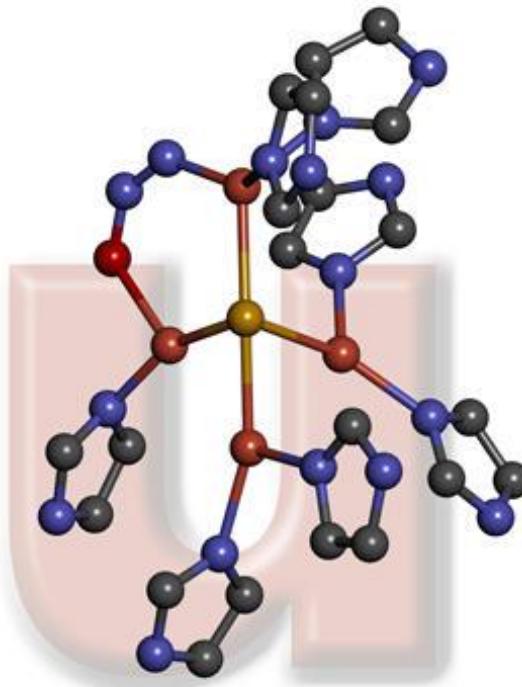
Human Ferritin

# Copper Active Sites in Biology

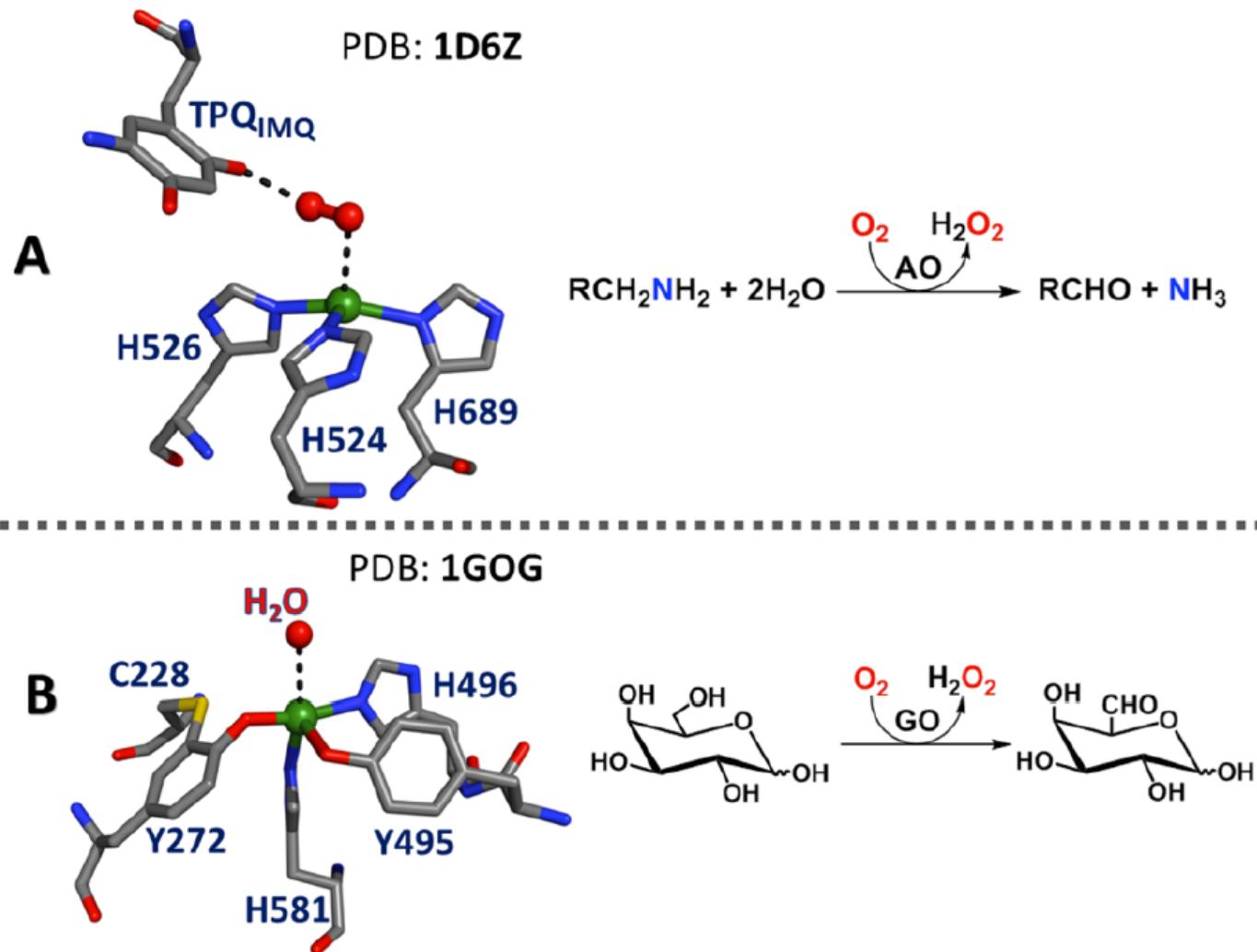
*O<sub>2</sub> Activation*



*N<sub>2</sub>O Activation*



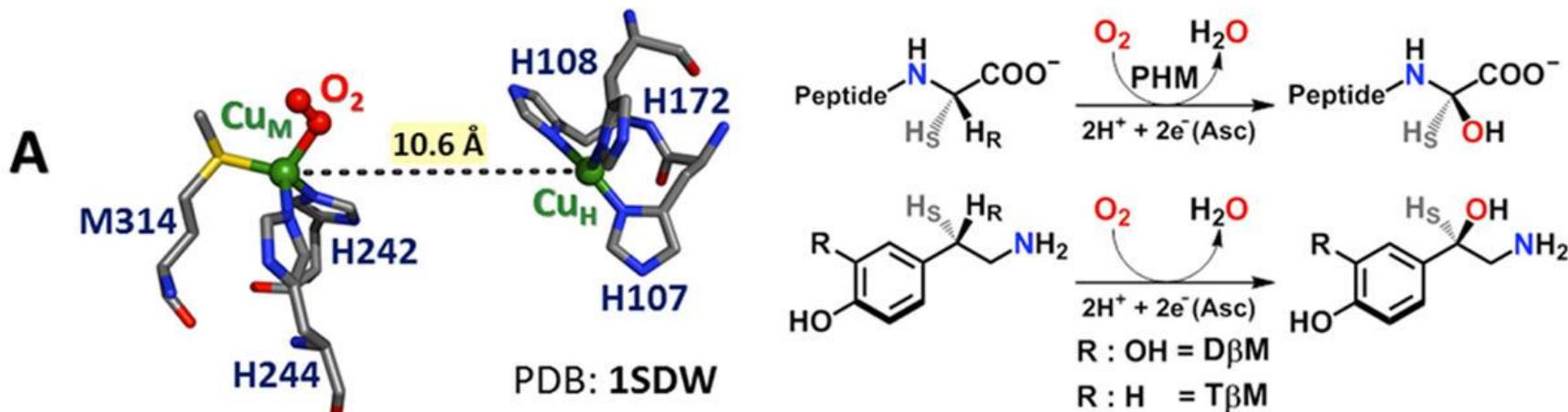
*O<sub>2</sub> Reduction*



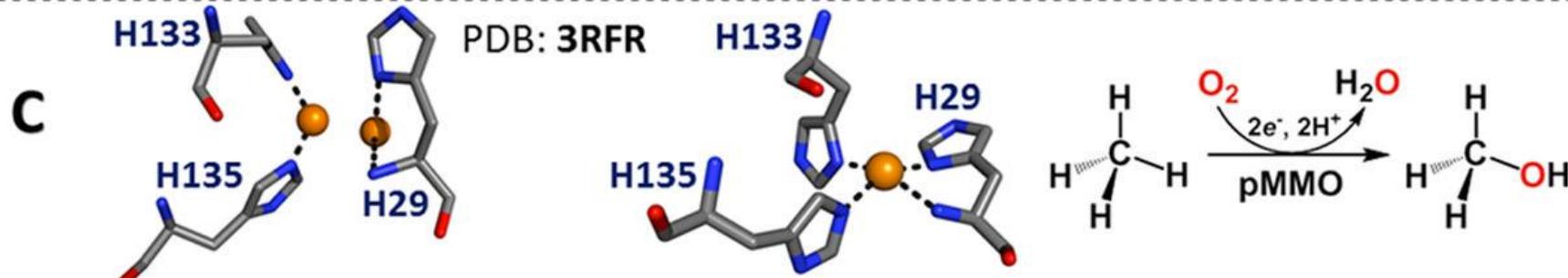
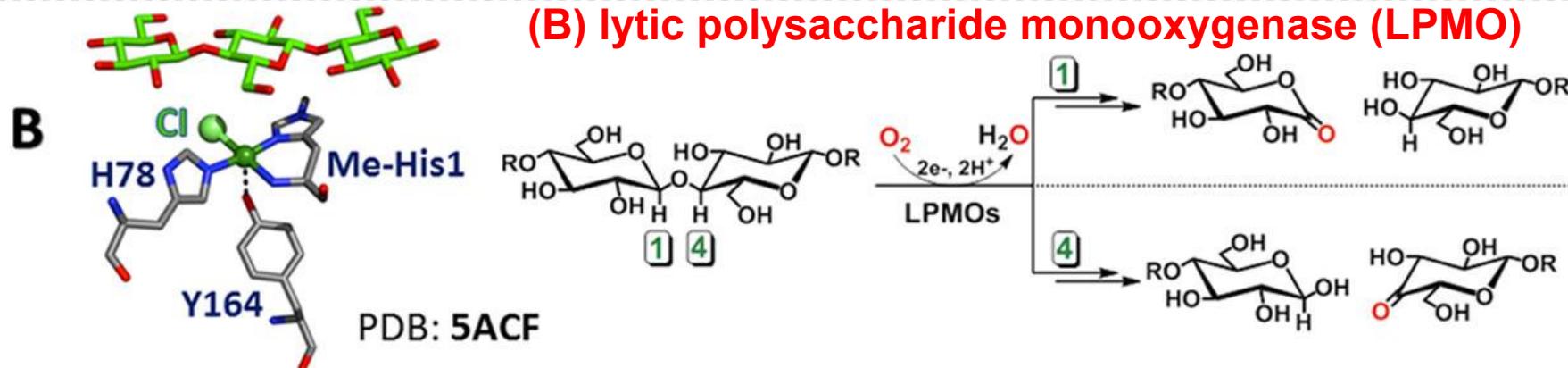
**Figure 53.** Active site structures and O<sub>2</sub>-reduction/substrate oxidation reactions of mononuclear copper oxidases (A) amine oxidase and (B) galactose oxidase. See text for discussion.

# Copper in action

## (A) peptidylglycine $\alpha$ -hydroxylating monooxygenase (PHM)

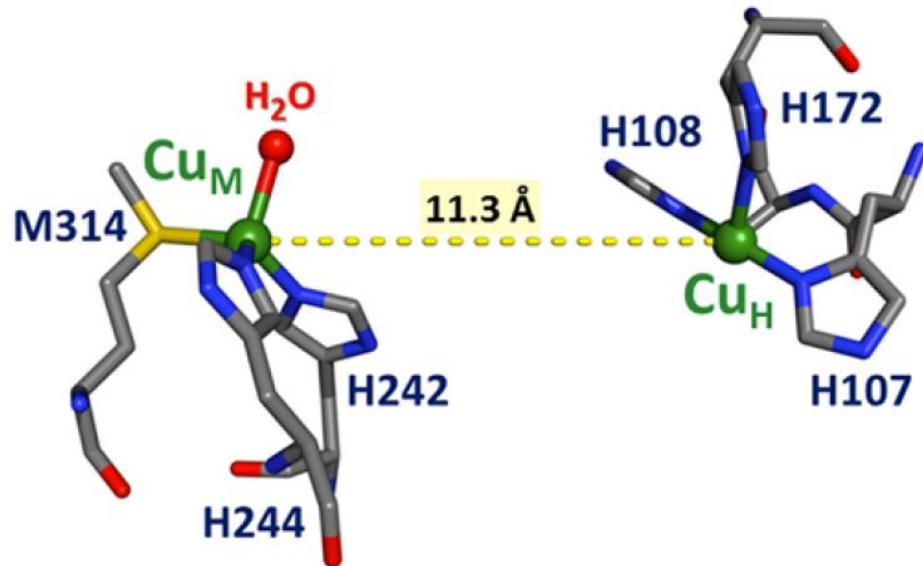
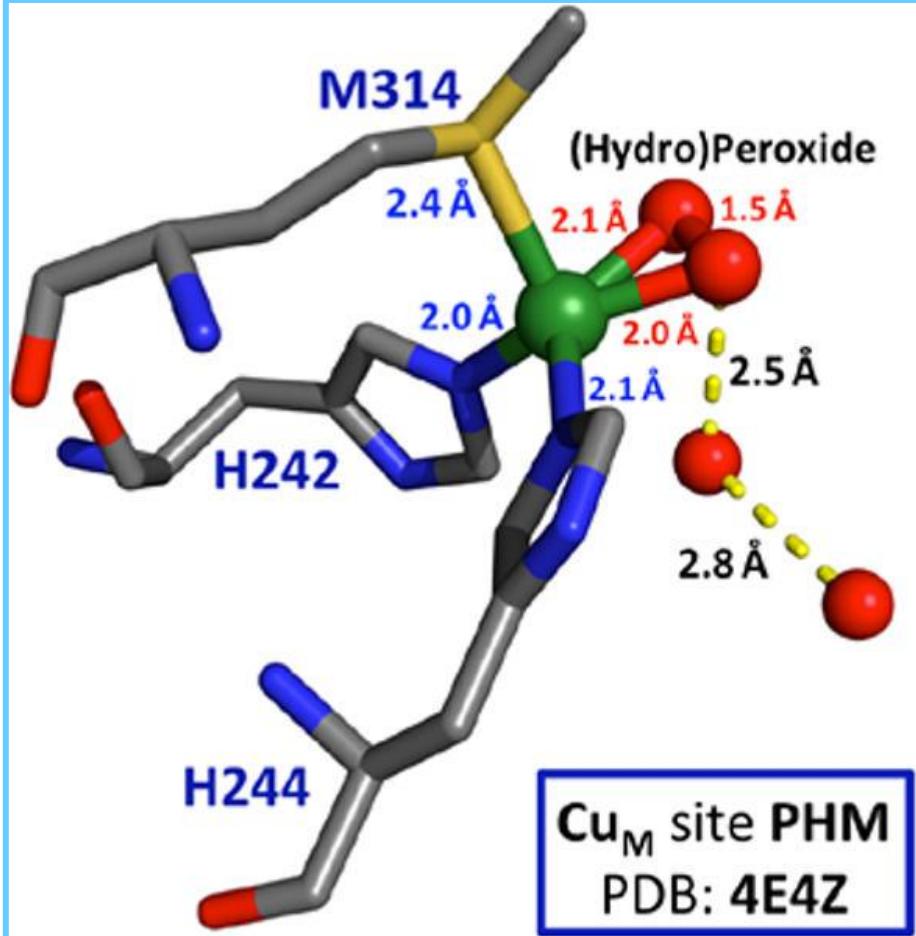


## (B) lytic polysaccharide monooxygenase (LPMO)

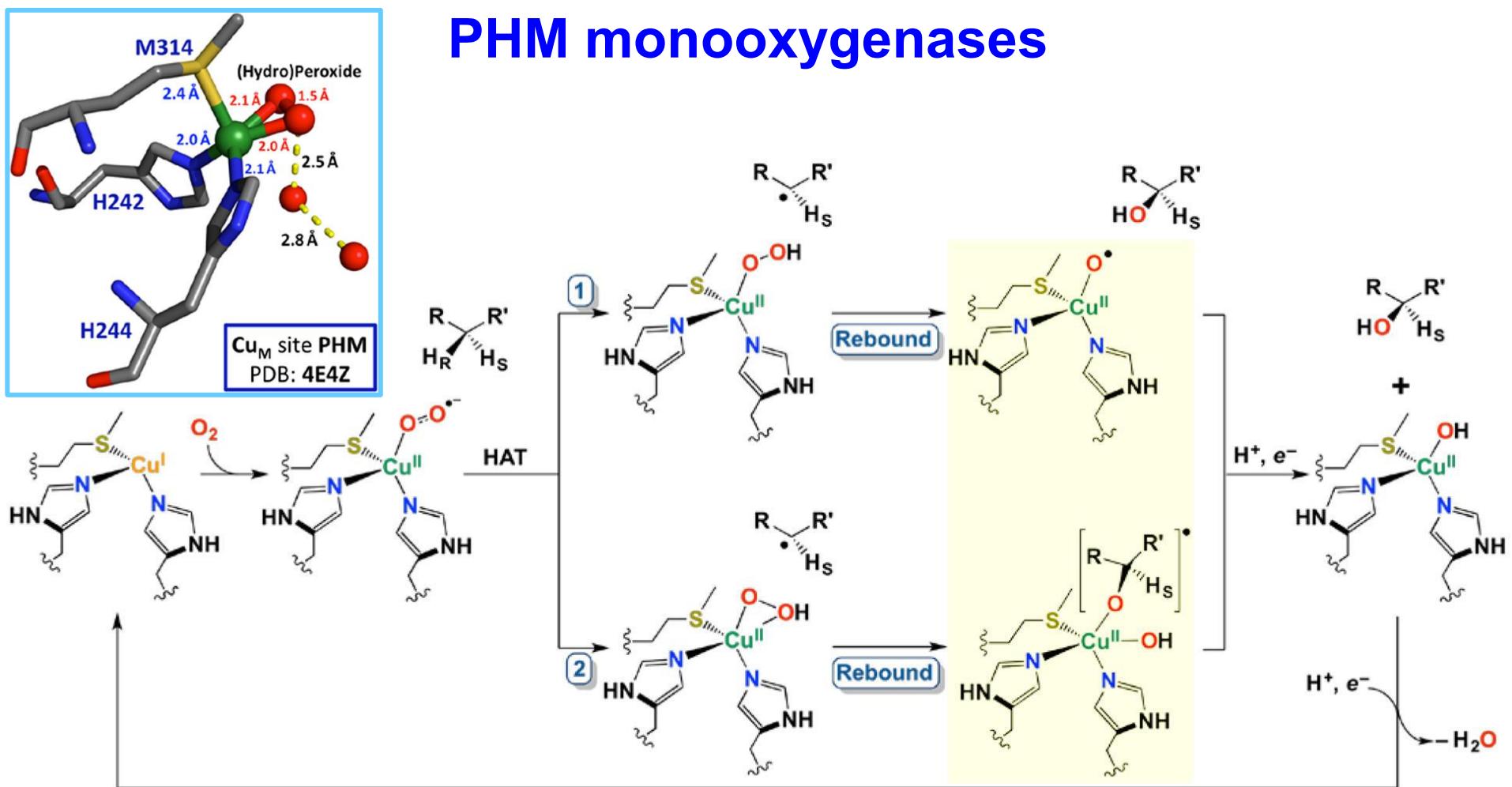


## (C) particulate methane monooxygenase (pMMO)

# PHM monooxygenases

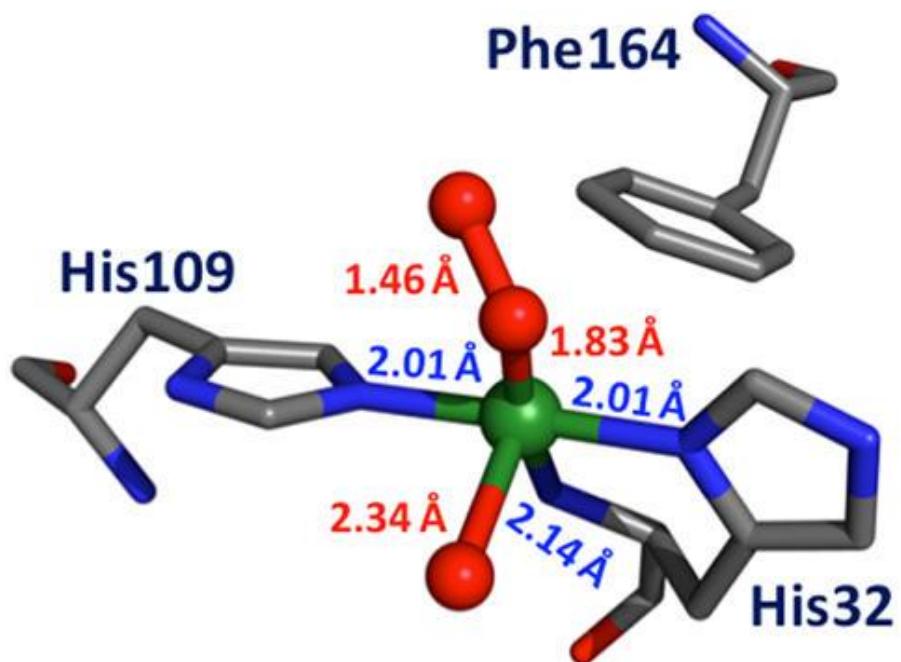


# PHM monooxygenases

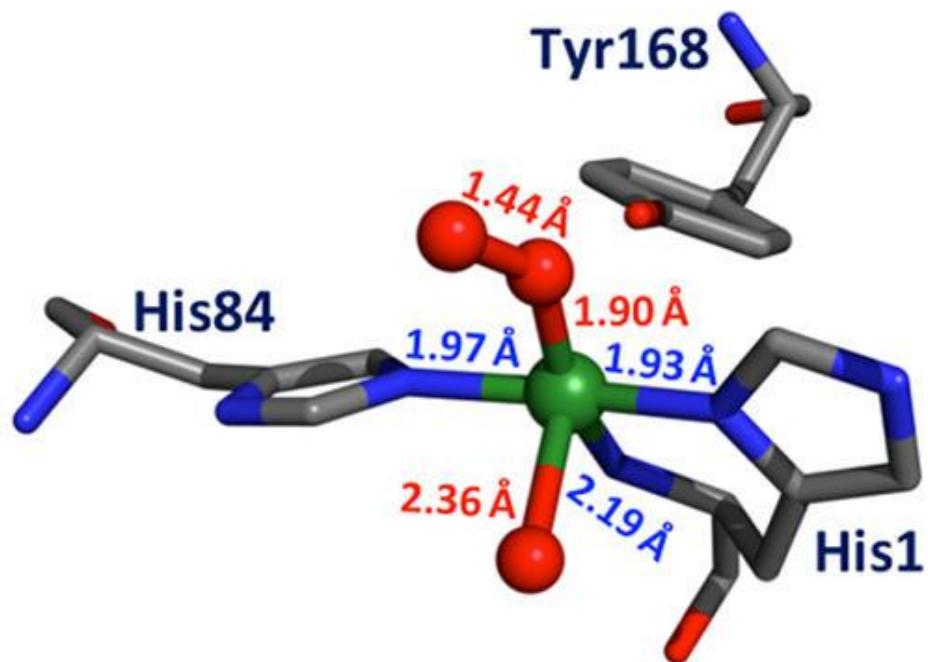


Postulated steps in the mechanism of action of PHM and related monooxygenases including key steps where the cupric-superoxide species initially formed upon  $\text{O}_2$  binding carries out a hydrogen atom abstraction on substrate yielding either an end-on (pathway 1) or side-on (pathway 2) cupric-hydroperoxide. Subsequent rebound of the substrate radical to the  $\text{Cu-OOH}$  gives a highly oxidizing  $\text{Cu}^{\text{II}}\text{-oxyl}$  (i.e.,  $\text{Cu}^{\text{II}}\text{-O}^\bullet$ ) or  $\text{Cu}^{\text{II}}\text{-substrate radical}$  intermediate, respectively (highlighted in yellow). An electron, drawn from the enzyme  $\text{Cu}_H$  site (Figure 54A), and a proton react with the radical intermediate to release the hydroxylated alcohol product leaving a  $\text{Cu}^{\text{II}}\text{-OH}$  moiety which can be reduced to copper(I) to restart the catalytic cycle.

# Lytic polysaccharide monooxygenases (LPMO)

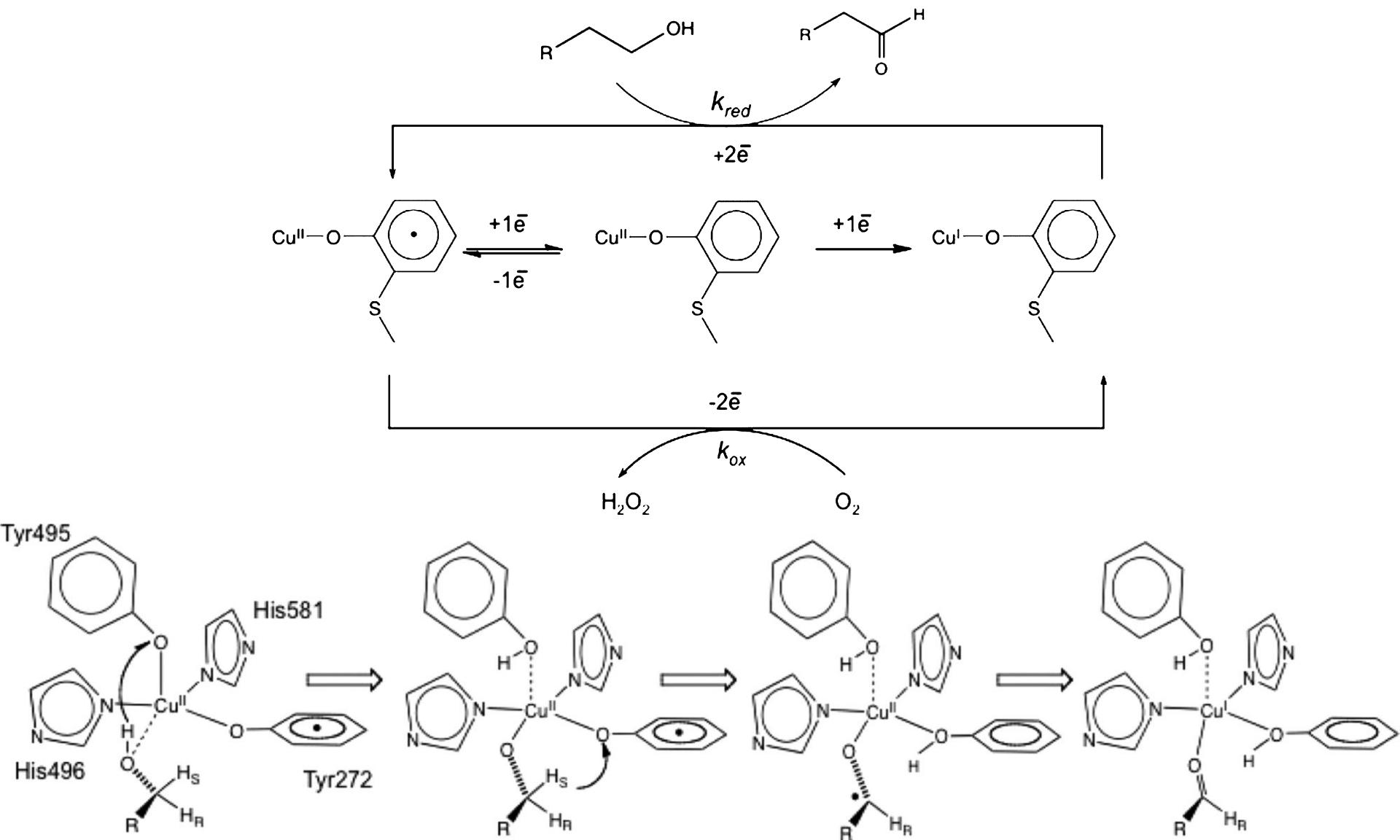


(A) *Jonesia denitrificans* LPMO (PDB: 5VG0)

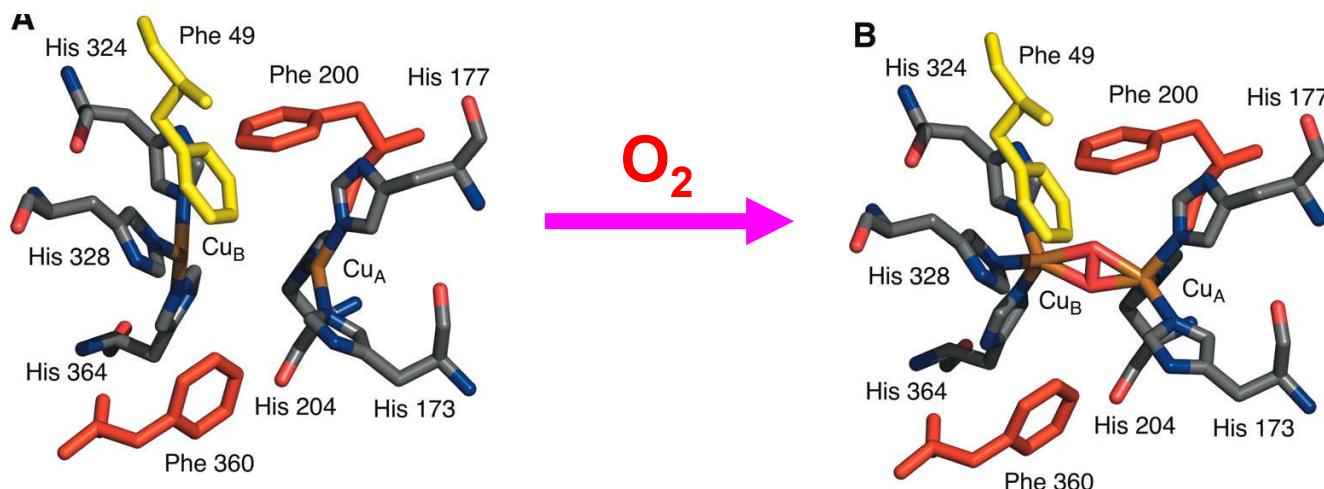


(B) *Neurospora crassa* LPMO (PDB: 5TKH)

# Galactose Oxidase (GO)

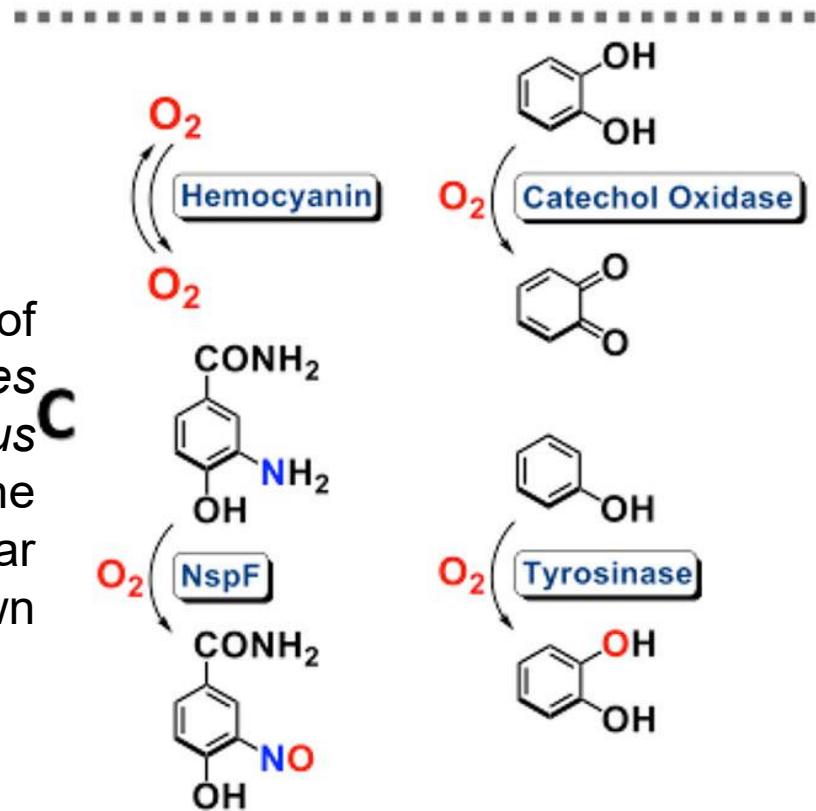
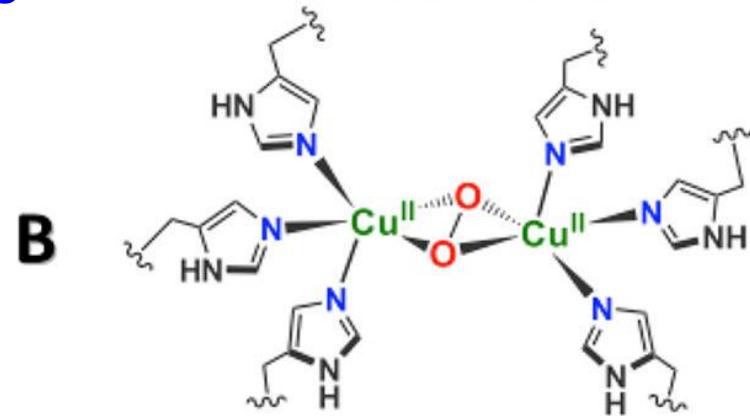
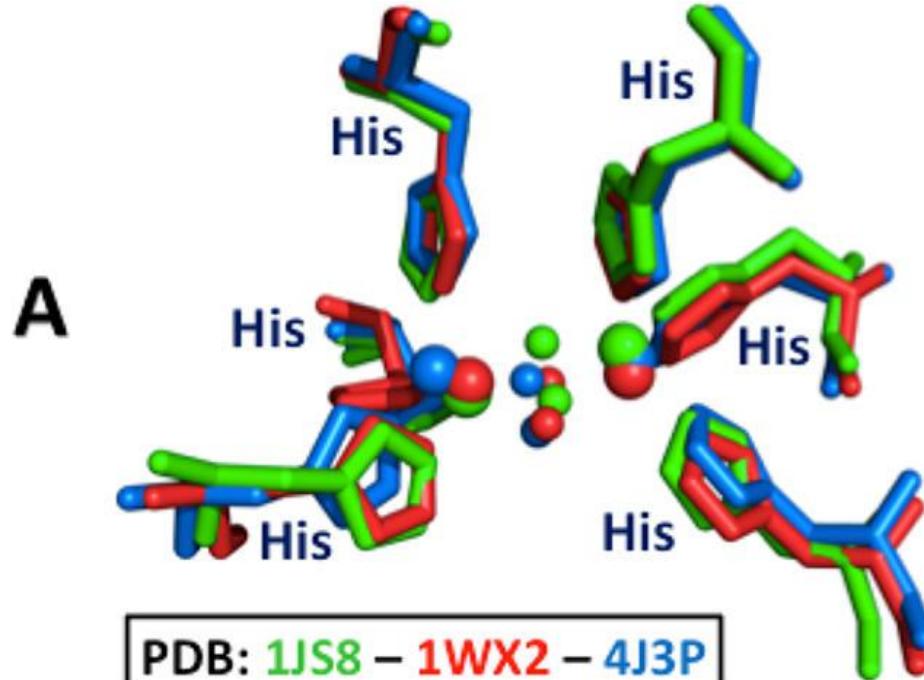


# Why Horseshoe crab blood is blue?



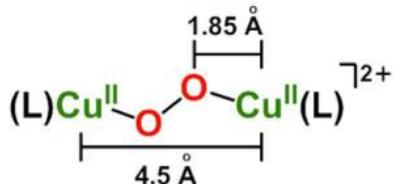
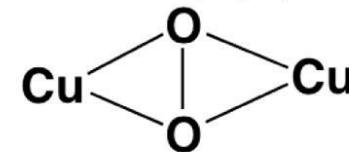
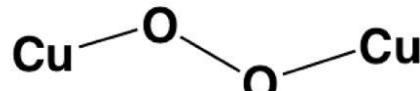
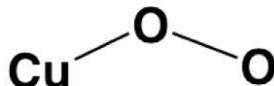
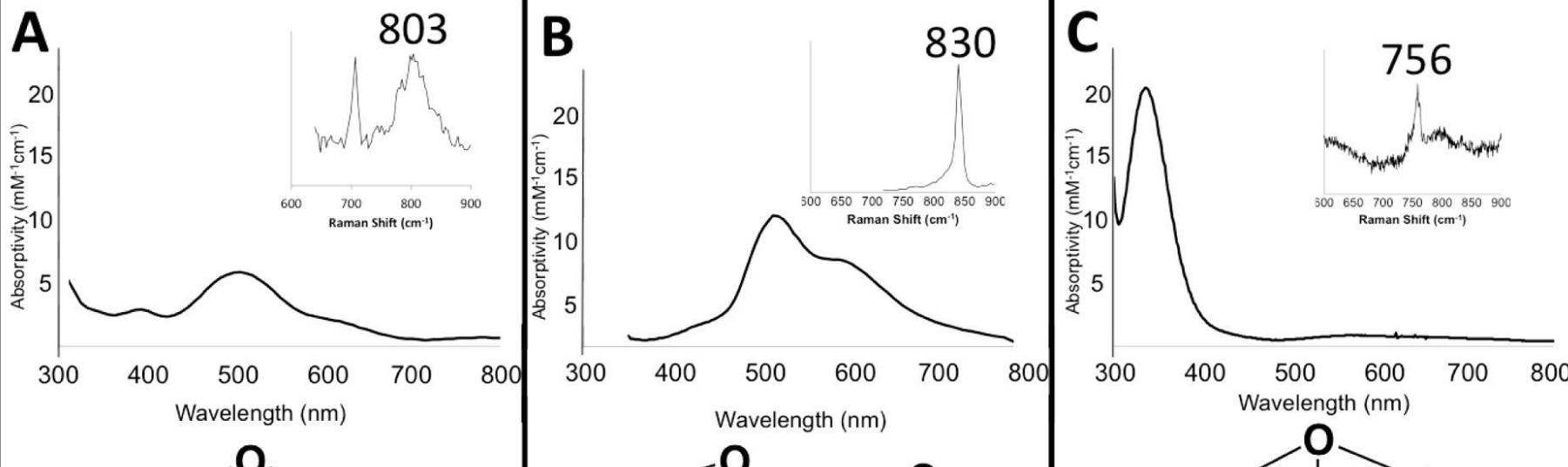
Deoxy-Hc (A) and oxy-Hc (B) from *Li. polyphemus* shows a large geometric change at the active site upon oxygen binding (the  $\text{Cu} \bullet \bullet \bullet \text{Cu}$  distance decreases by  $1.0 \text{ \AA}$ )

# Dicopper enzymes

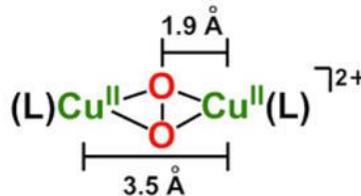


(A) Overlaid active site crystal structures of octopus hemocyanin (green), *Streptomyces castaneoglobisporus* tyrosinase (red), *Aspergillus oryzae* catechol oxidase (blue), with O<sub>2</sub> in the active sites highlighting their structurally similar active sites (copper and oxygen atoms are shown as large and small spheres, respectively).

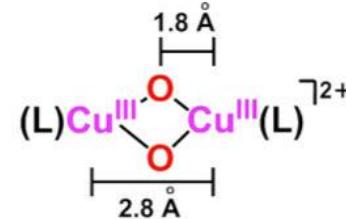
# Spectroscopic signature



*trans*- $\mu$ -1,2-peroxo ( ${}^{\text{T}}\text{P}$ )  
end-on



$\mu$ - $\eta^2:\eta^2$ -peroxo ( ${}^{\text{S}}\text{P}$ )  
side-on



bis- $\mu$ -oxo (O)

**UV-Vis:**  
 $\lambda: 500 - 550 \text{ nm} (\varepsilon: 4 - 13.5 \text{ mM}^{-1}\text{cm}^{-1})$   
 $\lambda: 590 - 650 \text{ nm} (\varepsilon: 2 - 11 \text{ mM}^{-1}\text{cm}^{-1})$

**rRaman:**  
 $\nu(\text{O}-\text{O}): 812 - 847 \text{ cm}^{-1} (\Delta^{18}\text{O}_2: 43 - 51 \text{ cm}^{-1})$   
 $\nu(\text{Cu}-\text{O}): 530 - 561 \text{ cm}^{-1} (\Delta^{18}\text{O}_2: 20 - 28 \text{ cm}^{-1})$

**UV-Vis:**  
 $\lambda: 332 - 380 \text{ nm} (\varepsilon: 11 - 25 \text{ mM}^{-1}\text{cm}^{-1})$   
 $\lambda: 518 - 551 \text{ nm} (\varepsilon: 0.8 - 3 \text{ mM}^{-1}\text{cm}^{-1})$

**rRaman:**  
 $\nu(\text{O}-\text{O}): 713 - 765 \text{ cm}^{-1} (\Delta^{18}\text{O}_2: 38 - 43 \text{ cm}^{-1})$

**UV-Vis:**  
 $\lambda: 297 - 379 \text{ nm} (\varepsilon: 10 - 21 \text{ mM}^{-1}\text{cm}^{-1})$   
 $\lambda: 397 - 448 \text{ nm} (\varepsilon: 10 - 28 \text{ mM}^{-1}\text{cm}^{-1})$

**rRaman:**  
 $\nu(\text{Cu}-\text{O}): 580 - 653 \text{ cm}^{-1} (\Delta^{18}\text{O}_2: 22 - 31 \text{ cm}^{-1})$