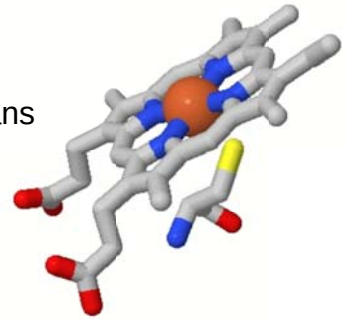
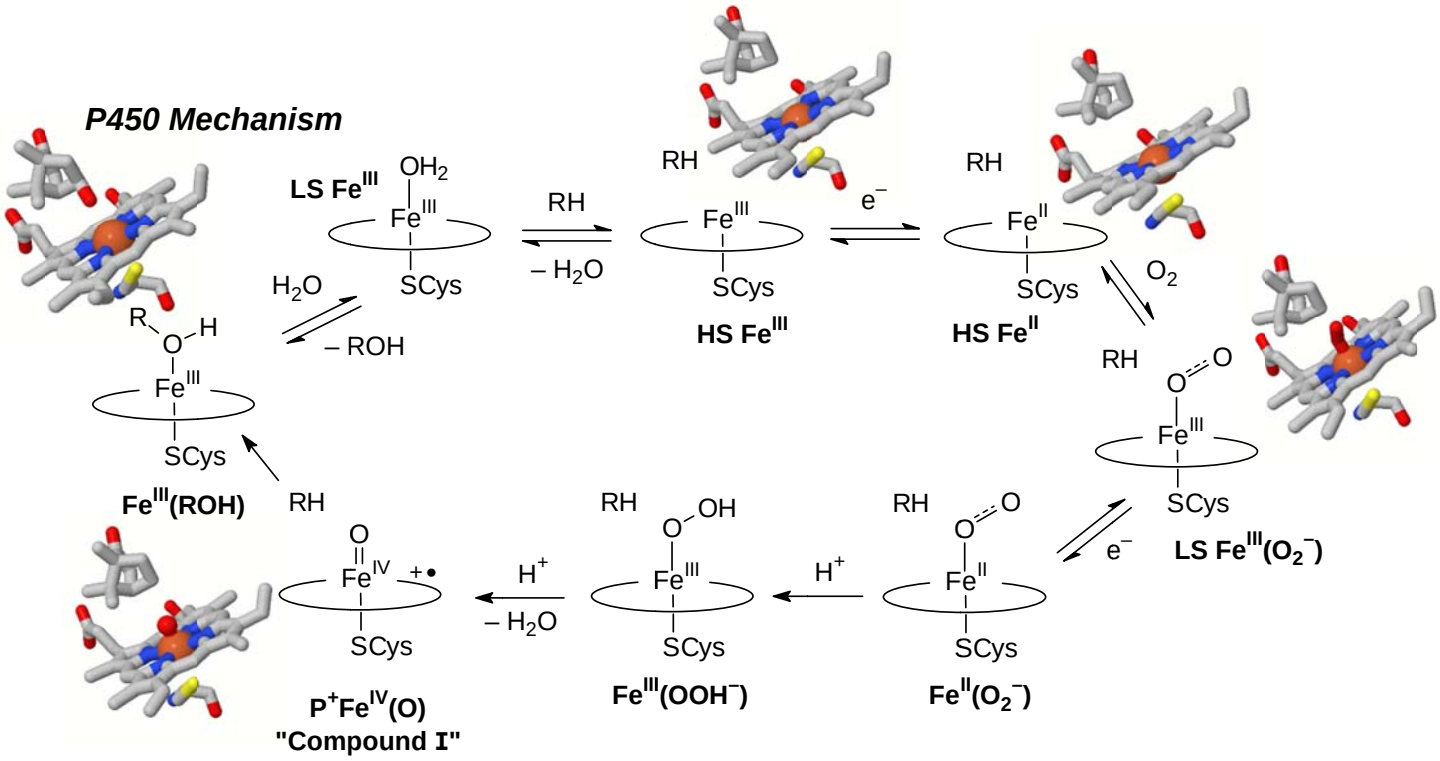
Cytochromes P450

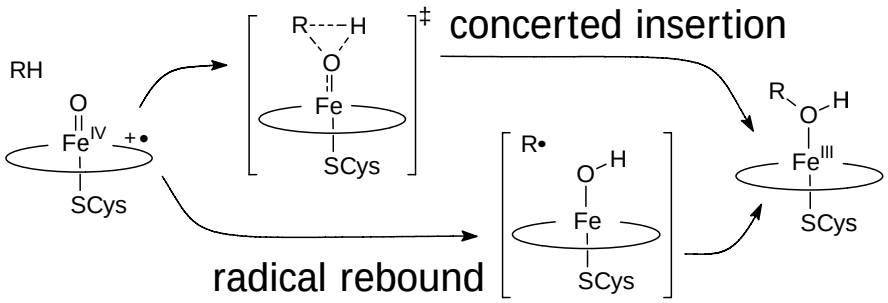


- large & diverse family of enzymes: ~8000 known, 57 in humans
- found in plants, animals, bacteria, archaea
- common heme + cysS active site
- differing functions / often multiple substrates:
  - drug metabolism
  - biosynthesis of steroids
- remarkable selective CH activation reaction: RH + $\mathbf{O_2}$ + $2e^-$ + $2H^+$ → R**O**H + H_2**O**
- electrons from NAD(P)H, usually via an FMN/FAD or Fd reducing protein

P450 Mechanism

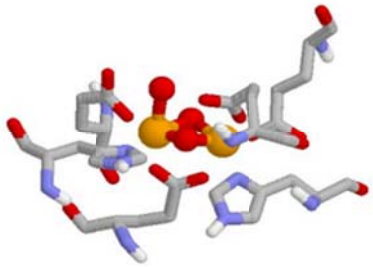


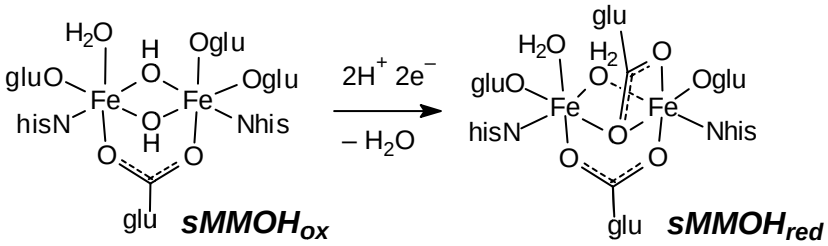
- Catalytic cycle very well studied: most intermediates characterized structurally!
- Binding of substrate to hydrophobic pocket occurs first
- O_2 bound, reduced, protonated, cleaved, generating “Compound I”
- Cmp I selectively inserts O atom into one C-H bond; potentially competing mechanisms, but two-step radical rebound pathway is most likely to be predominant



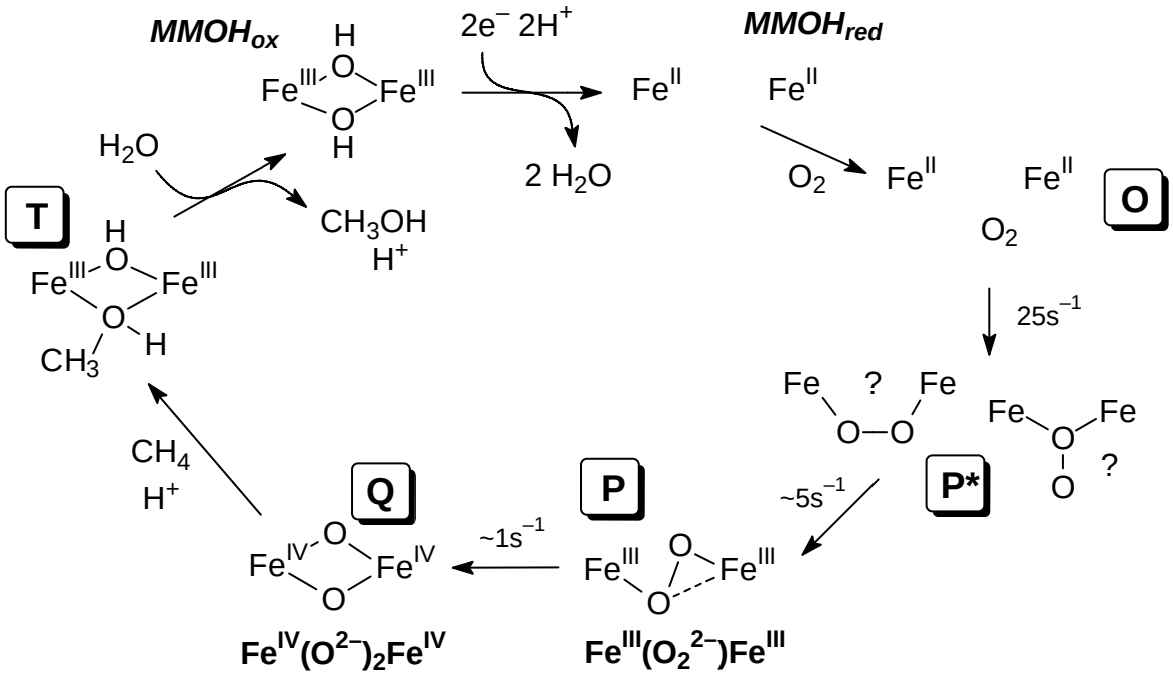
soluble Methane Monooxygenase (sMMO)

- MMOs are sole source of C and energy for methanotrophic bacteria
- sMMO best studied: membrane-bound pMMO is complex Cu-based
- sMMO system is three components: MMOR, MMOB, MMOH
- MMOH (hydroxylase) is best studied, of greatest interest
- MMOH is large (251kDa) $\alpha_2\beta_2\gamma_2$ dimer
- carboxylate-rich non-heme diiron active site, in four α-helix bundle
- selective CH activation of methane(!): $CH_4 + \mathbf{O_2} + 2e^- + 2H^+ \rightarrow CH_3\mathbf{O}H + H_2\mathbf{O}$
- e^- from NADH, transferred to MMOH via MMOR: FeS/FAD protein





sMMO Mechanism



- No structural characterization of key intermediates, but much spectroscopic / computational work
- O_2 bound, reduced, cleaved, generating “Compound Q”
- Q selectively inserts O atom into one C-H bond: as with P450, potentially competing radical vs concerted mechanisms, but radical process is likely predominant