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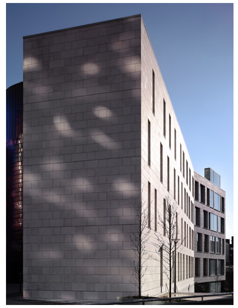

Enzymatic oxygen atom transfer reactions: Trends explained with Valence Bond Theory.

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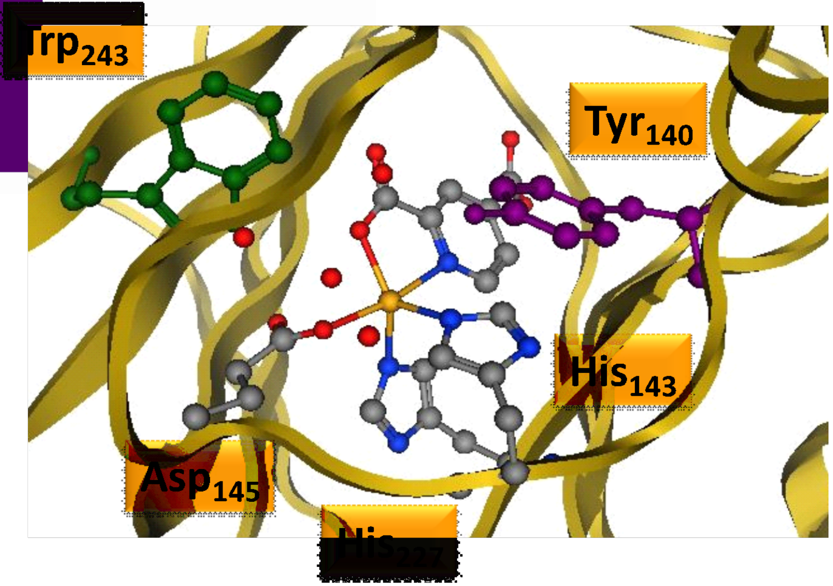
Nonheme Enzymes.

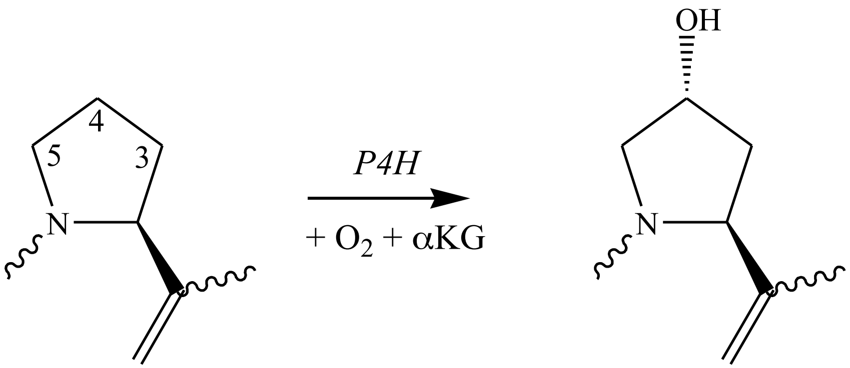


Prolyl-4-hydroxylase (P4H)

Nonheme enzymes:

Involved in:

- Oxygen sensing
- Cellular responses to hypoxia
- Collagen cross-linking
- DNA & RNA repair mechanisms



Nonheme enzyme with 2His/1Asp ligand system.

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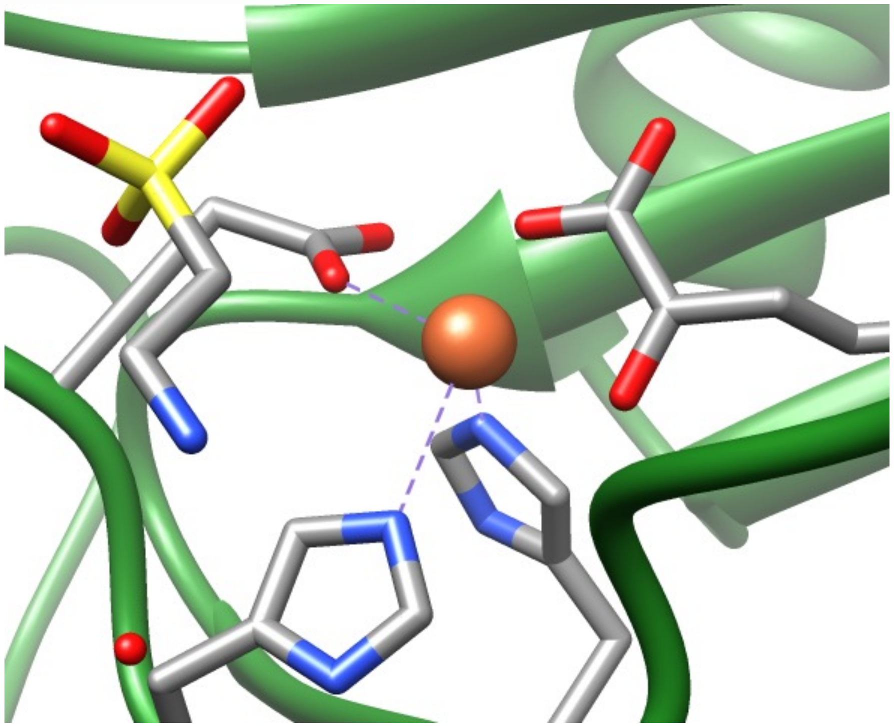
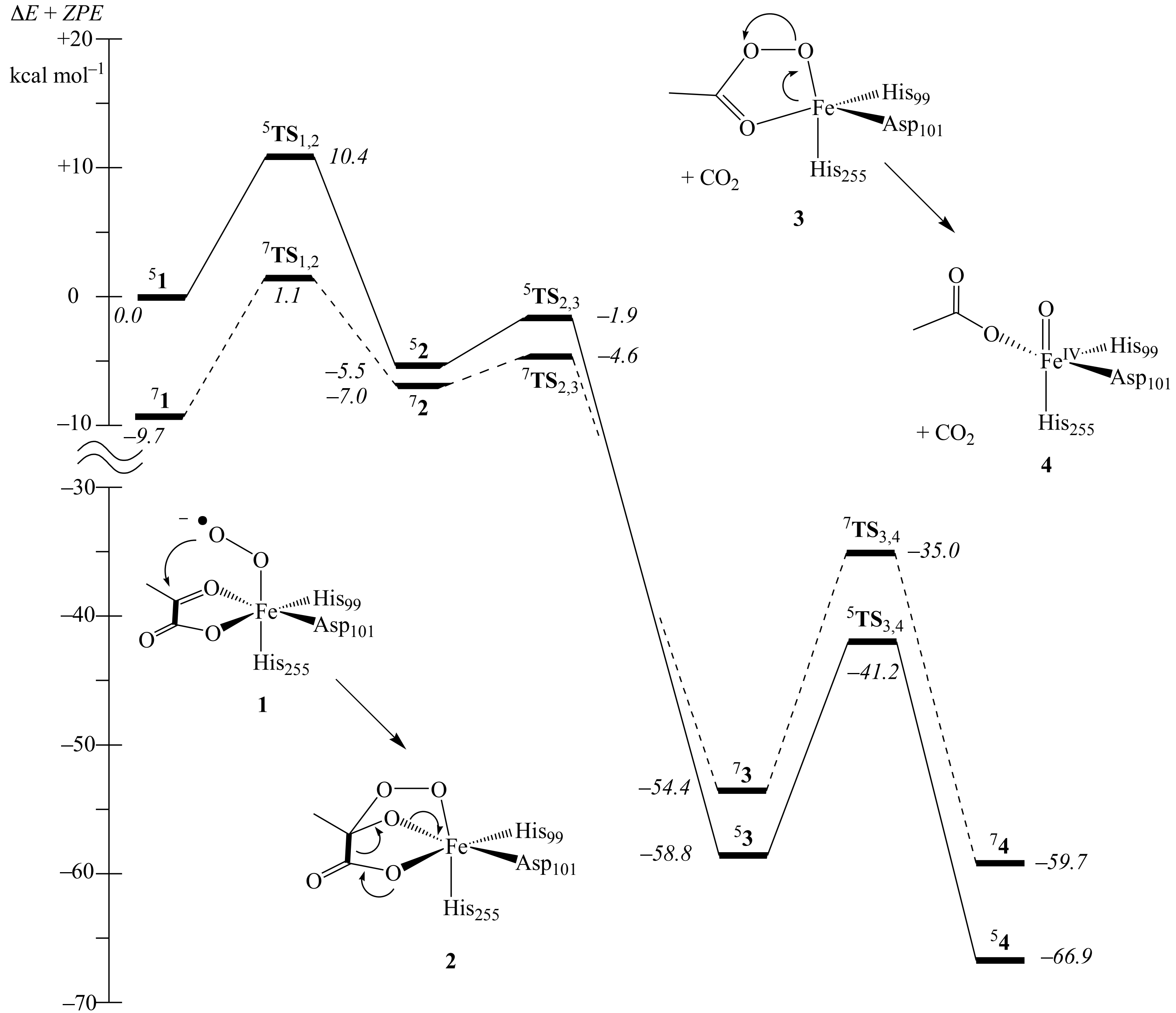
Non-heme iron enzymes with a 2-His/1-Asp motif.



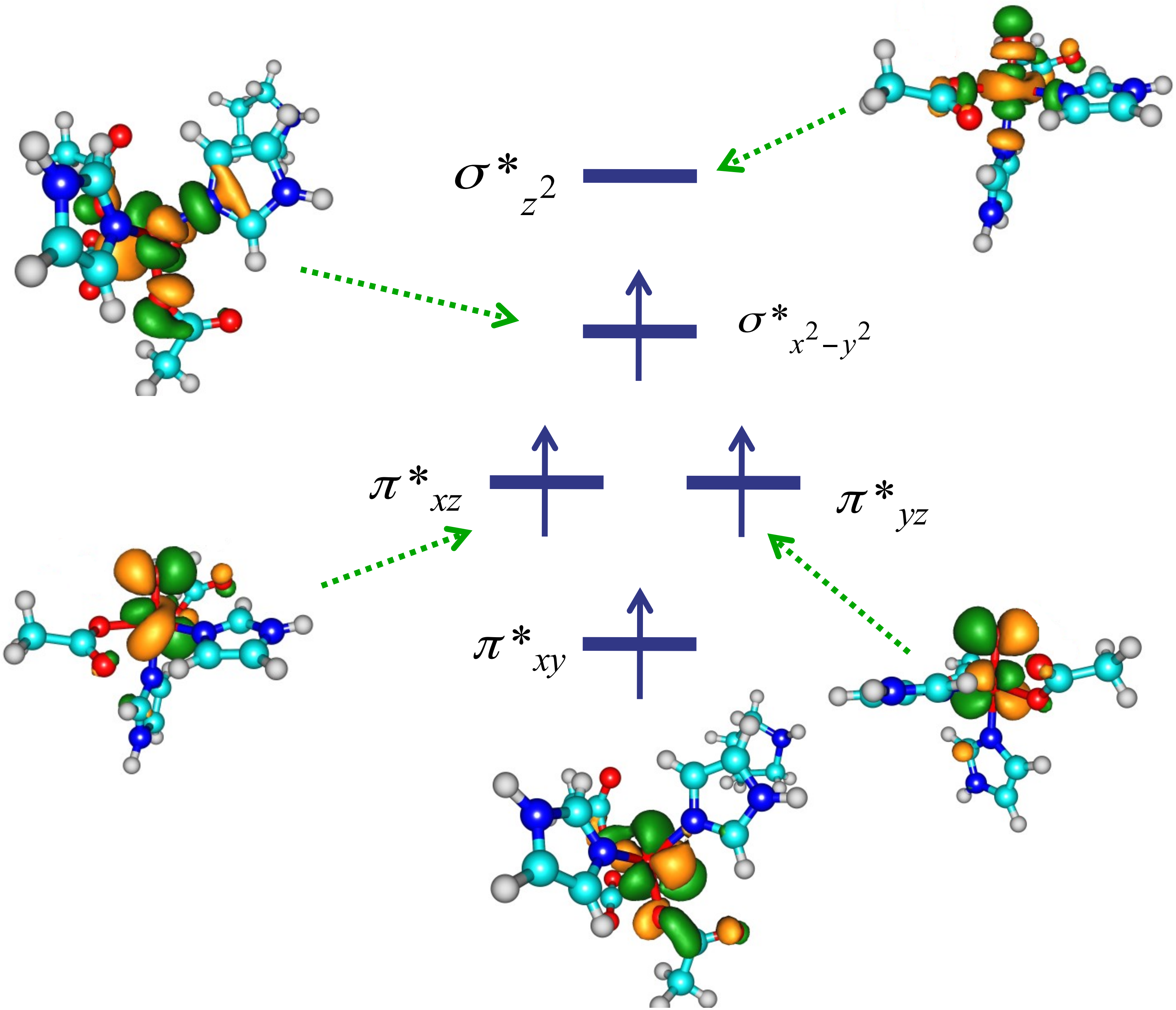
Taurine/α-ketoglutarate dioxygenase (TauD)

Has 2-His/1-Asp ligand system.

Does aliphatic hydroxylation.

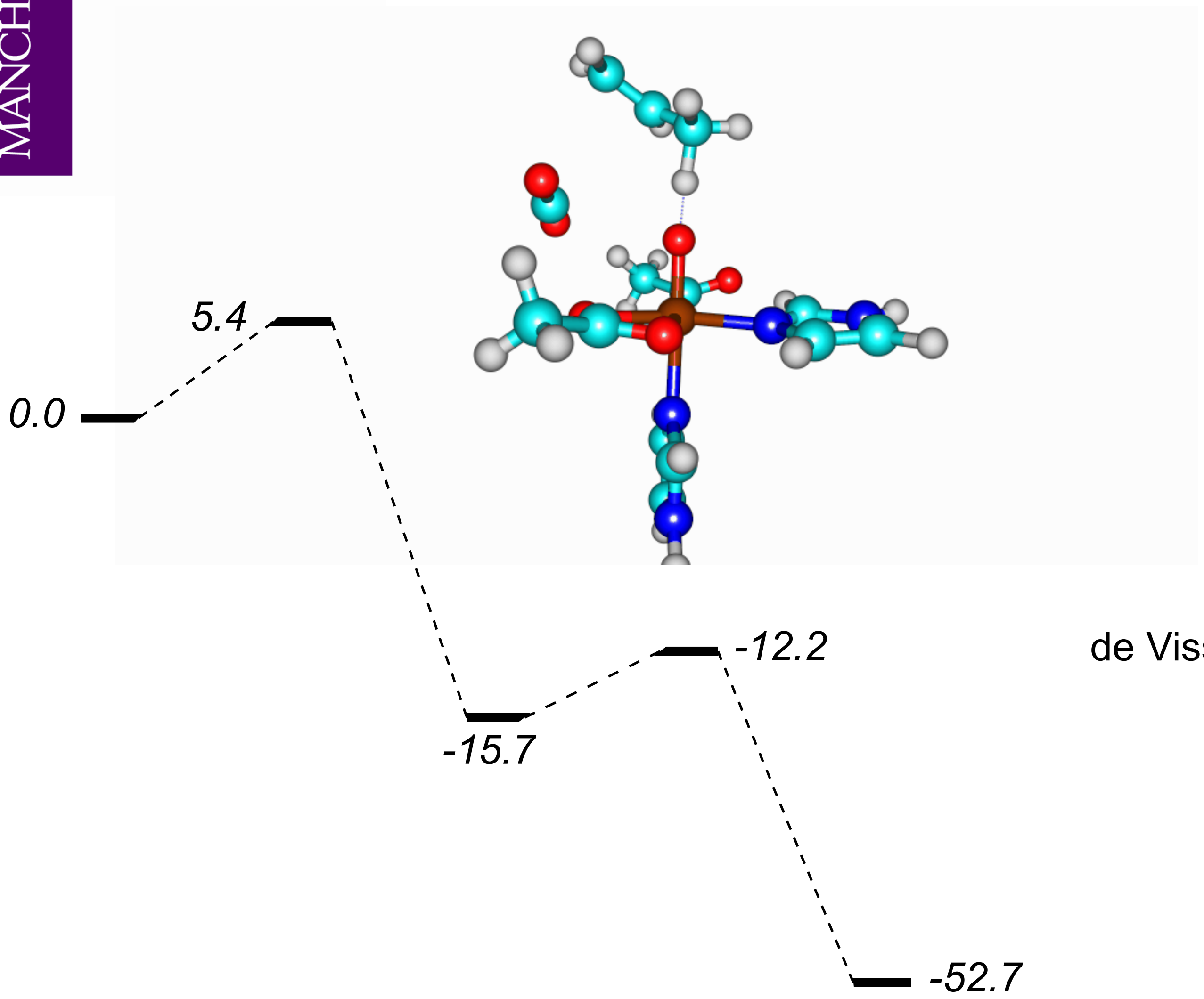


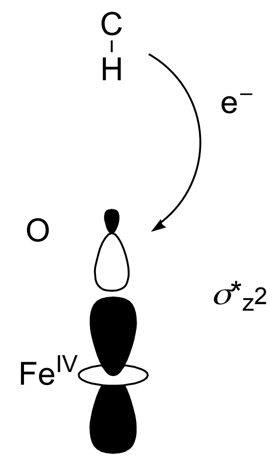
de Visser *Chem. Commun*. **2007**, 171–173.



$\sigma^*_{z^2}$
$\sigma^*_{x^2-y^2}$
π^*_{xz}
π^*_{yz}
π^*_{xy}

TauD reactivity.

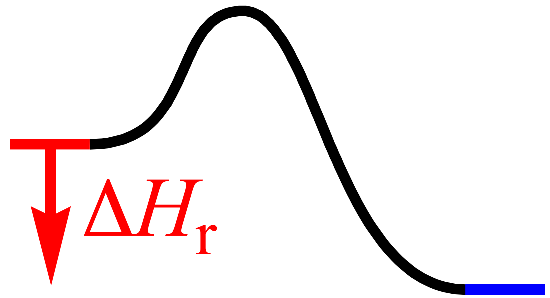




de Visser *J. Am. Chem. Soc.* **2006**, *128*, 15809–15818.

de Visser *J. Am. Chem. Soc.* **2006**, *128*, 9813–9824.

Hydrogen-Abstraction



- Thermodynamically, the H-abstraction reaction is described by the following equations:

$$\mathrm{Fe(IV){=}O(L)} + \mathrm{SubH} \rightarrow \mathrm{Fe(III)(OH)(L)} + \mathrm{Sub}^{\bullet}$$

$$\Delta H_{\mathrm{r}} = BDE_{\mathrm{C-H}} - BDE_{\mathrm{O-H}}$$

$$\mathrm{SubH} \rightarrow \mathrm{Sub}^{\bullet} + \mathrm{H}^{\bullet} + BDE_{\mathrm{C-H}}$$

$$\mathrm{Fe(III)(OH)(L)} \rightarrow \mathrm{Fe(IV){=}O(L)} + \mathrm{H}^{\bullet} + BDE_{\mathrm{O-H}}$$

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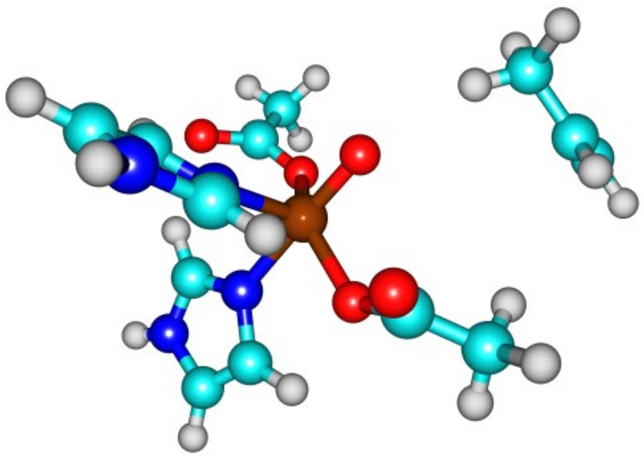
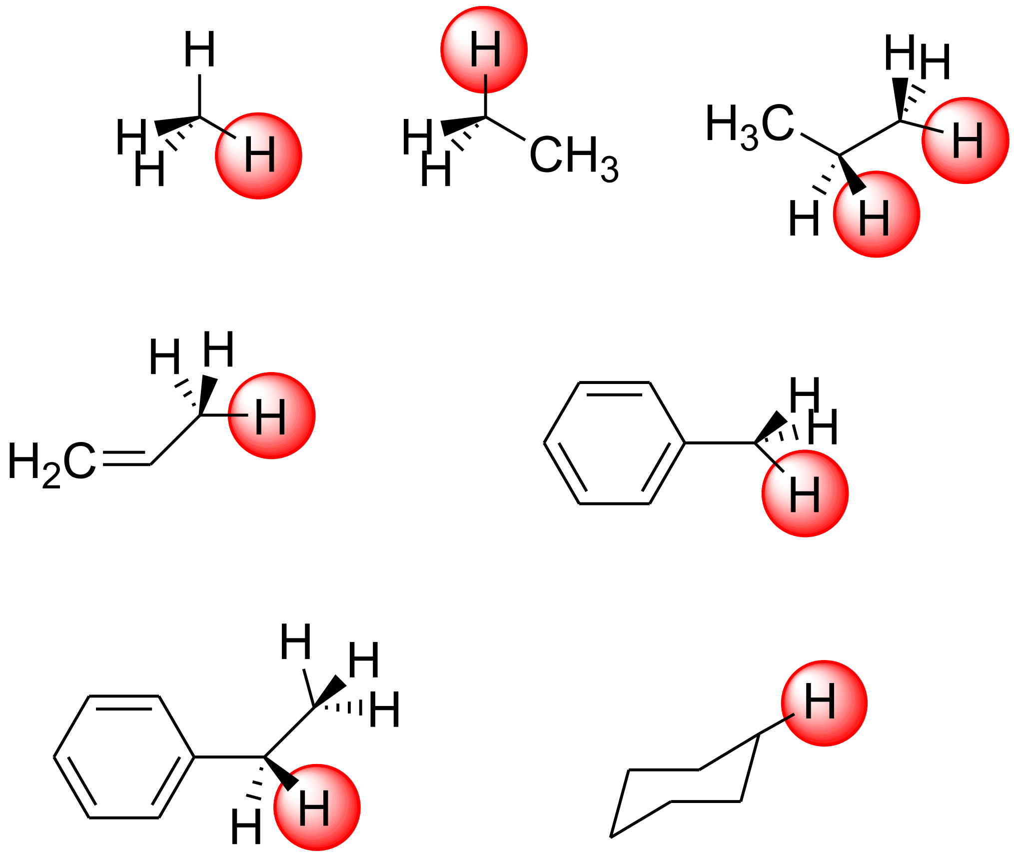
$$\mathrm{Fe(IV)}{=}\mathrm{O} + \mathrm{SubH} \rightarrow \mathrm{Fe(III)}{-}\mathrm{OH} + \mathrm{Sub}\bullet$$

$$\Delta H_{r} = BDE_{\mathrm{C-H}} - BDE_{\mathrm{O-H}}$$

Reaction exothermicity & barrier height versus BDE



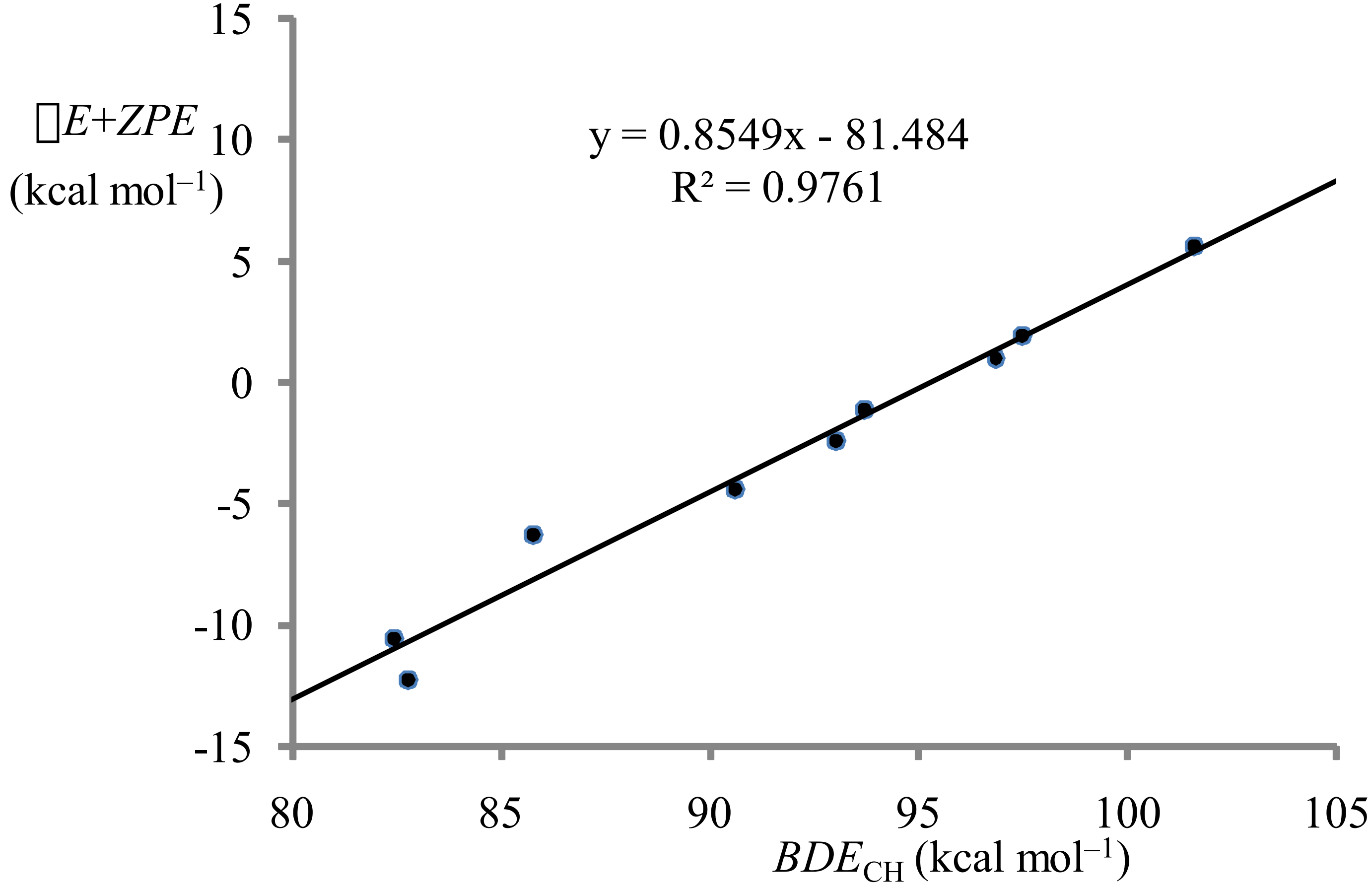


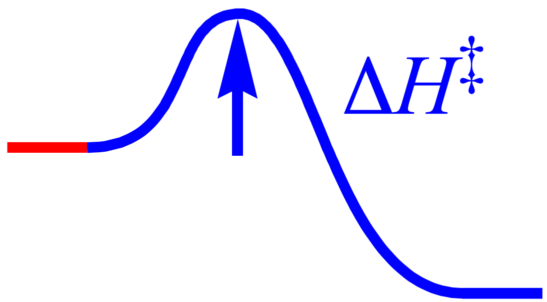
Latifi, Bagherzadeh & de Visser *Chem. Eur. J.* **2009**, *15*, 6651–6662.

$$Fe(IV){=}O + SubH \rightarrow Fe(III){-}OH + Sub\bullet$$

$$\Delta H_r = BDE_{C-H} - BDE_{O-H}$$

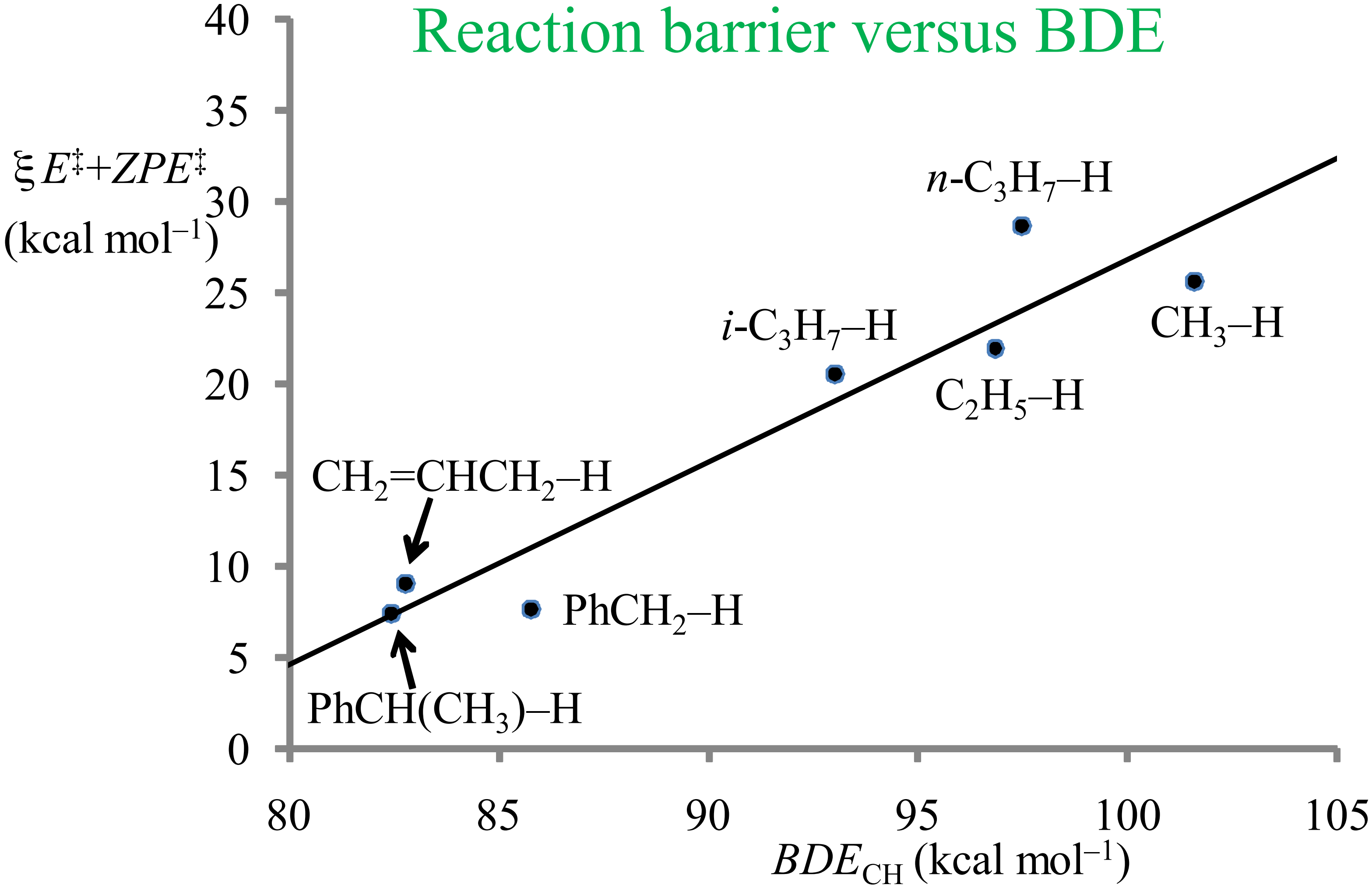
Reaction exothermicity versus BDE

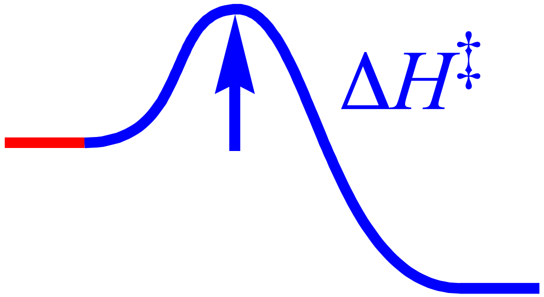




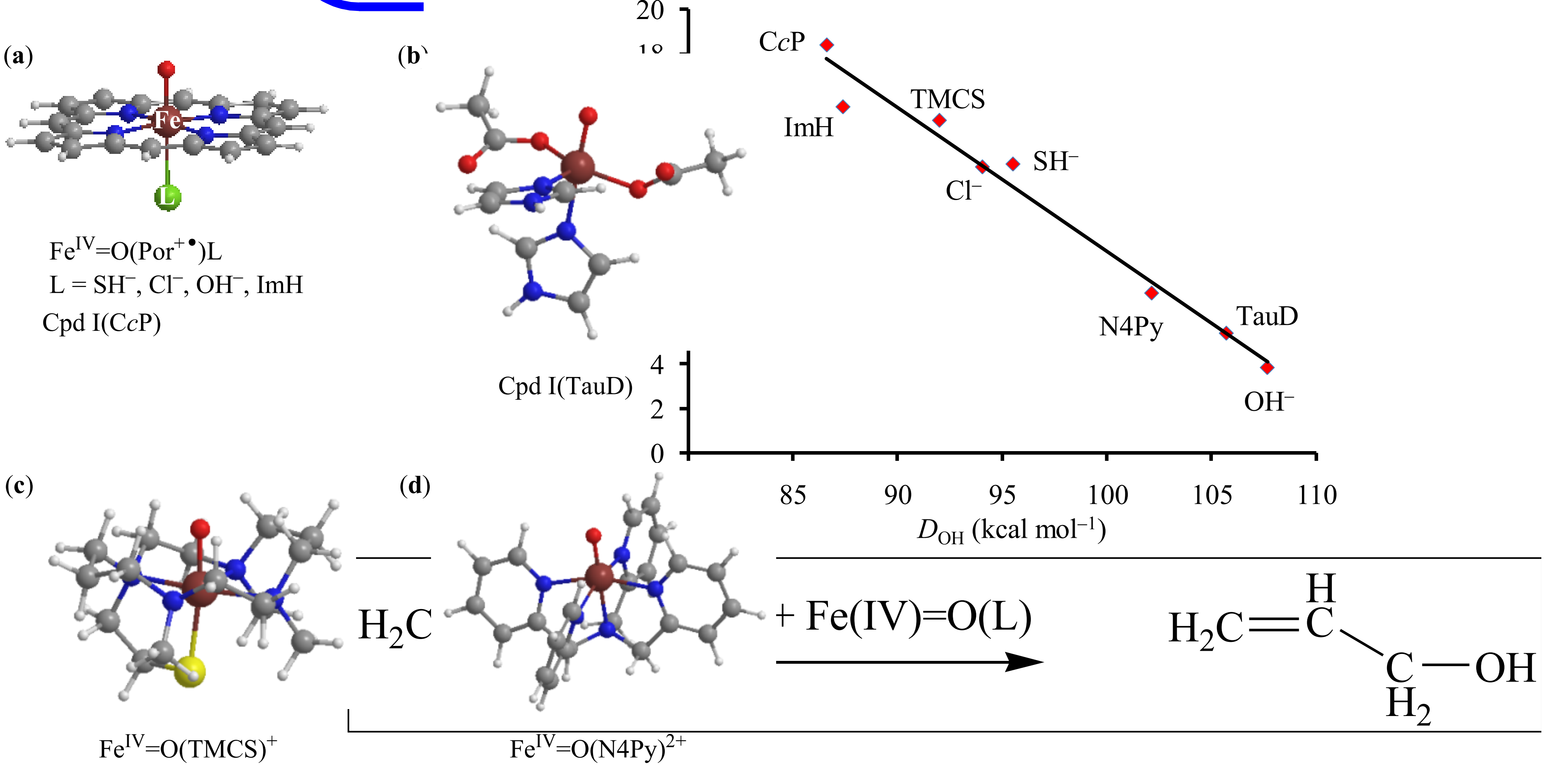
$$\mathrm{Fe(IV){=}O + SubH \longrightarrow Fe(III){-}OH + Sub\bullet}$$

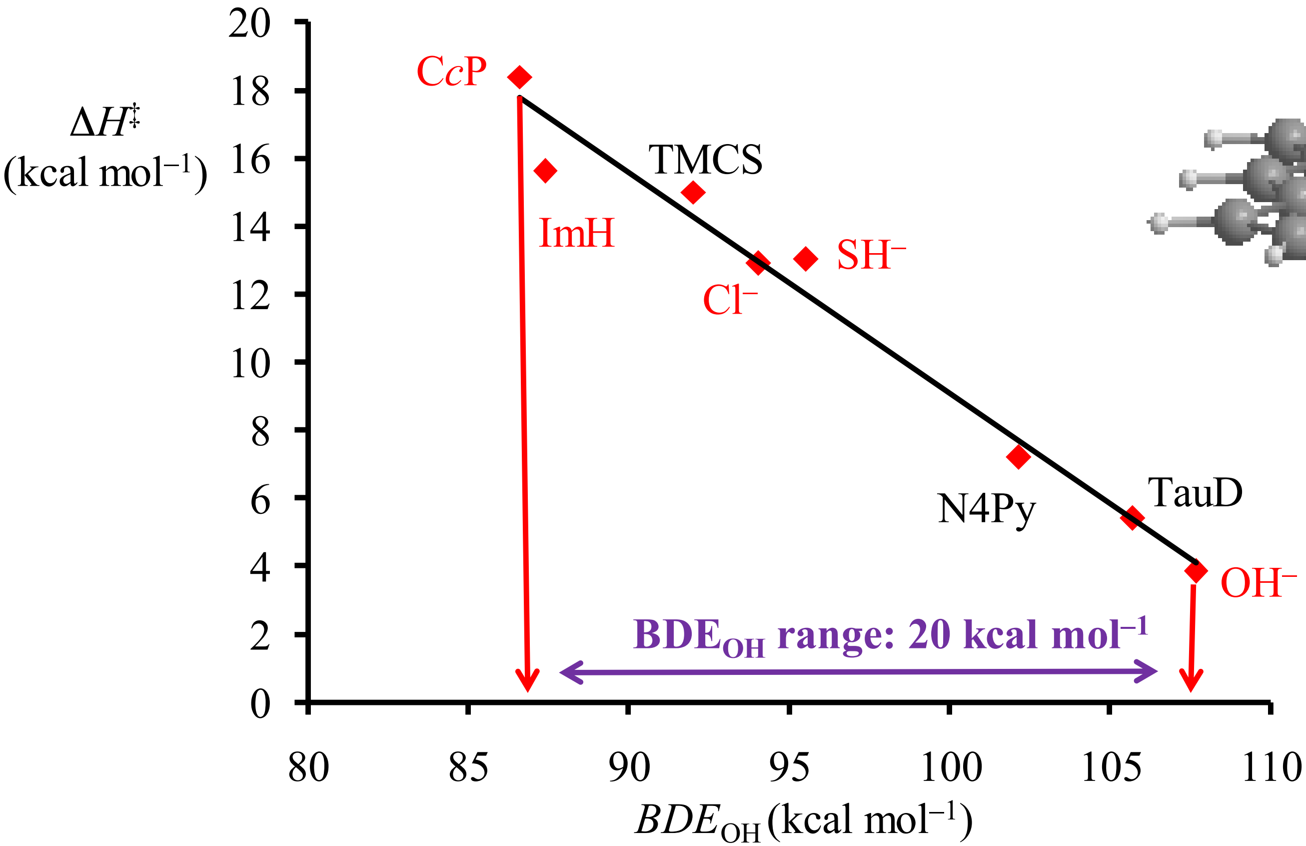
$$\Delta H_{\mathrm{r}} = BDE_{\mathrm{C-H}} - BDE_{\mathrm{O-H}}$$

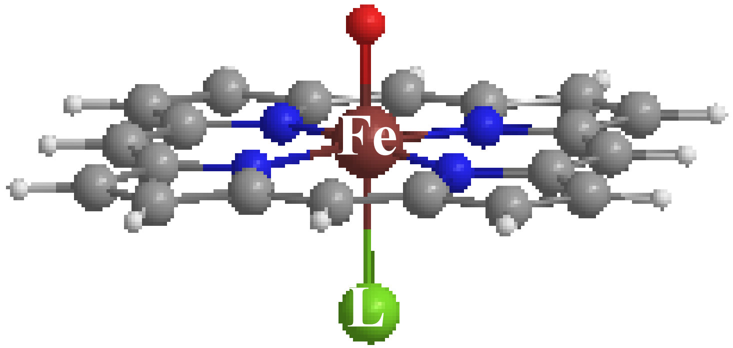




Barrier height versus BDE_{OH}







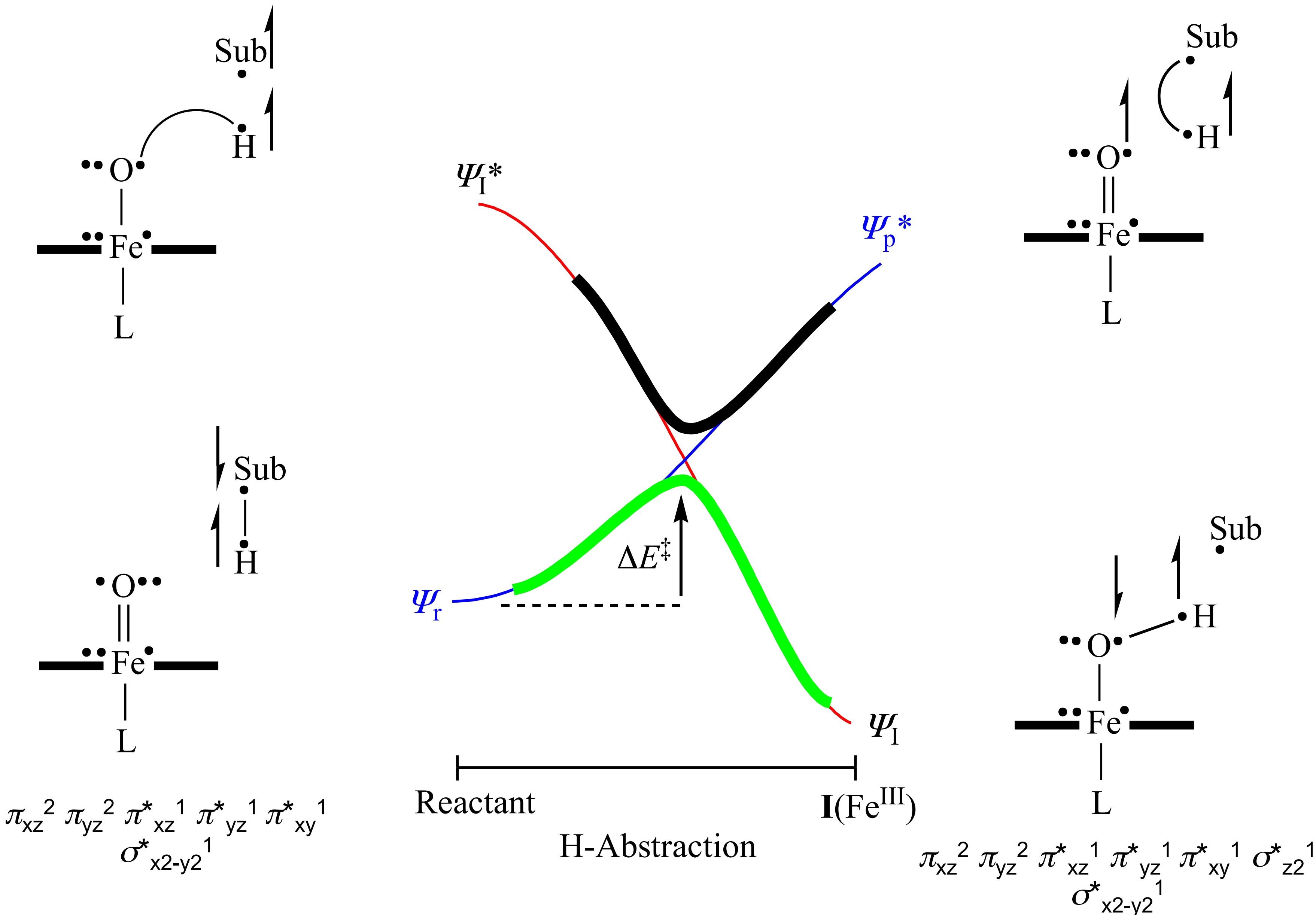
- Axial ligand on iron(IV)-oxo porphyrin(+•) gives 20 kcal mol^{-1} difference in BDE$_{OH}$!
- Best oxidant: L = OH$^-$; poor oxidant: ImH.
- Interestingly, the P450 axial ligand is midway in between those.

de Visser *J. Am. Chem. Soc.* **2010**, *132*, 1087–1097

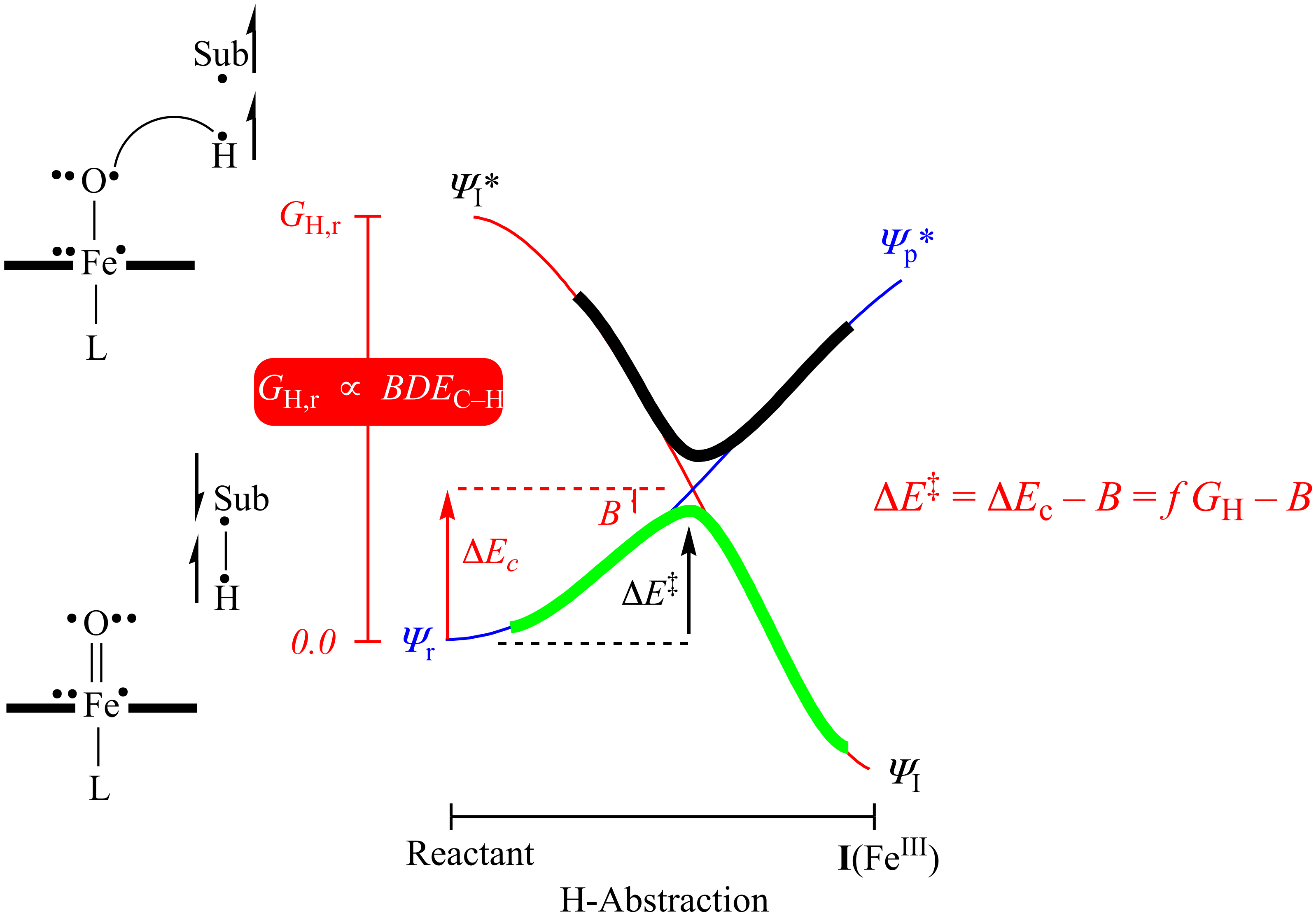
H-Abstraction correlations

- Thus, H-abstraction barrier correlates with both BDE_{CH} & BDE_{OH}.
- Barrier heights can be predicted from BDE_{CH} & BDE_{OH} values.
- Moreover, dramatic differences in axial ligand effect seen.
- What is the origin of these correlations?

- **Try Valence Bond Theory!**



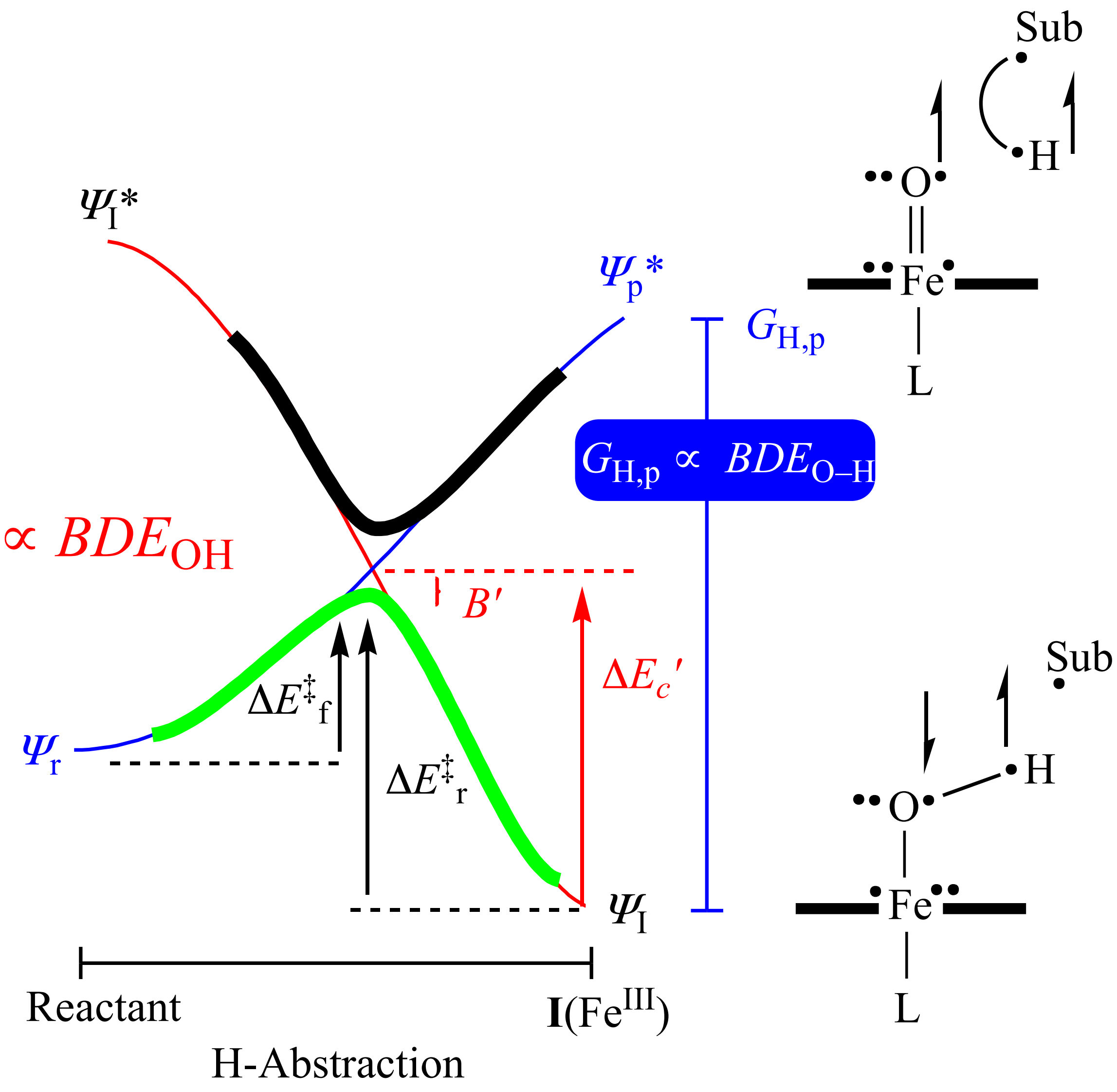
Shaik, Kumar & de Visser *J. Am. Chem. Soc.* **2008**, *130*, 10128–10140
de Visser *J. Am. Chem. Soc.* **2010**, *132*, 1087–1097



Shaik, Kumar & de Visser *J. Am. Chem. Soc.* **2008**, *130*, 10128–10140
de Visser *J. Am. Chem. Soc.* **2010**, *132*, 1087–1097

$$\Delta E^{\ddagger}_{r} = f\,'G_{H,p} - B'$$

$$\Delta E^{\ddagger}_{f} = \Delta E^{\ddagger}_{r} - \Delta H_{r} \propto BDE_{OH}$$



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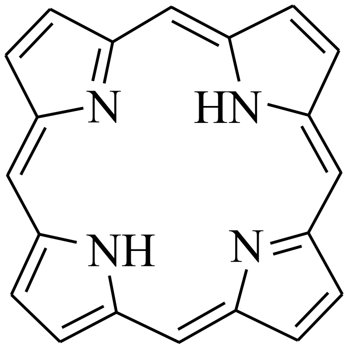
VB curve crossing diagram

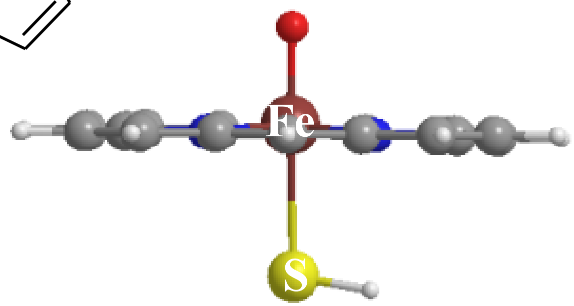
- Is qualitative way to rationalize hydrogen abstraction reactions.
- Explains that the mechanism is stepwise via a radical intermediate.
- Explains the electron transfer mechanisms.
- Shows that the barrier height correlates with the strength of the C–H/O–H bonds.

Shaik, Kumar & de Visser *J. Am. Chem. Soc.* **2008**, *130*, 10128–10140
Latifi, Bagherzadeh & de Visser *Chem. Eur. J.* **2009**, *15*, 6651–6662
De Visser, *J. Am. Chem. Soc.* **2010**, *131*, 1087–1097.

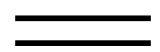
Substrate epoxidation?

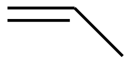


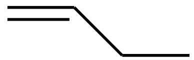
Cpd I(SH)

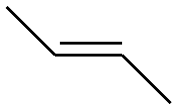


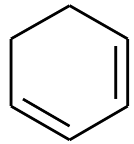
Substrates:

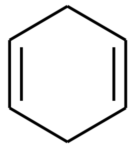
1 

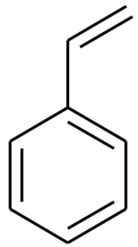
2 

3 

4 

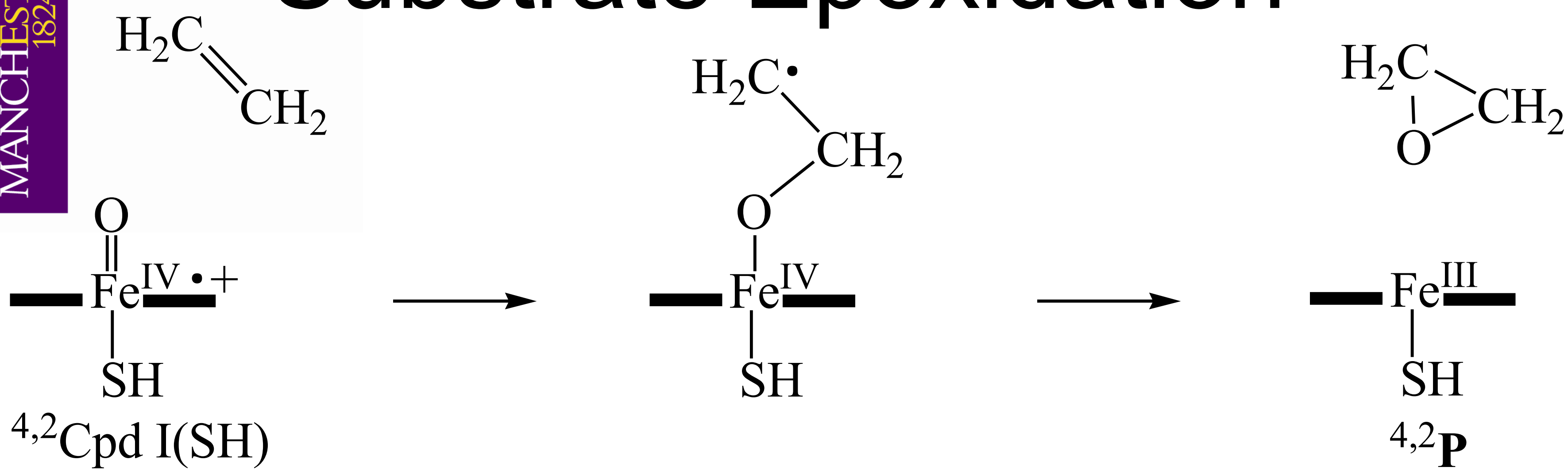
5 

6 

7 

Kumar, Karamzadeh, Sastry & de Visser, *J. Am. Chem. Soc.* **2010**, *132*, 7656–7667.

Substrate Epoxidation



- First step: breaking of C=C double bond and formation of C–O bond.
- Does rate constant/barrier height correlate with the Ionization Potential of olefin and BDE_{OH}?

Kumar, Karamzadeh, Sastry & de Visser, *J. Am. Chem. Soc*. **2010**, *132*, 7656–7667.

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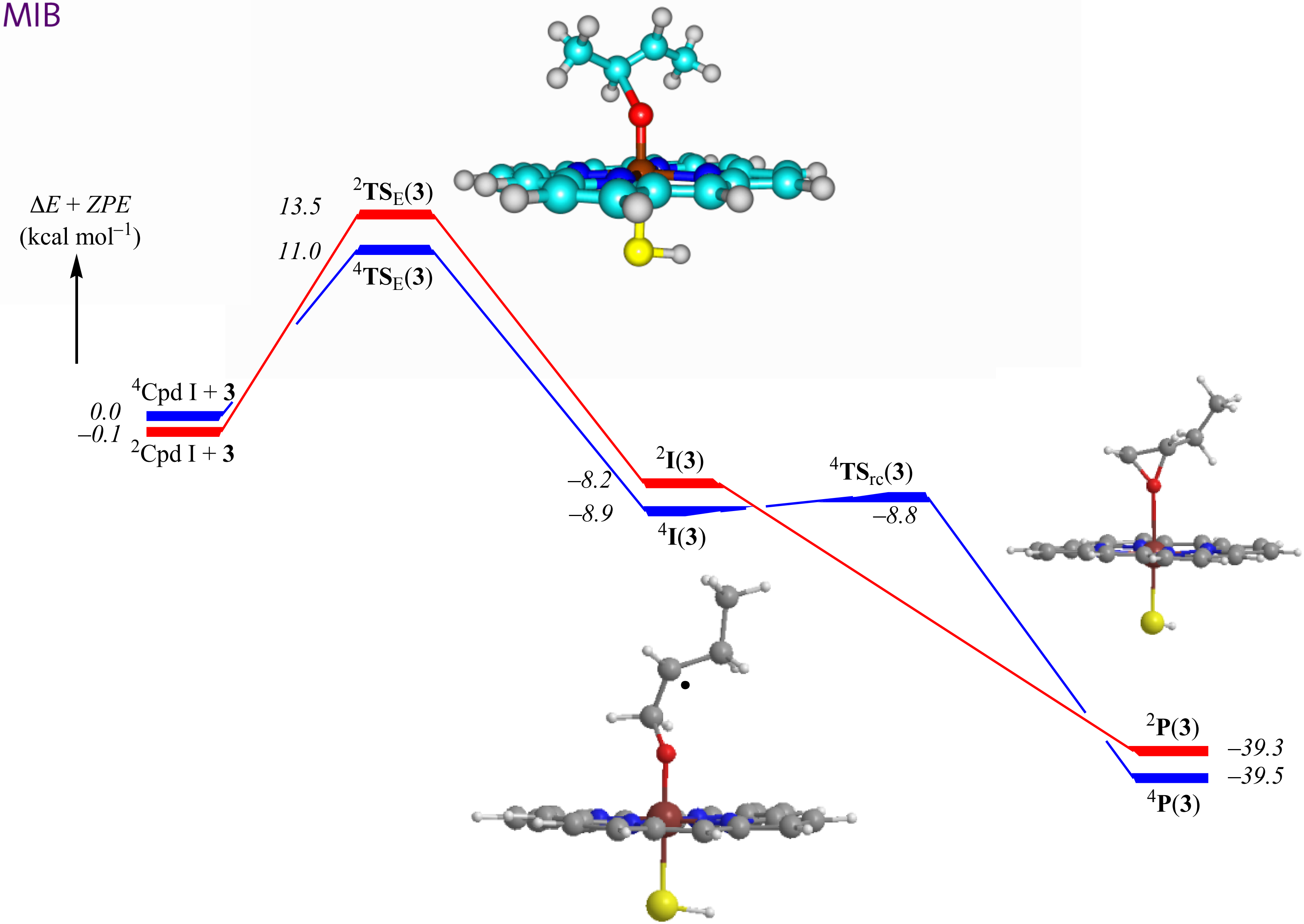
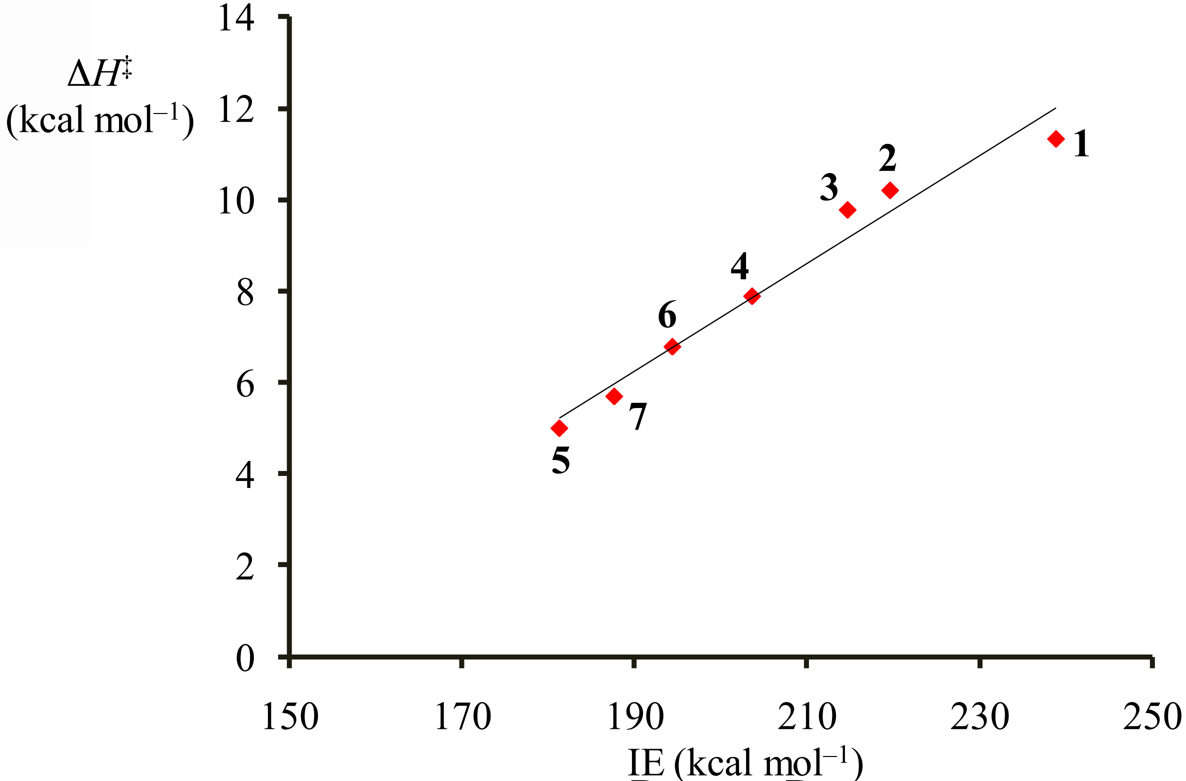
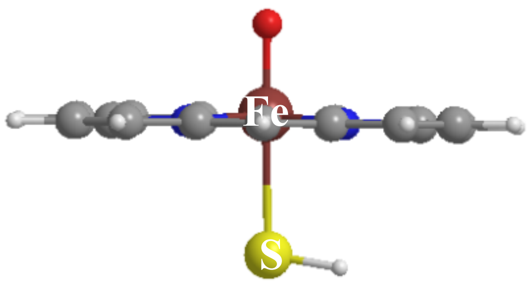
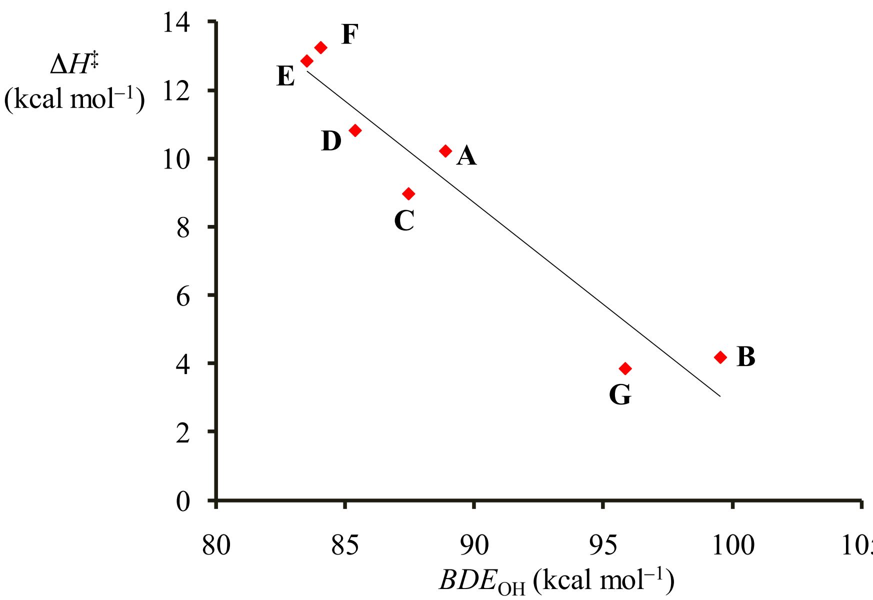


Correlations

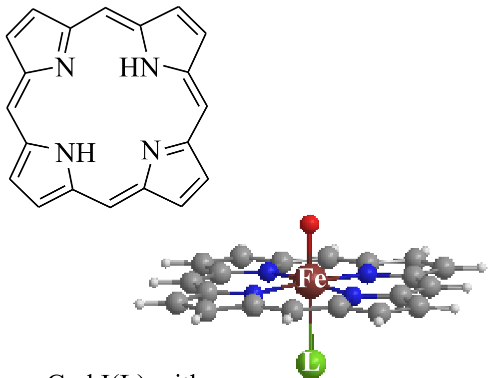




Correlations.

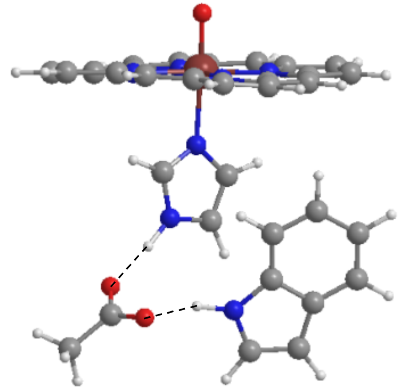


(a)

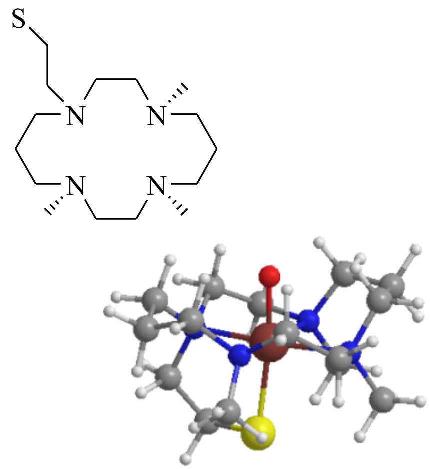


Cpd I(L) with
L = SH^-, Cl^-, OH^-, ImP

(b)

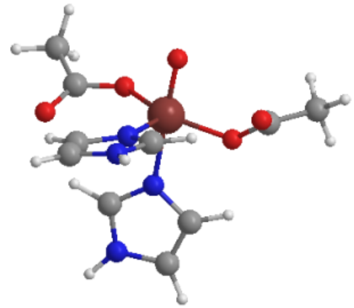


Cpd I(C*c*P)



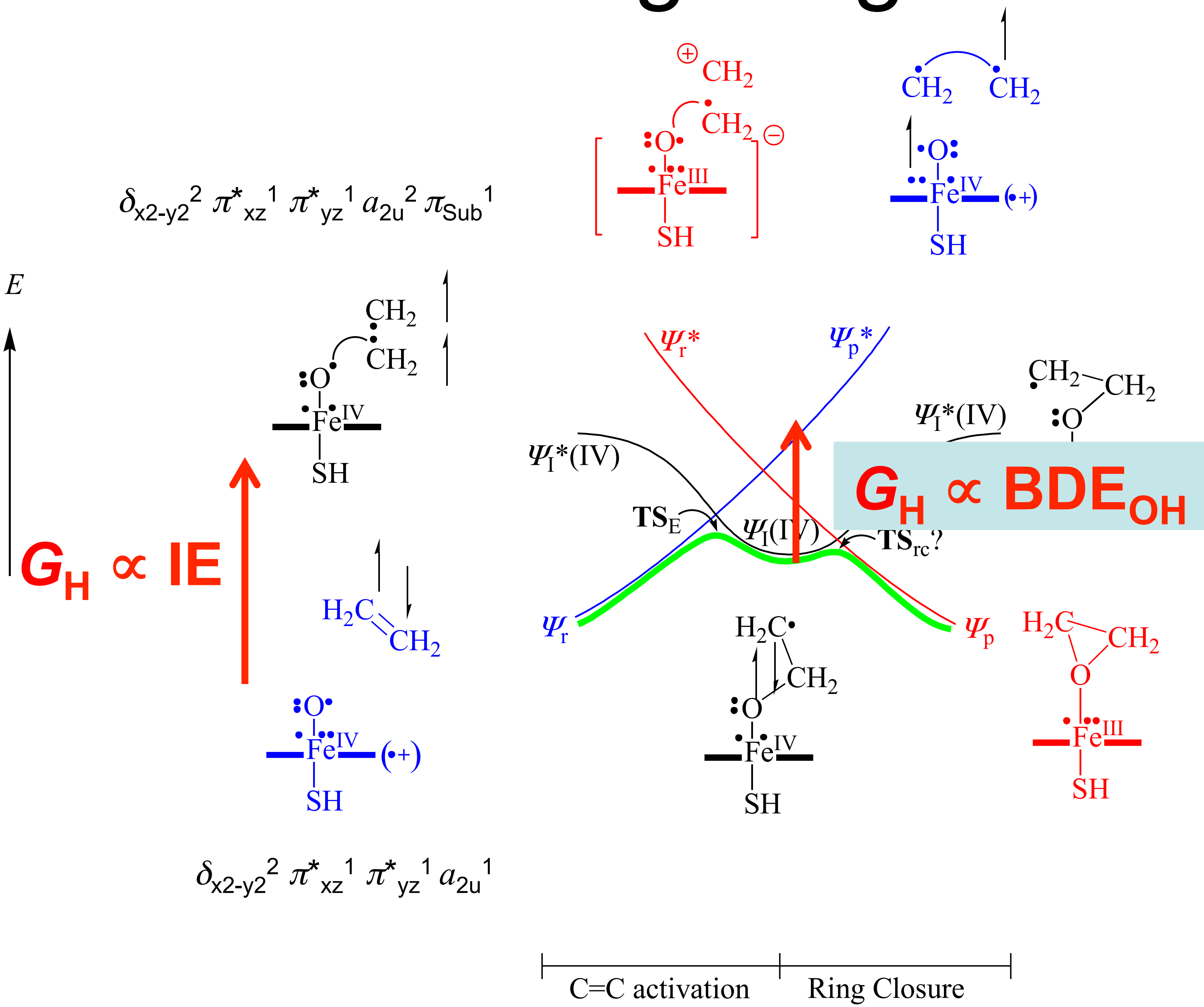
Fe^{IV}=O(TMCS)$^+$

(d)



Cpd I(TauD)

VB Curve Crossing Diagram



Epoxidation.

- Stepwise mechanism via radical intermediate.
- Barrier of olefin epoxidation correlates with $IE_{substrate}$ and BDE_{OH}.
- Barriers explained with a VB diagram.
- Recent studies on substrate sulfoxidation by iron(IV)-oxo complexes also gave correlations with $IE_{substrate}$ and BDE_{OH}.

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Overall summary

- DFT calculations done on non-heme iron dioxygenases and heme iron monoxygenases.
- Efficient oxidants of oxygen atom transfer reactions.
- Ligand (cis/trans) effects established.
- Predictive trends for H-atom abstraction.
- VB diagrams used to explain the trends.

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