Biomimetic Hydrogen Production and Activation: The Hydrogenases

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2006 Summer Research Group

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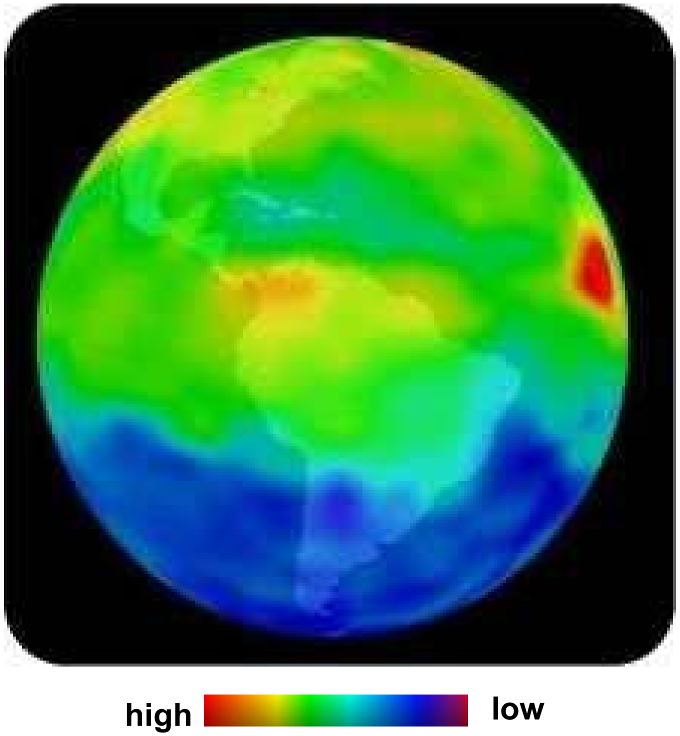
Mike Hall, Don Darensbourg,
Manny Soriaga

Motivation for Research on Hydrogenases: 2006

Looming Energy Crisis

Stockbridge, Ga.
Aug. 31, 2005.
(AP Photo/Gene Blythe)

Pollution and Global Warming



CO concentration

http://www.ecology.com/ecology-today/tracking-air-pollution/

Motivation for Research on Hydrogenases: ca. 1930

Marjory Stephenson and the River Ouse, Cambridge U.K.

Discoverer of hydrogenases in microorganisms, isolated from polluted river mud, which mediate methane formation

- Fermentation of glucose by anaerobic Methanoarchaea

Glucose ➔ acetate/formate + CO_2 + H_2

$H_2 + CO_2 \rightarrow CH_4 + 2\,H_2O$

- “Bact. Coli has been shown to catalyse the reaction:

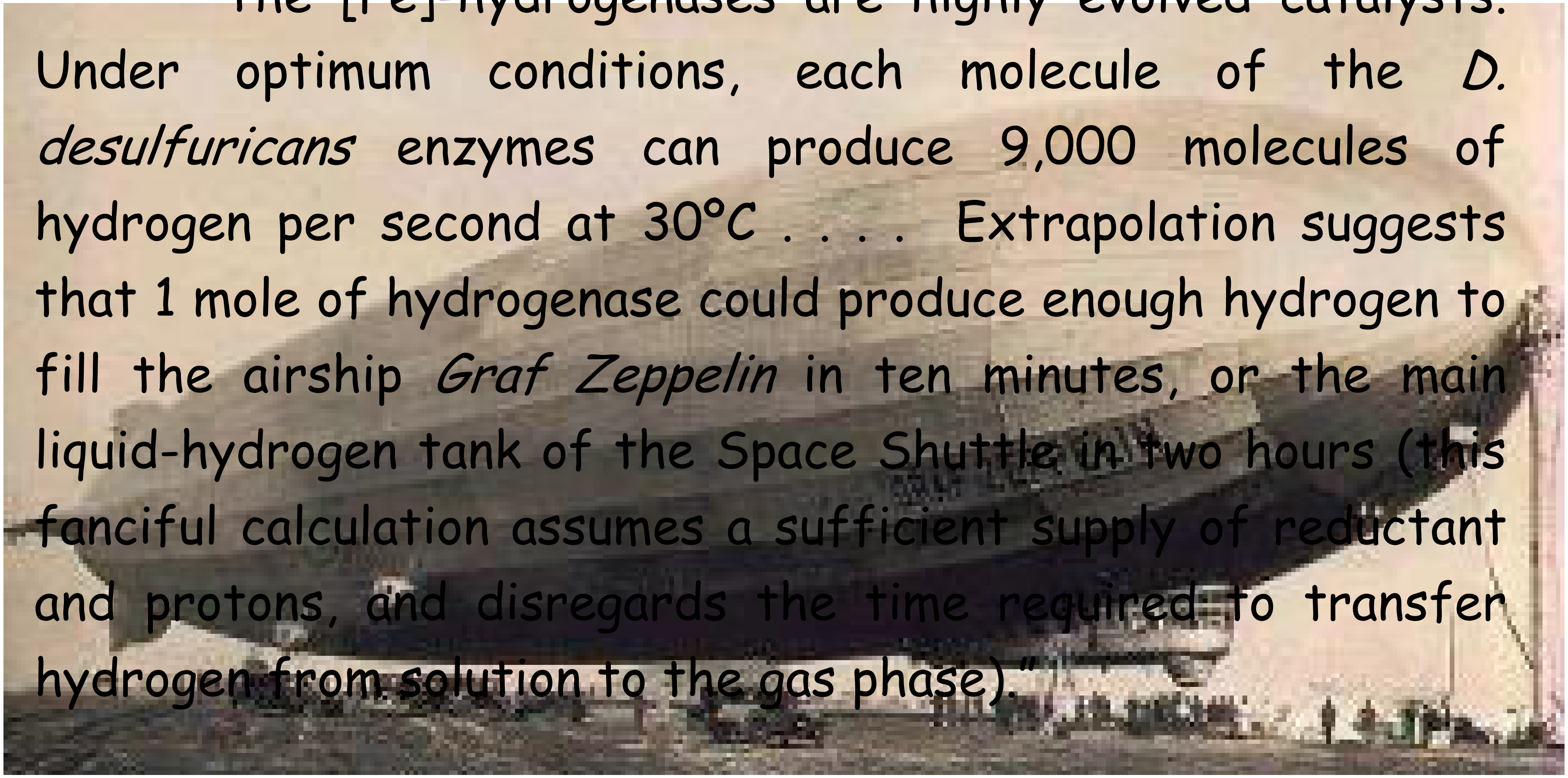
$$H_2 \leftrightarrows 2\,H^+ + 2\,e^-$$

In a completely reversible way. The hydrogenase system is the most negative reversible oxidation-reduction as yet described in living cells.”

(pH = 7.02, H_2 pressure = 600 mm Hg, Potential = -.401 V.

Hydrogenase Sophistication

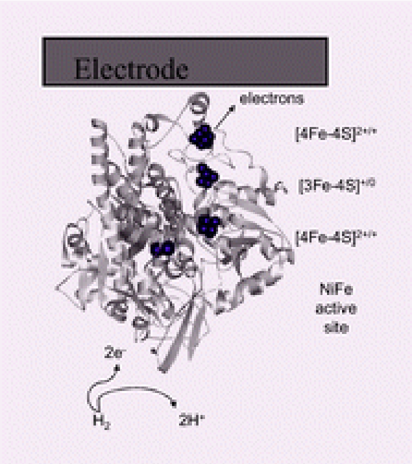
Richard Cammack, (*Nature*, *Vol. 397*, 1999)



"The [Fe]-hydrogenases are highly evolved catalysts. Under optimum conditions, each molecule of the *D. desulfuricans* enzymes can produce 9,000 molecules of hydrogen per second at 30°C . . . . Extrapolation suggests that 1 mole of hydrogenase could produce enough hydrogen to fill the airship *Graf Zeppelin* in ten minutes, or the main liquid-hydrogen tank of the Space Shuttle in two hours (this fanciful calculation assumes a sufficient supply of reductant and protons, and disregards the time required to transfer hydrogen from solution to the gas phase)."

But, 1 mole = 90 kD = ca. 200 lbs.

Electrocatalysis of H_2 Uptake



Direct comparison of the electrocatalytic oxidation of hydrogen by an enzyme and a platinum catalyst

Anne K. Jones, Emma Sillery, Simon P. J. Albracht, and Fraser A. Armstrong

Chem. Commun, **2002**, 866-867.

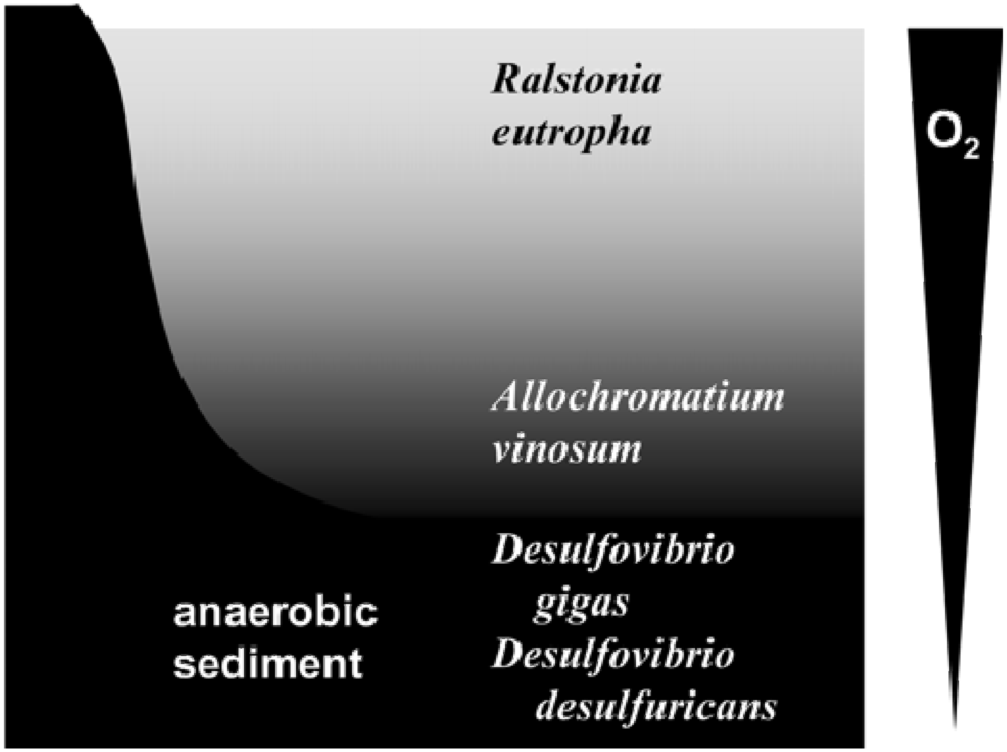
Results: Molecules of *Allochromatium vinosum* [NiFe]-hydrogenase adsorbed on a pyrolytic **graphite electrode** the nickel–iron active site **catalyzes hydrogen oxidation at a diffusion-controlled rate matching that achieved by platinum**.

OK!... then use the enzymes...

But, the general impression is...
The enzymes are derived from air-sensitive, extremophiles.

Oxidative tolerance of Hydrogenases in various microorganisms

The "Pond"



Aerobic Knallgas Bacterium: ambient O_2 tolerated

Transition zone: Photosynthetic purple sulfur bacterium

Sulfate-reducing Bacteria anaerobes

All have mechanisms for recovery from oxygen stress :
A challenge for the development of bio-inspired catalysts

Vincent, et al., JACS, 2005

Hydrogenases

$$H_2 \rightleftharpoons 2\,H^+ + 2\,e^-$$

$$H_2 \rightleftharpoons H^+ + H^-$$

$$D_2O + H_2 \rightleftharpoons HDO + HD$$

Methanogenic

Photosynthetic ← Bacteria, Archaea, and Eucarya → Nitrogen fixing

Sulfate reducing

4Fe4S Cluster-Containing

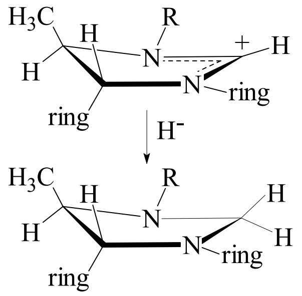
[FeFe]

- ♦ H_2 production
- ♦ Activity 10 – 100 x [NiFe]H_2ase
- ♦ Most O_2 sensitive H_2ase

[NiFe] / [NiFeSe]

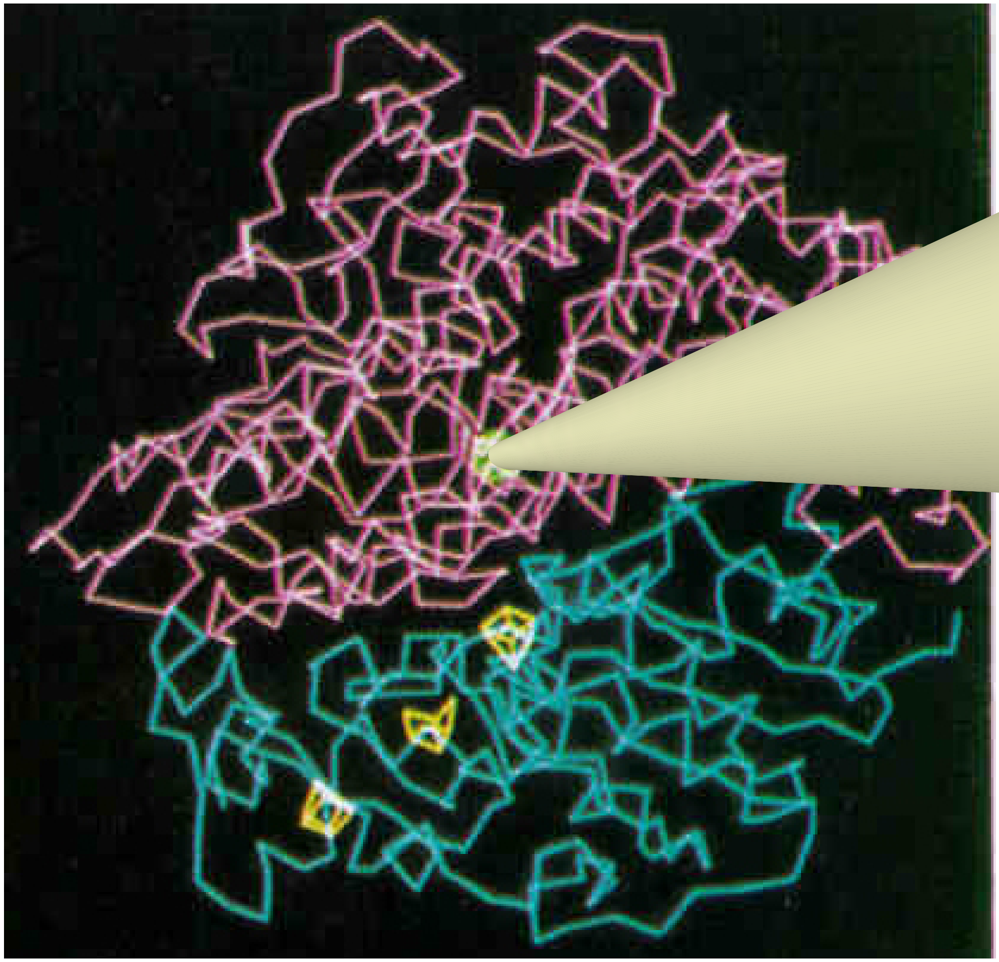
- ♦ H_2 consumption
- ♦ Majority of H_2ases
- ♦ H_2 affinity 100 x [Fe]H_2ase
- ♦ Terminal S-Cys → Se-Cys

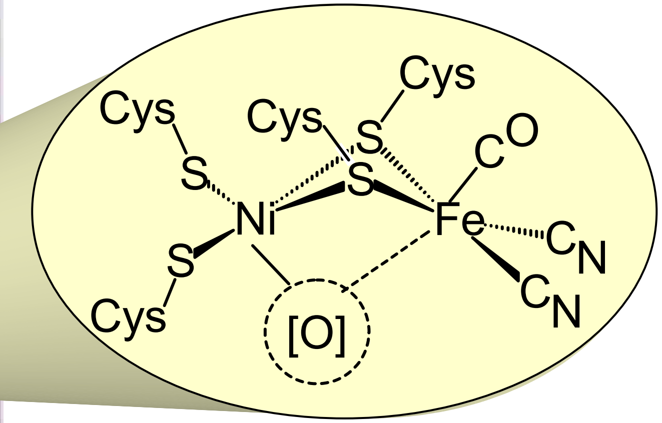
??Fe(CO)$_2$



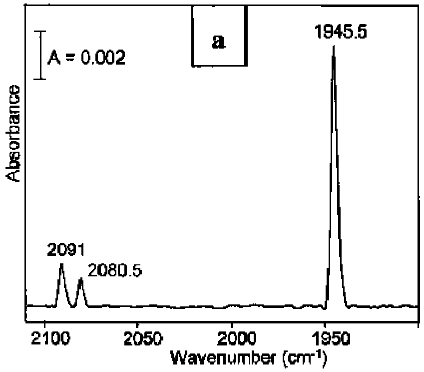
Thauer

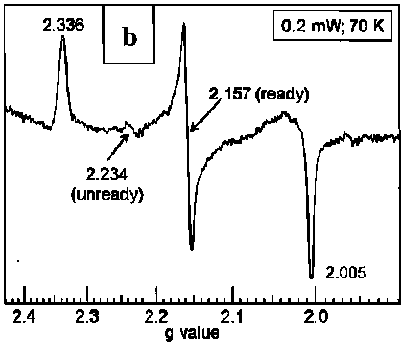
[NiFe] Hydrogenase from Desulfovibrio gigas





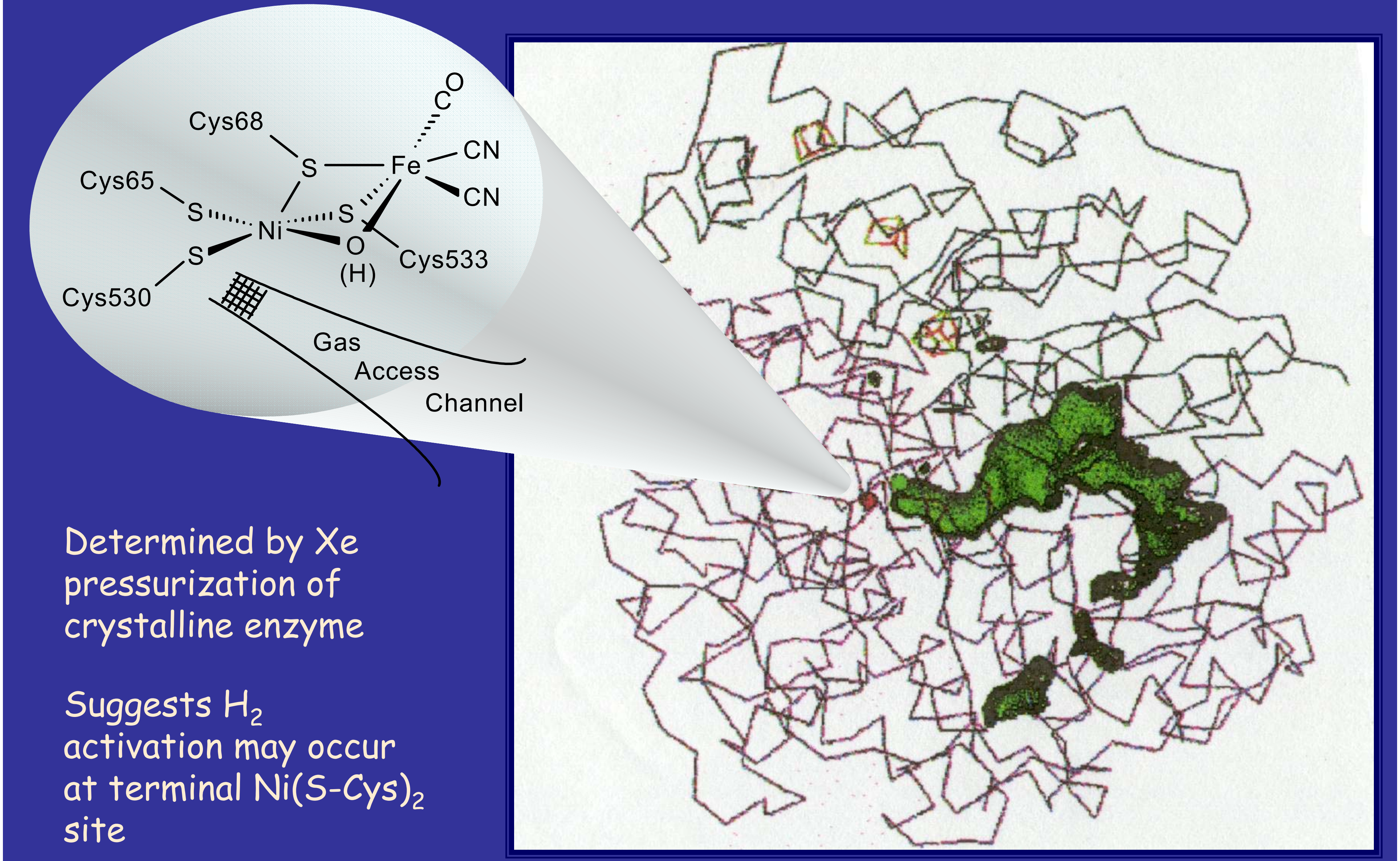
Fontecilla-Camps, *Nature*, **1995**





Fontecilla-Camps,
JBIC, **2005**

Gas Access Channels to the Active Site

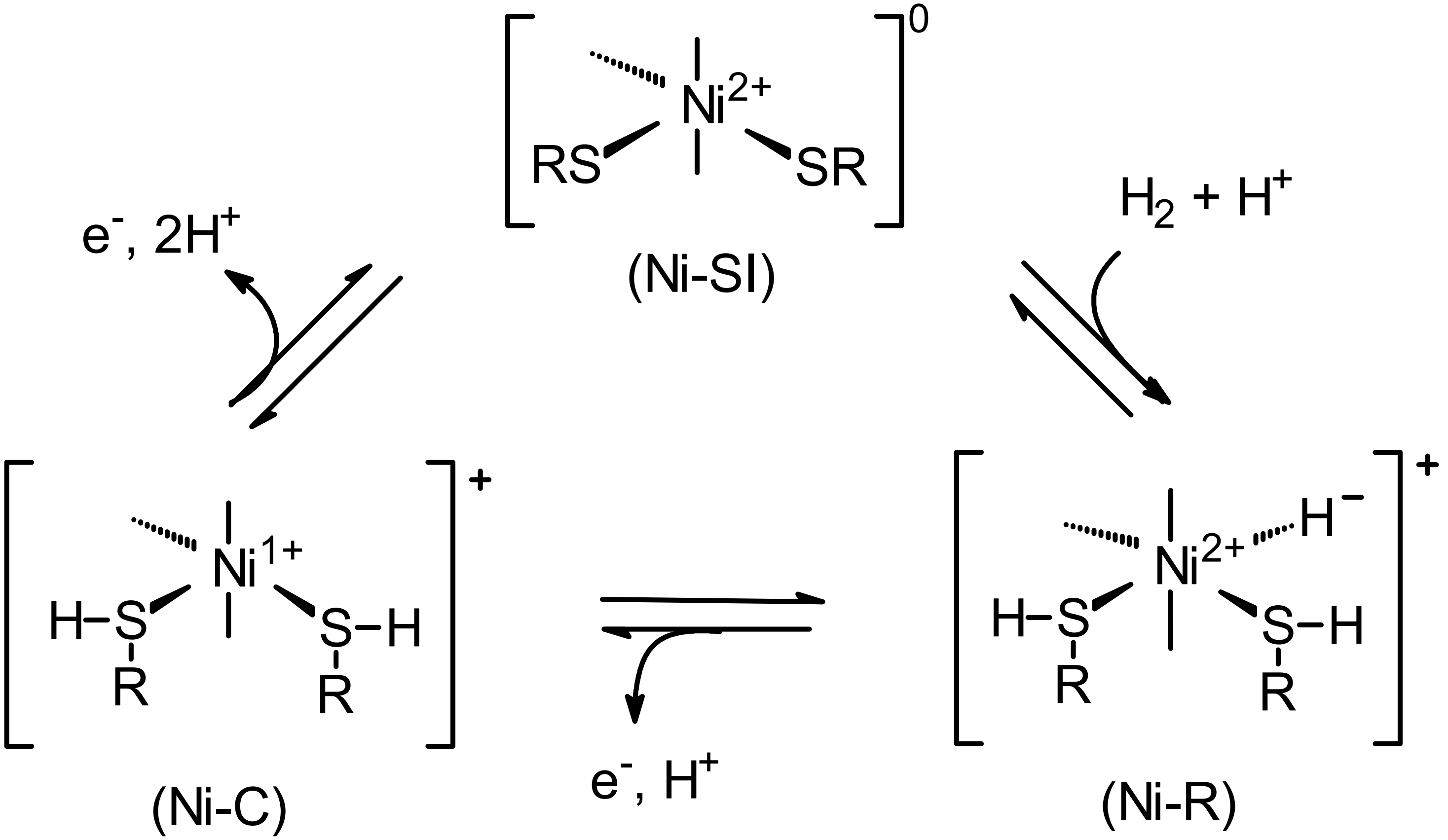


Determined by Xe pressurization of crystalline enzyme

Suggests H_2 activation may occur at terminal $Ni(S\text{-}Cys)_2$ site

Montet, et al. *Nat. Struct. Biol*, **1997**

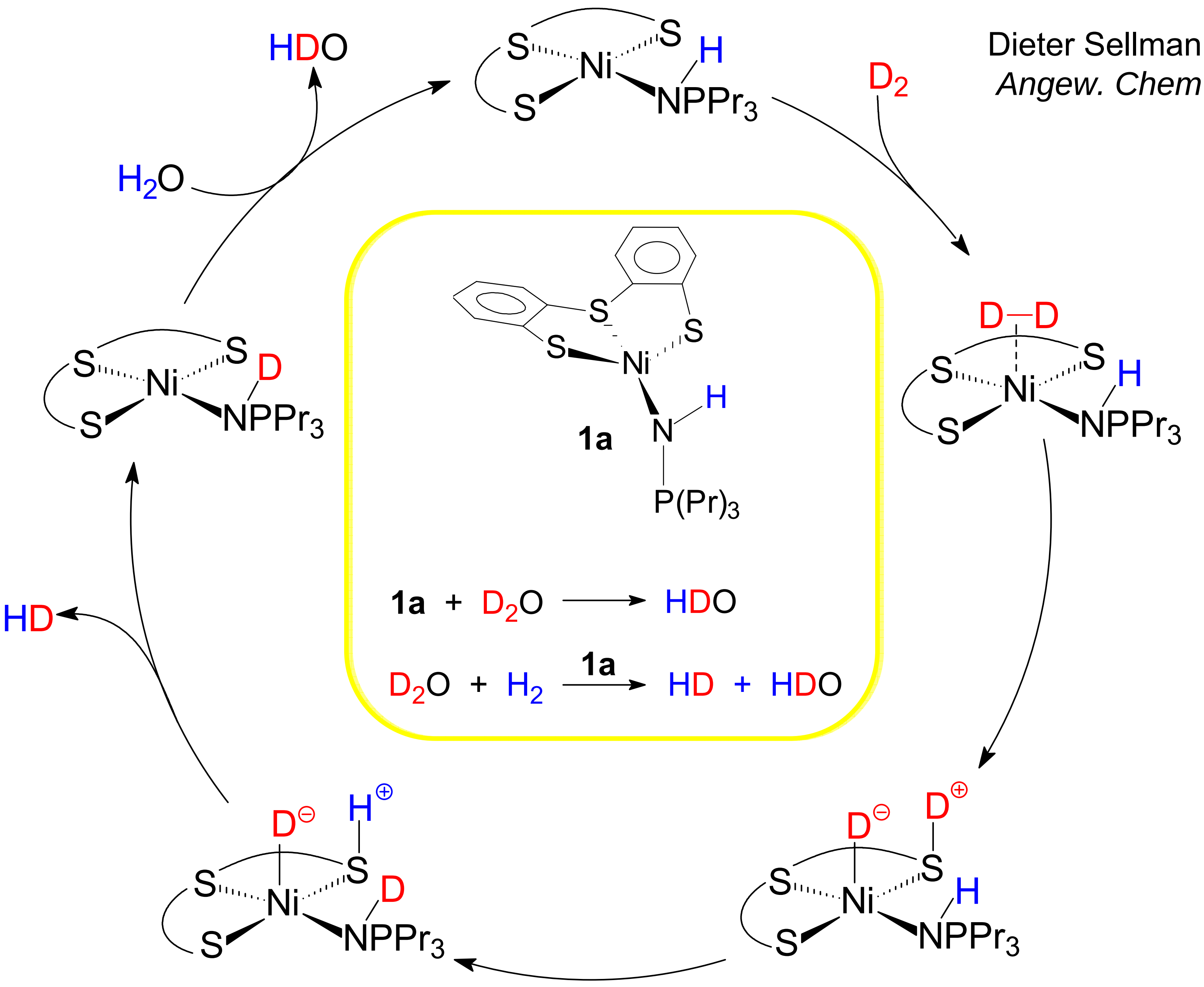
Lindahl's Mechanism for H_2 Uptake by Ni-cysteine



Lindahl *et al.*, *Biochem*istry, **1994**, *33*, 14339

S-based Reactivity: Mononuclear Nickel Dithiolate

Dieter Sellmann,
Angew. Chem. 2000

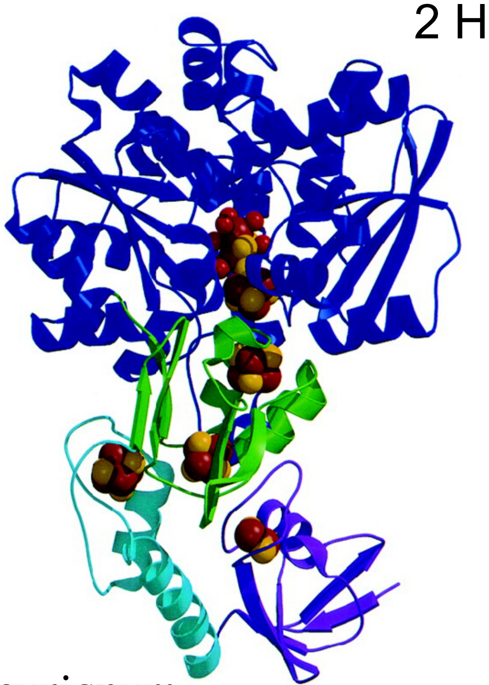


$\mathbf{1a} + D_2O \longrightarrow HDO$

$D_2O + H_2 \xrightarrow{\mathbf{1a}} HD + HDO$

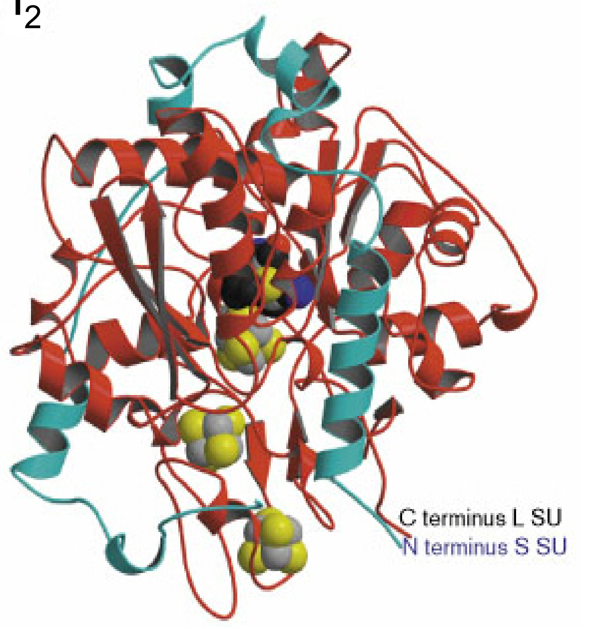
The Active Site of [Fe]-Hydrogenase

$2\,H^+ + 2\,e^- \rightleftharpoons H_2$



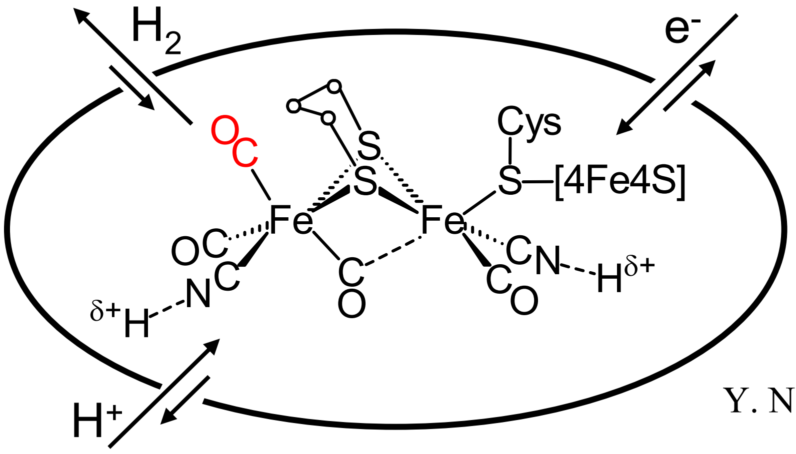
C. Pasteurianum

J. W. Peters, *Science* **1998**



D. desulfuricans

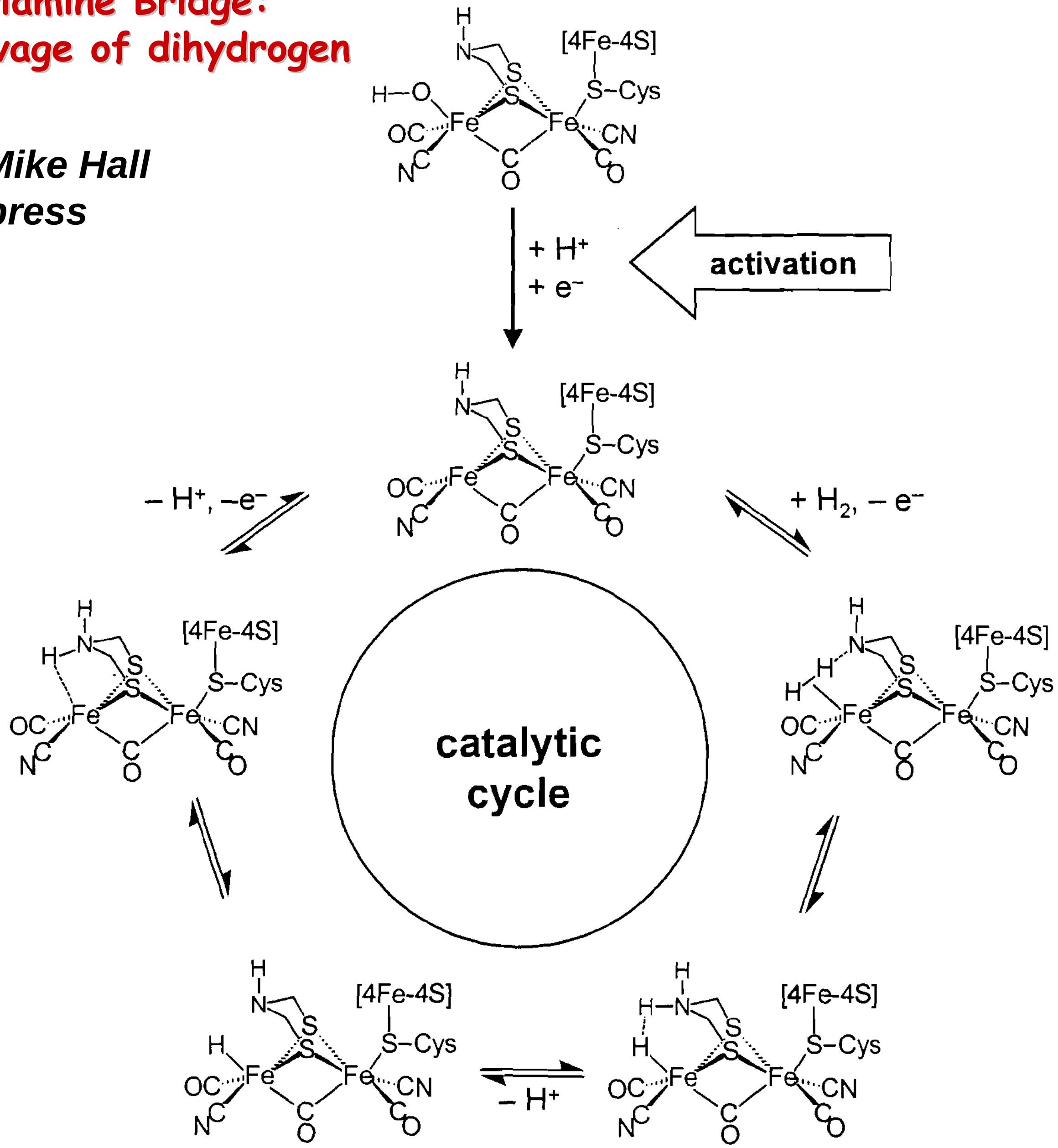
J. C. Fontecilla-Camps, *Structure* **1999**



Y. Nicolet, et al., TIBS, **2000**, 138.

The Dithiomethylamine Bridge: Heterolytic cleavage of dihydrogen

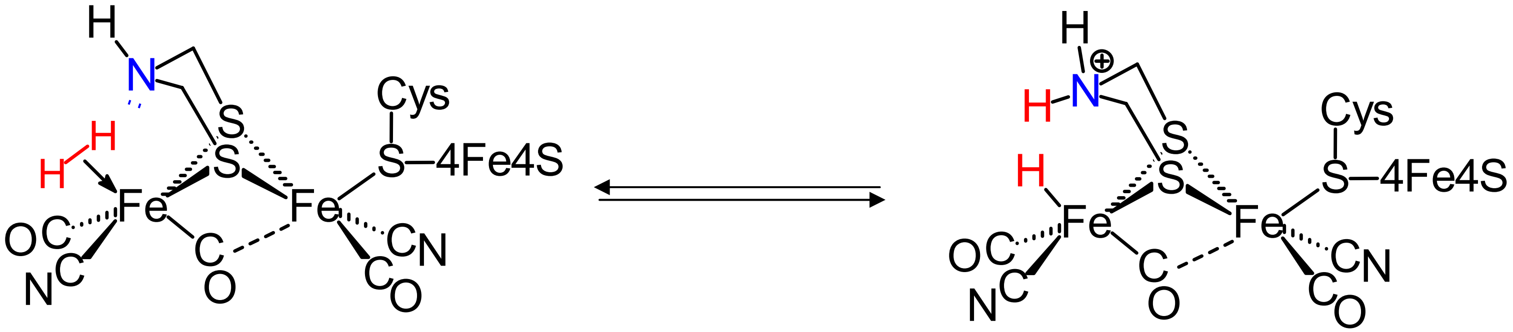
Jesse Tye and Mike Hall
Chem. Rev., in press



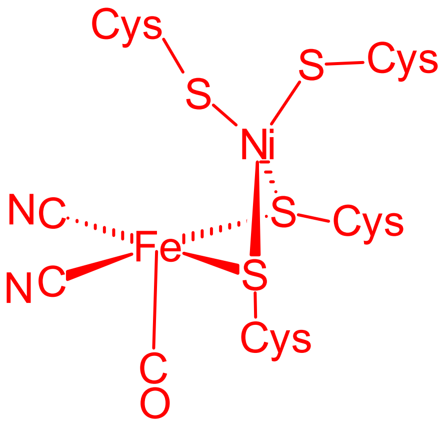
The Appeal of the Dithiomethylamine Bridge

⇨ Would assist in heterolytic H_2 cleavage

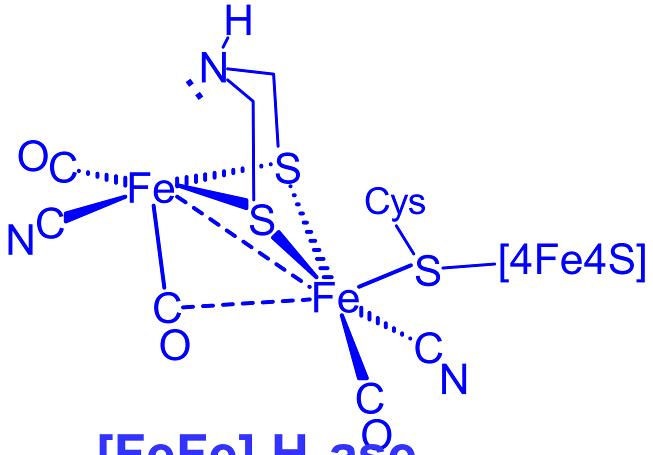
(3.1 Å) Cys178



⇨ Furthermore, a possible connection to [NiFe]H_2ase



[NiFe] H_2ase



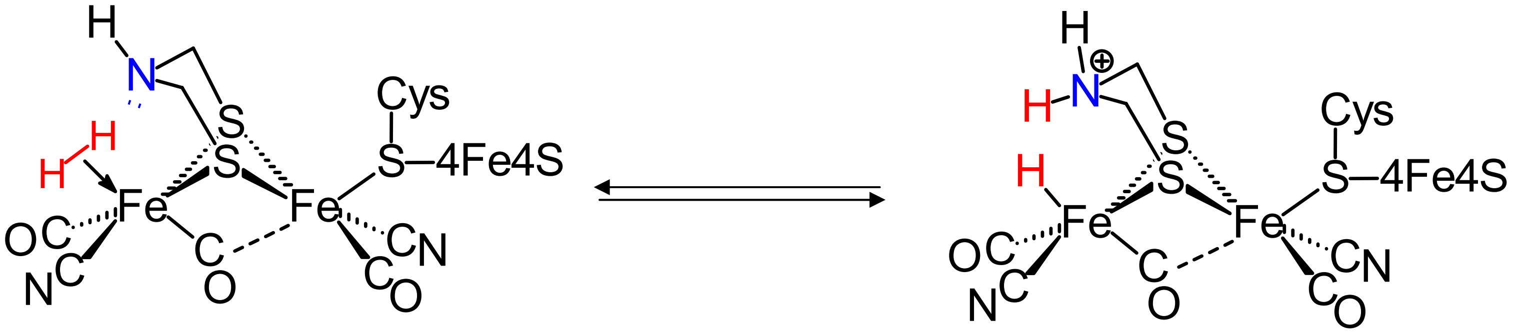
[FeFe] H_2ase

Fontecilla-Camps, *JACS*, **2001**

The Appeal of the Dithiomethylamine Bridge

⇨ Would assist in heterolytic H_2 cleavage

(3.1 Å) Cys178



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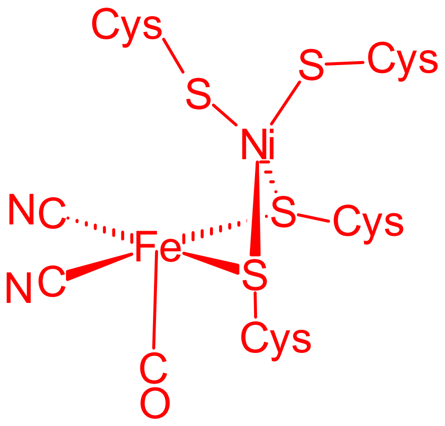
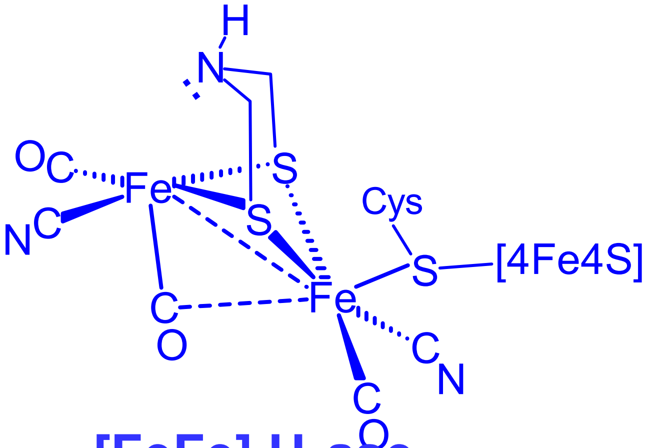


[NiFe] H_2ase



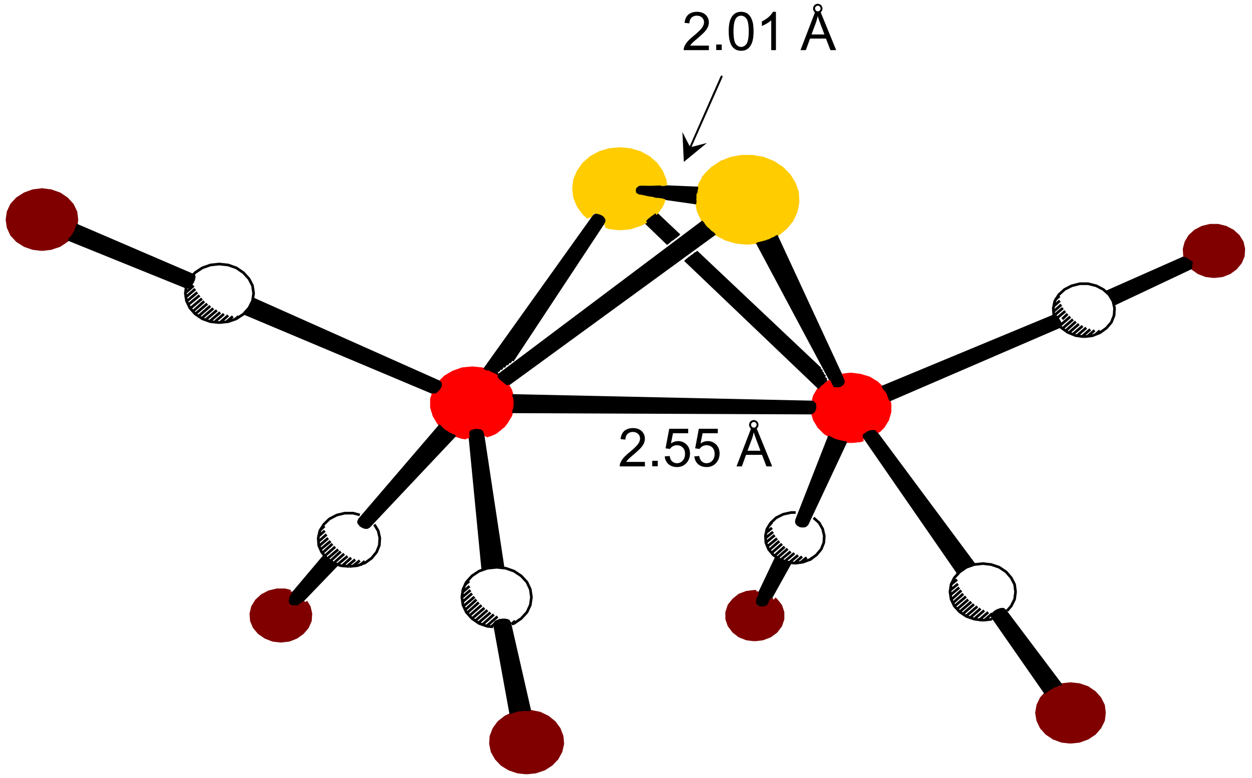
[FeFe] H_2ase

Fontecilla-Camps, *JACS*, **2001**

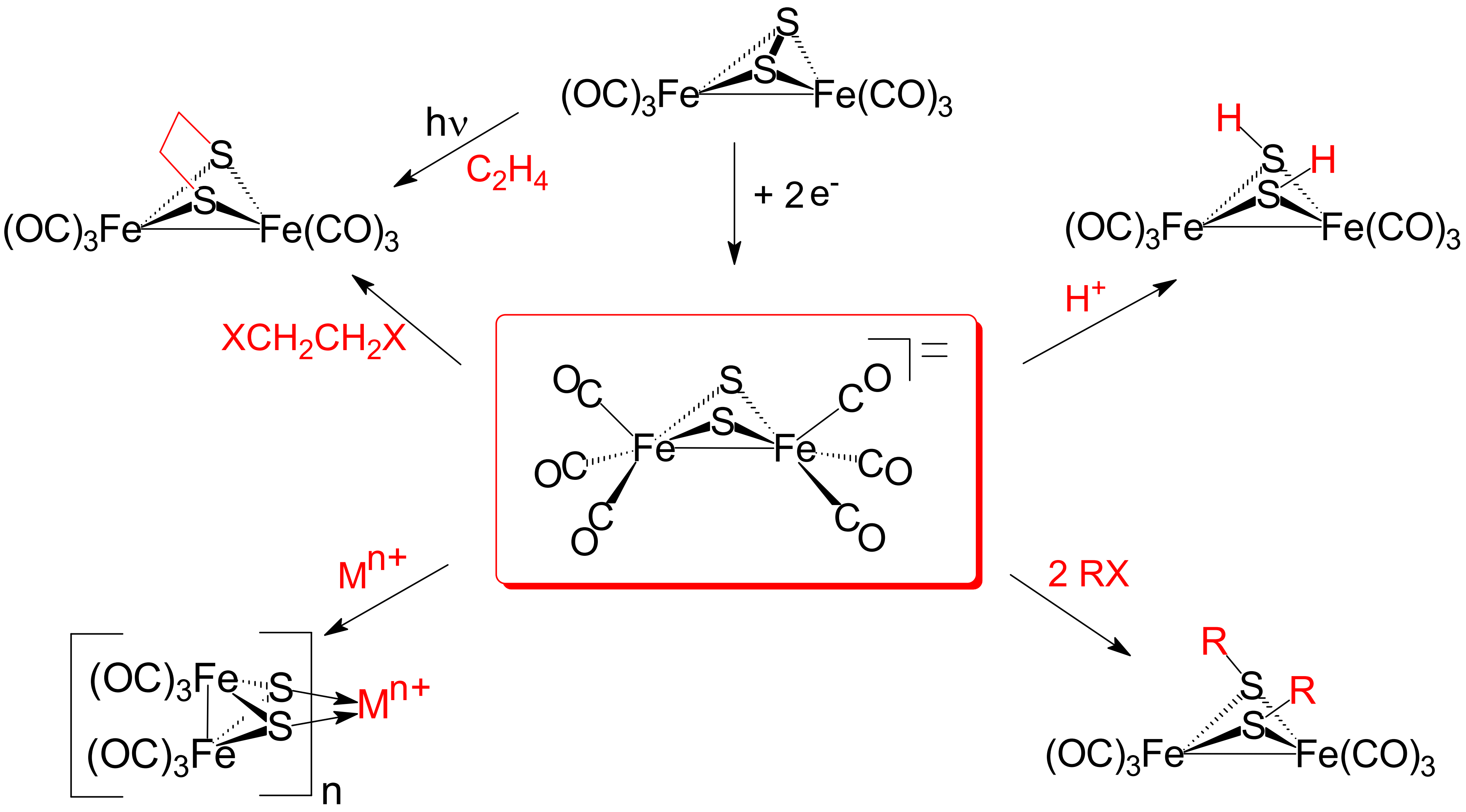
Hieber, Seyferth: $(\mu\text{-}S_2)Fe_2(CO)_6$

Binuclear Iron/Sulfur/Carbon Monoxide:
A Foundation Molecule for S-based Reactivity

$$Fe(CO)_5 + S_8 + KOH \xrightarrow{HCl} (\mu\text{-}S_2)Fe_2(CO)_6$$



Selections of Reactivity for $(\mu\text{-}S_2)Fe_2(CO)_6$ and $\mu(S)_2Fe_2(CO)_6$



M^{n+} = $Ni(dppe)^{2+}$, $CpCo^{2+}$,

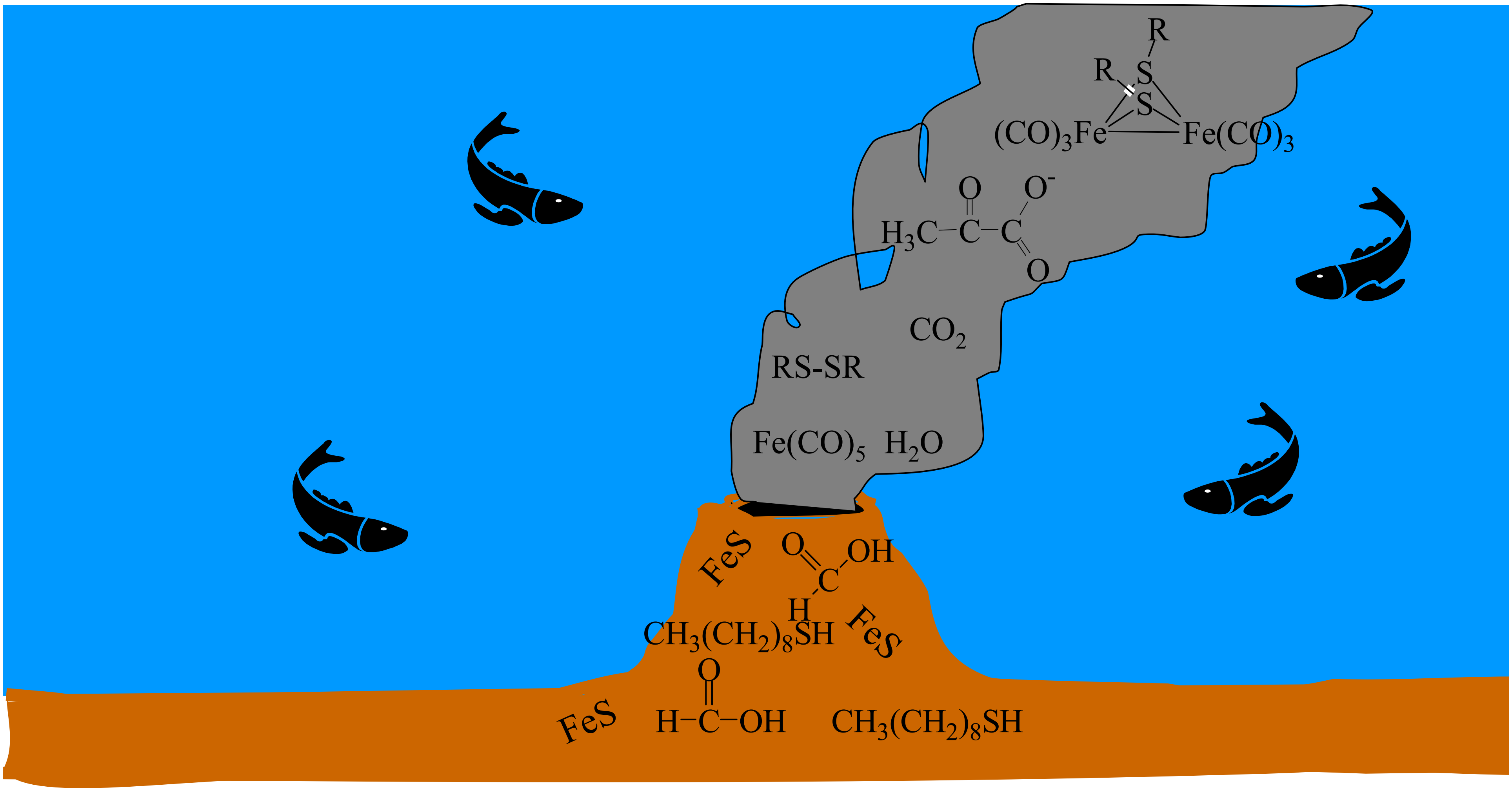
Fe^{2+}, $Pd(PPh_3)_2{}^{2+}$

Seyferth, et al., *Organometallics*, 1982

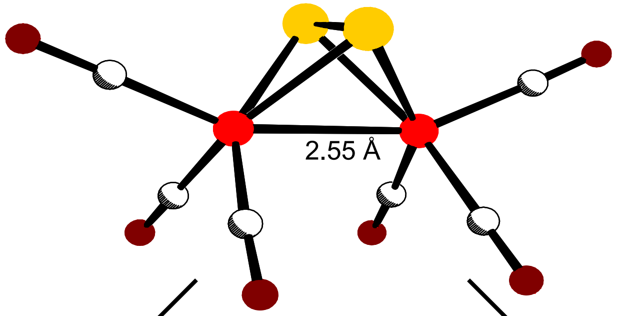
J. Organomet. Chem., 1981

Averill, et al., *Organometallics*, 1995

Primordial Carbonylated Iron-Sulfur Compounds and the Synthesis of Pyruvate - George Cody *et al. Science*, **2000**.



Fe / CO / S ⇒ CO-mobilized 2Fe2S

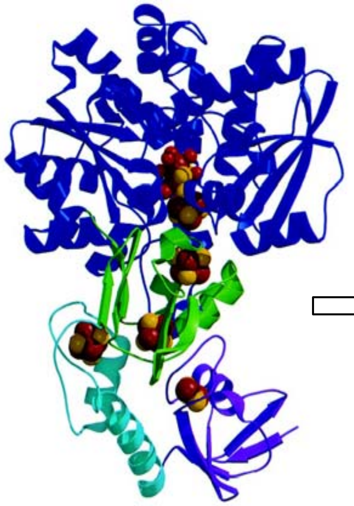


~ 4 x 10^9 years

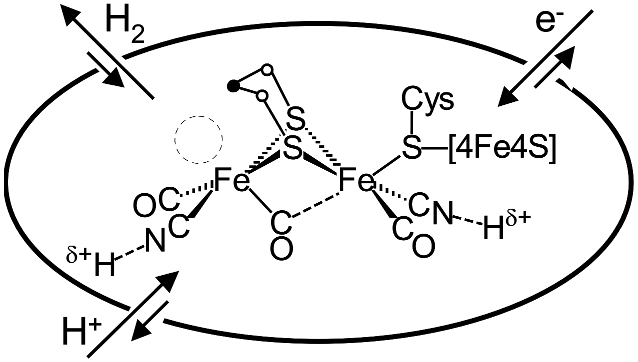
Reihlen, Hieber

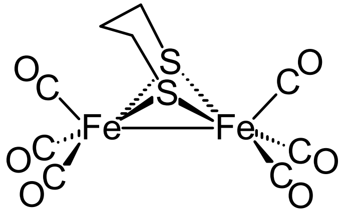
Seyferth, Huttner

~ 75 years



Active site of Fe-H_2ase
Nature



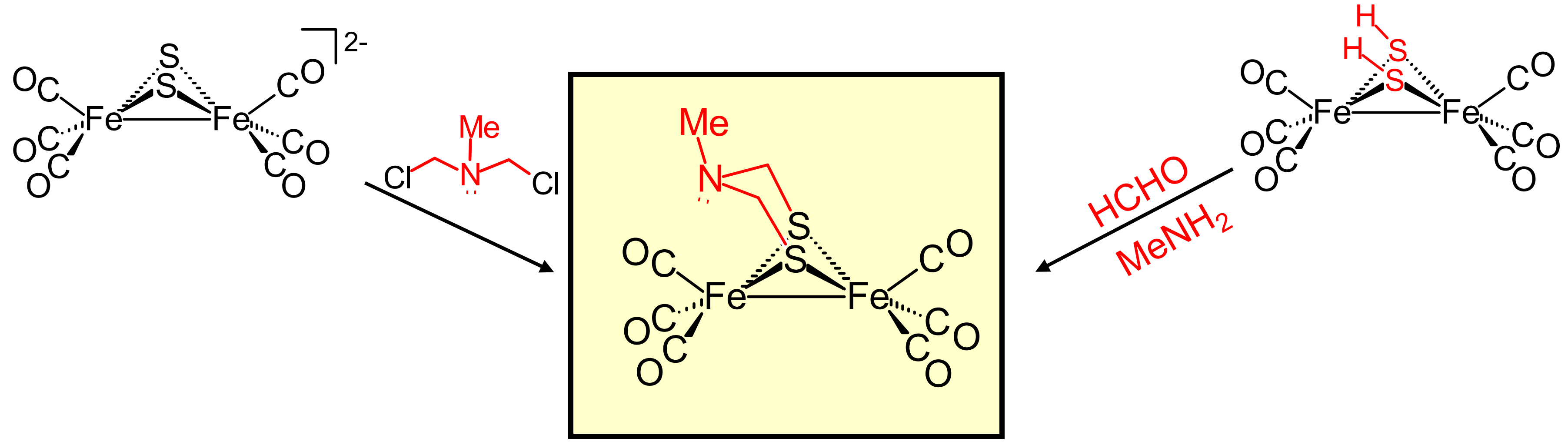


Model Complexes,

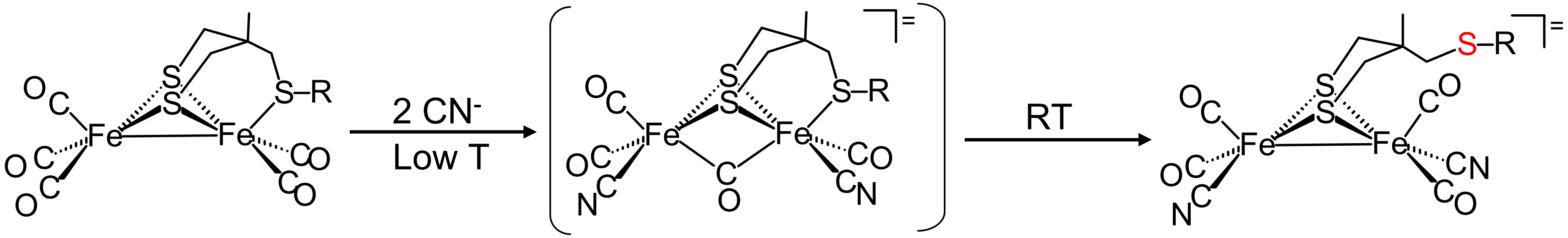
Rauchfuss, Pickett, Darensbourg,
Sun/Akermark, Song, Heinekey

Especially Impressive Models

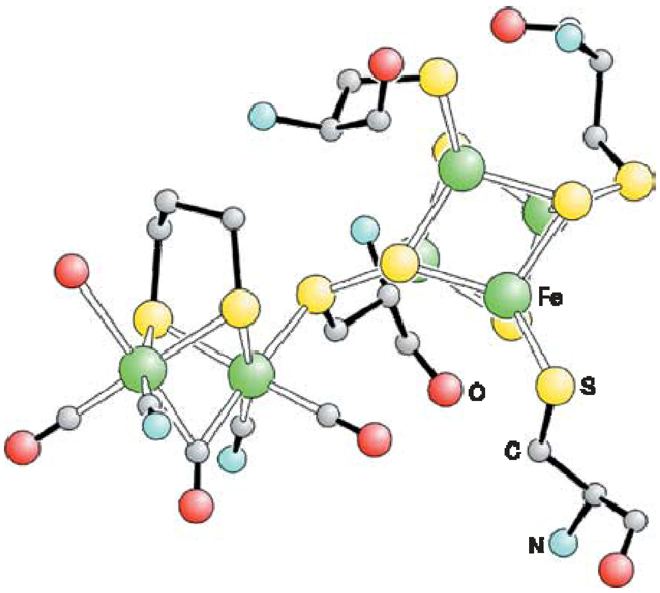
Rauchfuss



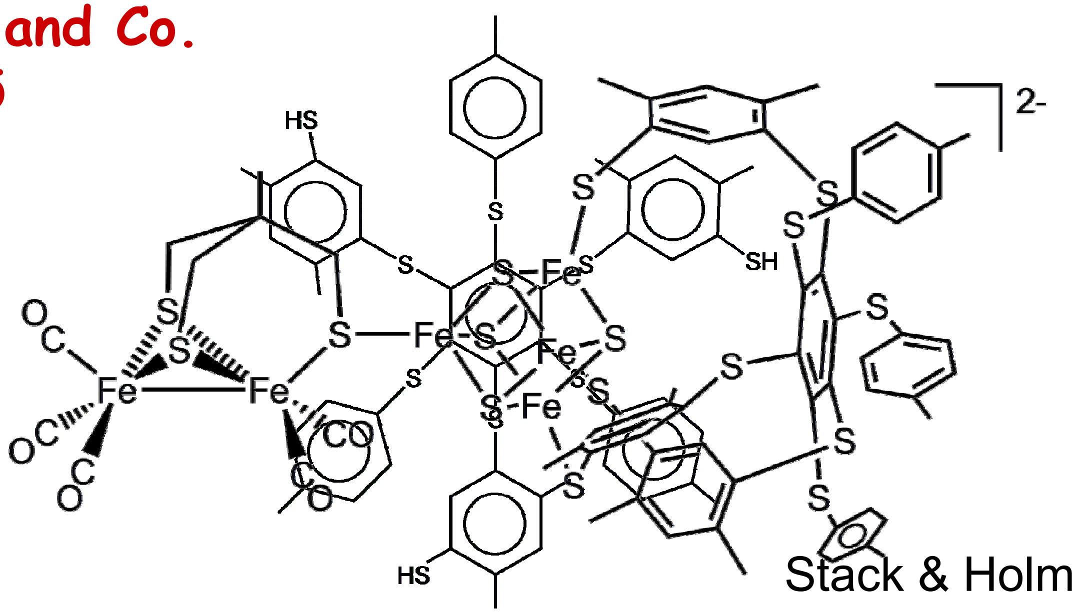
Pickett



The 6Fe6S H-Cluster complete:

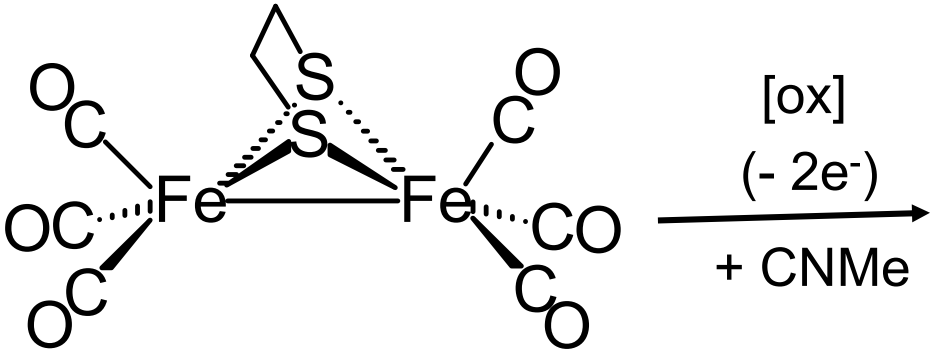


Closest structural model Chris Pickett and Co. Nature, 2005



Stack & Holm, *JACS*, **1987**

Rauchfuss Approach to a μ-CO Complex



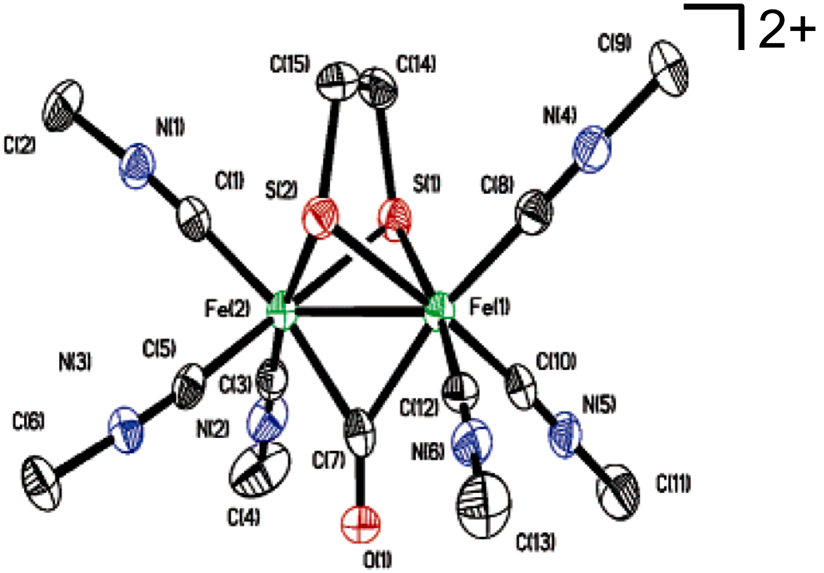
[ox]

(- 2e$^-$)

+ CNMe

$[(\mu\text{-CO})(\mu\text{-edt})Fe_2(CNMe)_6][PF_6]_2$

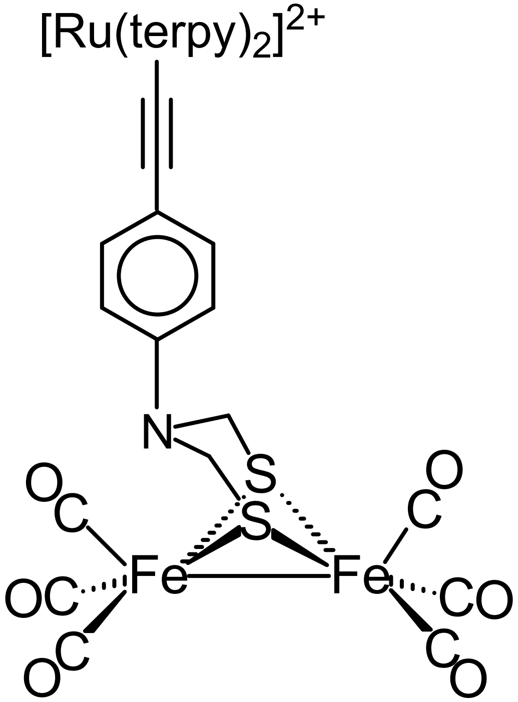
$\nu(CO) = 1914\ cm^{-1}$



Rauchfuss *et al.*, *J. Am. Chem. Soc.* **2004**, *126*, 15151

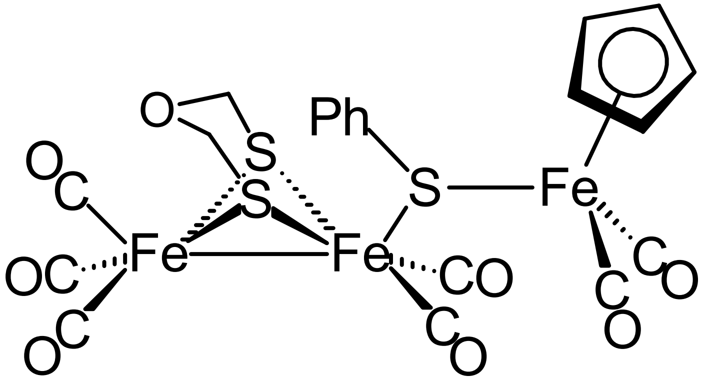
Other Advances:

Structural/Functional Model: in pursuit of Light-driven H_2 production



Åkermark and Sun
2003

Structural Models: Achieving the Thiolate bridge to another iron



Song
2004

Biomimetic Goals

Functional Models

H_2 uptake
Assay

H_2 production

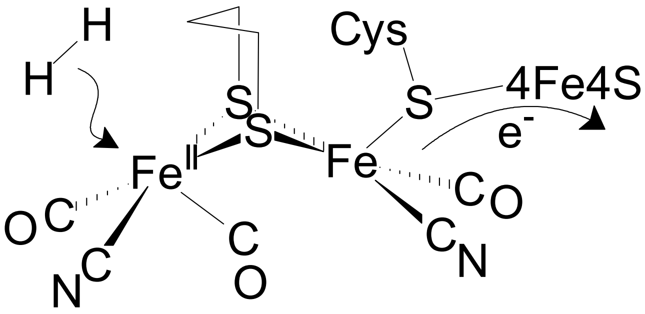
$$H_2 + D_2O \xrightarrow{\text{Catalyst}} HOD + HD$$

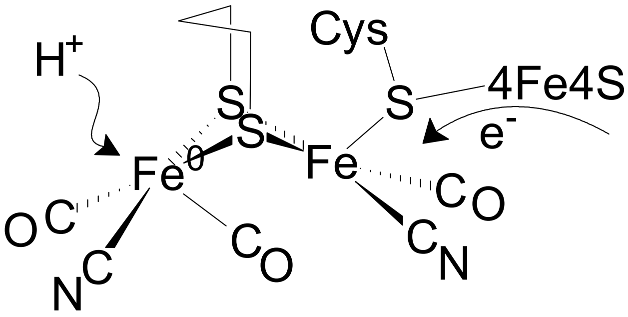
$$H_2 + D_2 \xrightarrow[H_2O]{\text{Catalyst}} 2HD$$

$$H^+ + e^- \xrightarrow{\text{Catalyst}} H_2$$

$\varepsilon \approx -0.5$ V

pH $\cong$ 7 (aqueous)

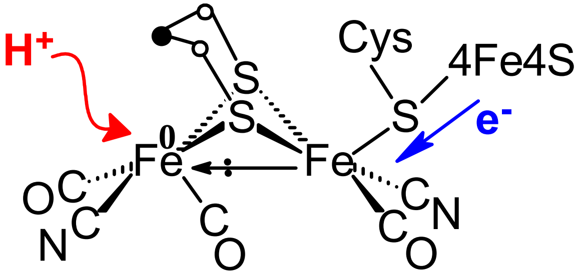




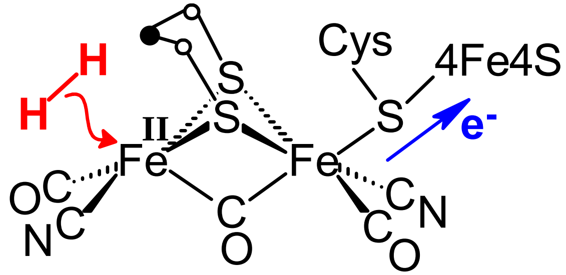
Need: $Fe^{II} = d^6$, O_h

Need: $Fe^0 \xrightarrow{H^+} Fe^{II}\text{—}H \xrightarrow{H^+} Fe^{II} \leftarrow \begin{matrix} H \\ | \\ H \end{matrix}$

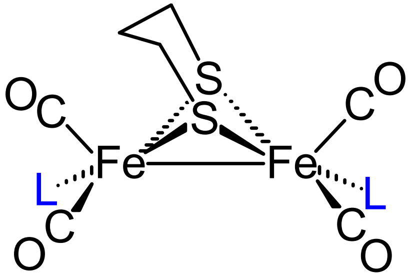
Summary of Model/Active Site Analogies



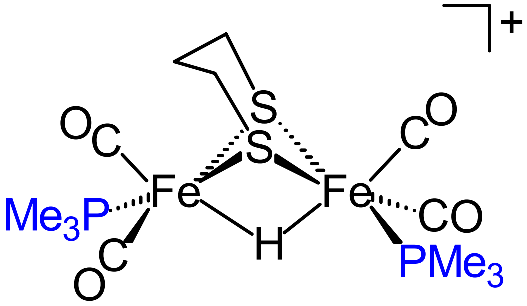
H^+ uptake and H_2 production



H_2 binding for e^- abstraction

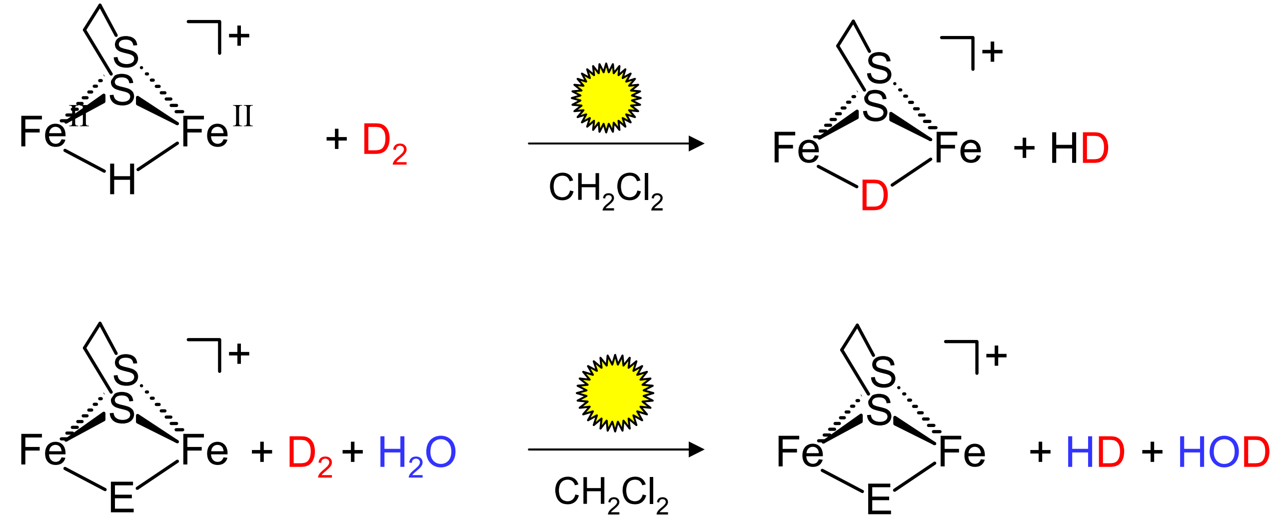


Fe^IFe^I

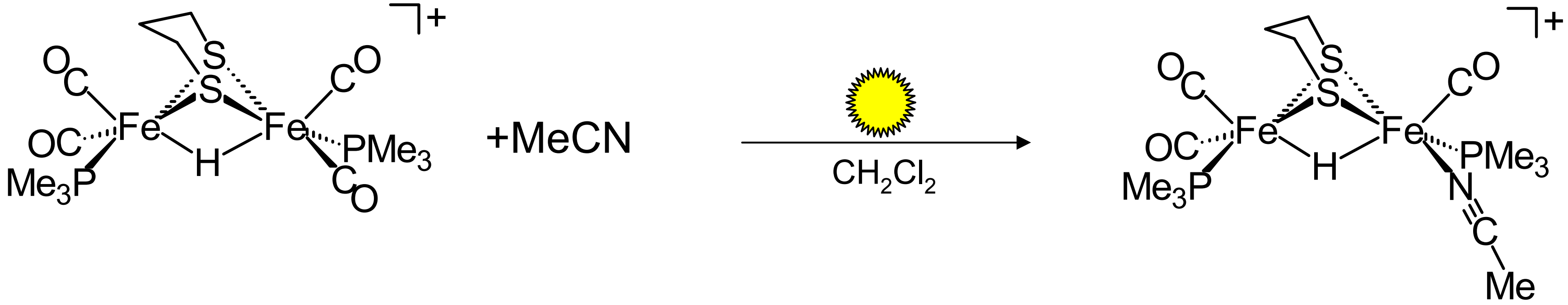


$Fe^{II}Fe^{II}$

H/D Exchange Experiments



E = H or SMe



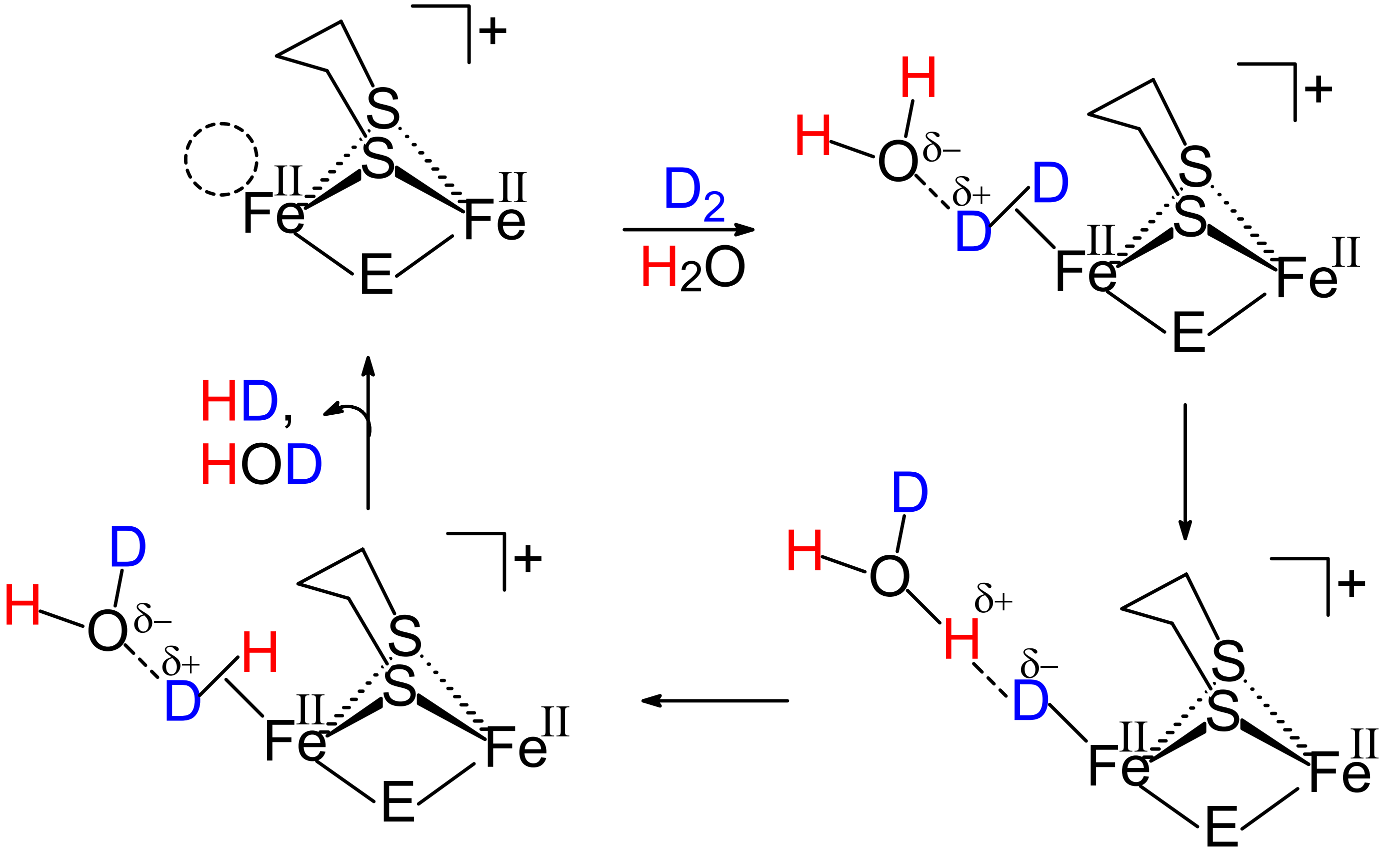
Zhao et al. *J. Am. Chem. Soc.* **2001**, *123*, 9710.; *Inorg. Chem.* **2002**, *41*, 3917.

Light Assisted H/D Exchange in D_2/H_2O Mixture Catalyzed by 1-E^+

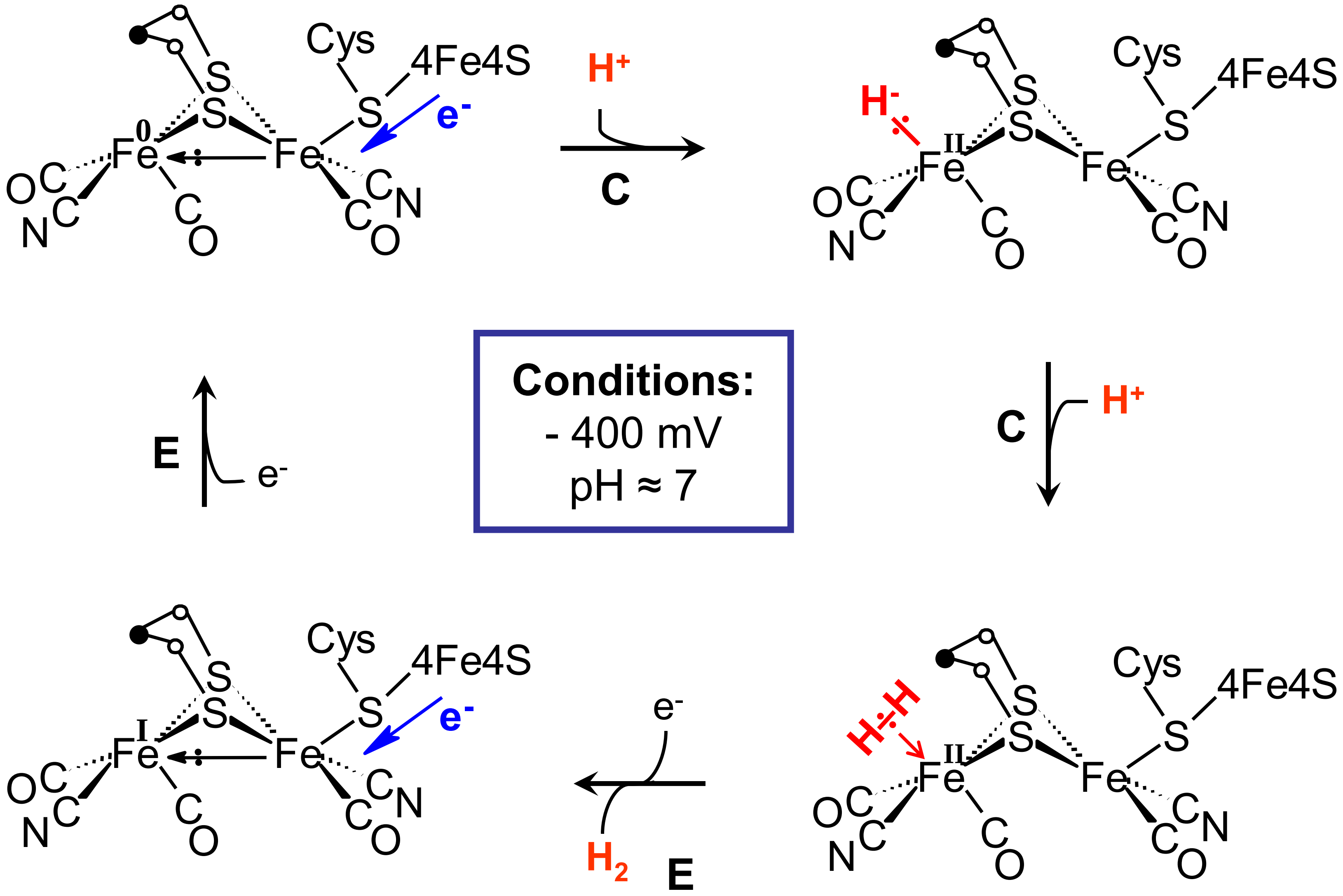
$$(\mu\text{-E})Fe_2^+ + D_2/H_2O \xrightarrow[\text{E = H or SMe}]{} (\mu\text{-E})Fe_2^+ + HOD + HD$$

Likely Mechanism

Open site Created by CO Loss



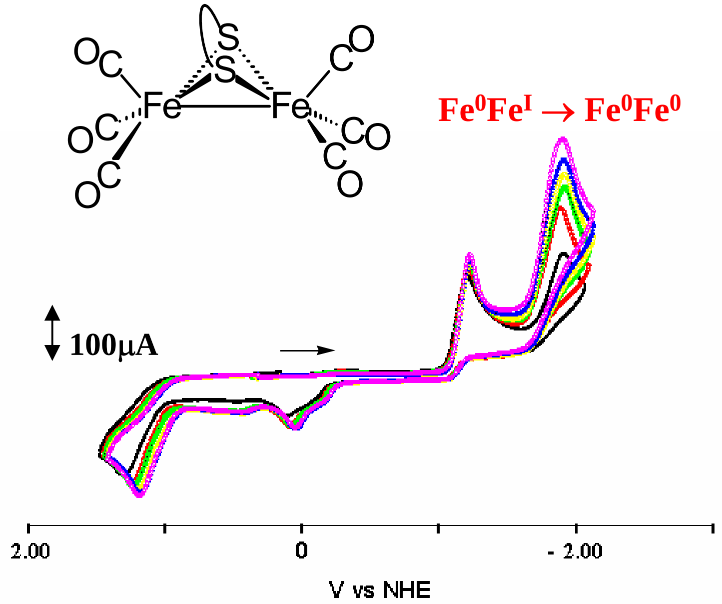
H^+ uptake and H_2 production in [FeFe]H_2ase active site

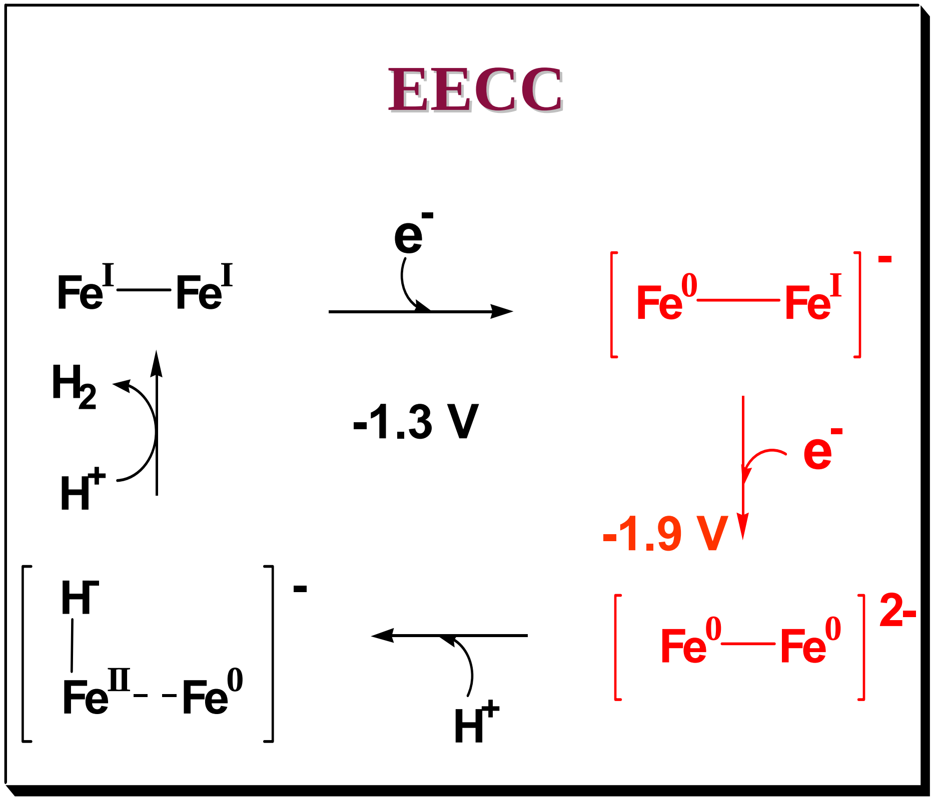


Conditions:
- 400 mV
pH ≈ 7

Electrochemical Mechanism: **CCEE**

Electrocatalytic H_2 Production from $Fe^{I}Fe^{I}$ Complexes and Weak Acid (HOAc) In CH3CN (2nd reduction: All-CO complexes)





EECC

Fe^{I}—Fe^{I} $\xrightarrow{e^-}$ $[Fe^{0}$—$Fe^{I}]^{-}$

-1.3 V

e^-

-1.9 V

$[Fe^{0}$—$Fe^{0}]^{2-}$

H^+

$[H^-$ | Fe^{II}- -$Fe^{0}]^{-}$

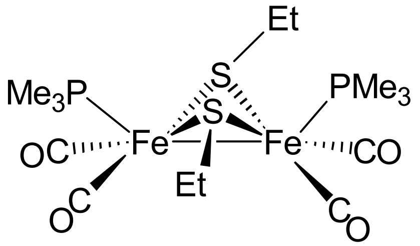
H_2

H^+

criteria for electrocatalysis

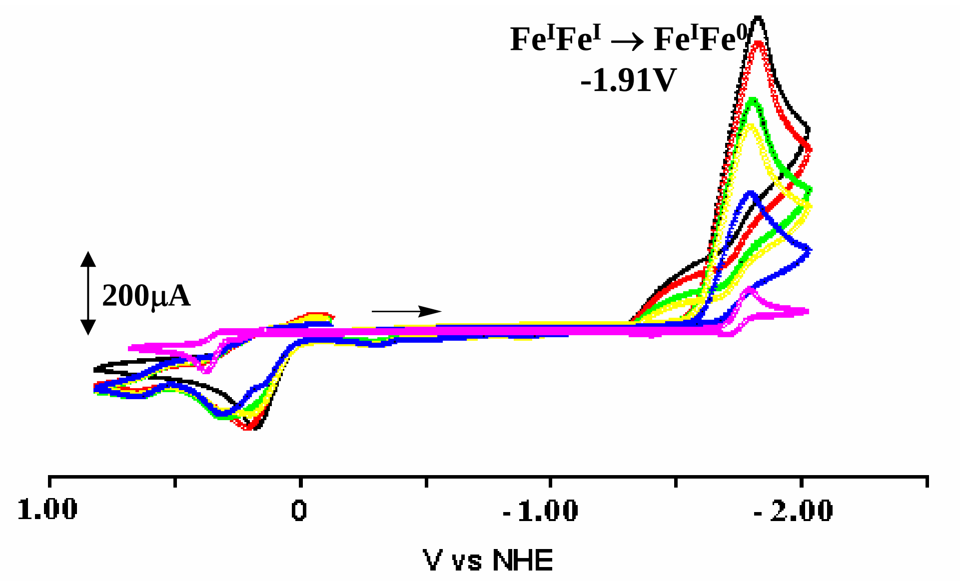
- current α [H^+]
- positive shift in potential from non-catalyzed HOAc reduction (–2.2 V at the glassy carbon electrode in the absence of the [FeFe]H_2ase model complex)

Mechanism for Electrocatalytic H_2 Production from Fe^IFe^I Complexes and Weak Acid (HOAc) (1st reduction: Phosphine derivatives)

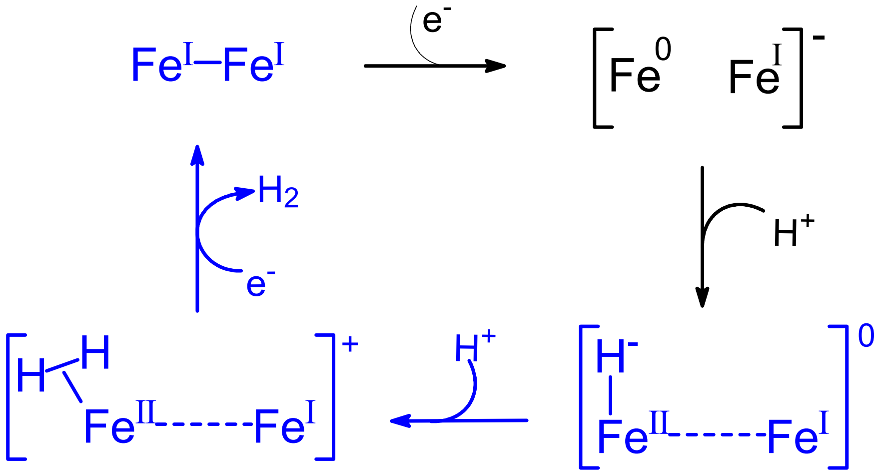


1-P

+ H^+
HOAc
(0-100 mM)



Fe^IFe^I Cycle: ECCE



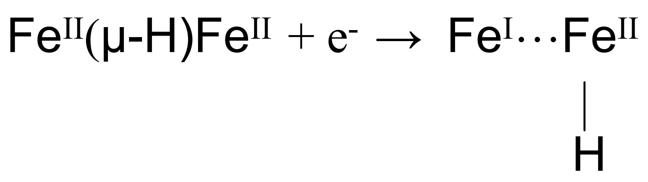
Summary of Early Electrocatalysis Results:

$(\mu\text{-SRS})[\text{Fe}^{\text{I}}(\text{CO})_3]_2$

- H_2 from weak acid uses Fe^0Fe^0 redox level and very negative potentials (~ -1.9 V)

$(\mu\text{-SRS})[\text{Fe}^{\text{I}}(\text{CO})_2\text{L}]_2$

- H_2 from weak acid uses $\text{Fe}^0\text{Fe}^{\text{I}}$ redox level, also at -1.8 to -1.9 V
- H_2 from strong acid uses $\text{Fe}^{\text{I}}\text{Fe}^{\text{II}}$ redox level at -1.1 V, going through protonated species

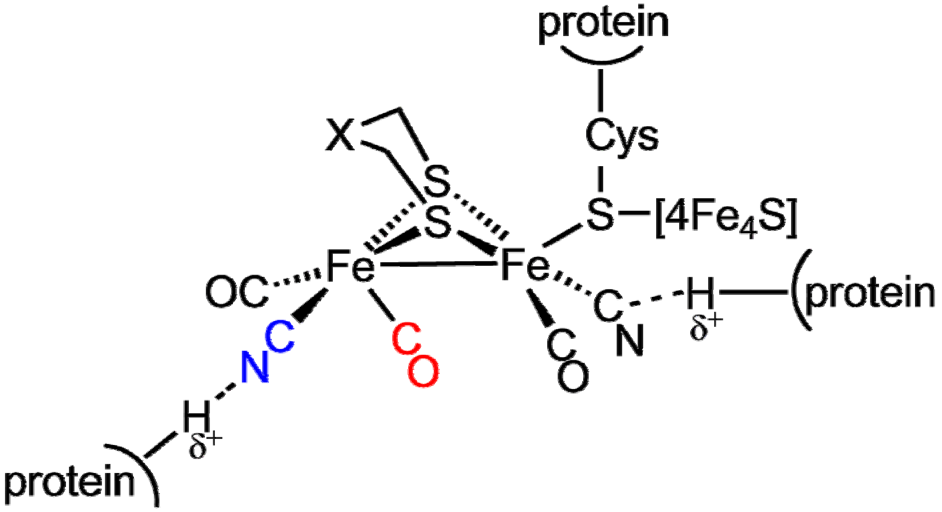


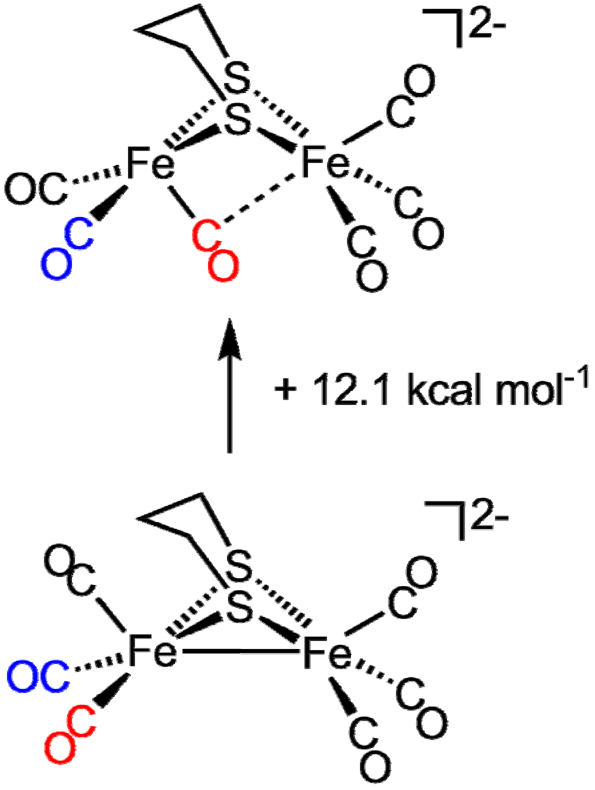
$$\text{Fe}^{\text{II}}(\mu\text{-H})\text{Fe}^{\text{II}} + e^- \rightarrow \text{Fe}^{\text{I}}\cdots\underset{\displaystyle \text{H}}{\underset{|}{\text{Fe}^{\text{II}}}}$$

Conclusion: Mild potentials need strong acid; **weak acids need highly negative potentials**.

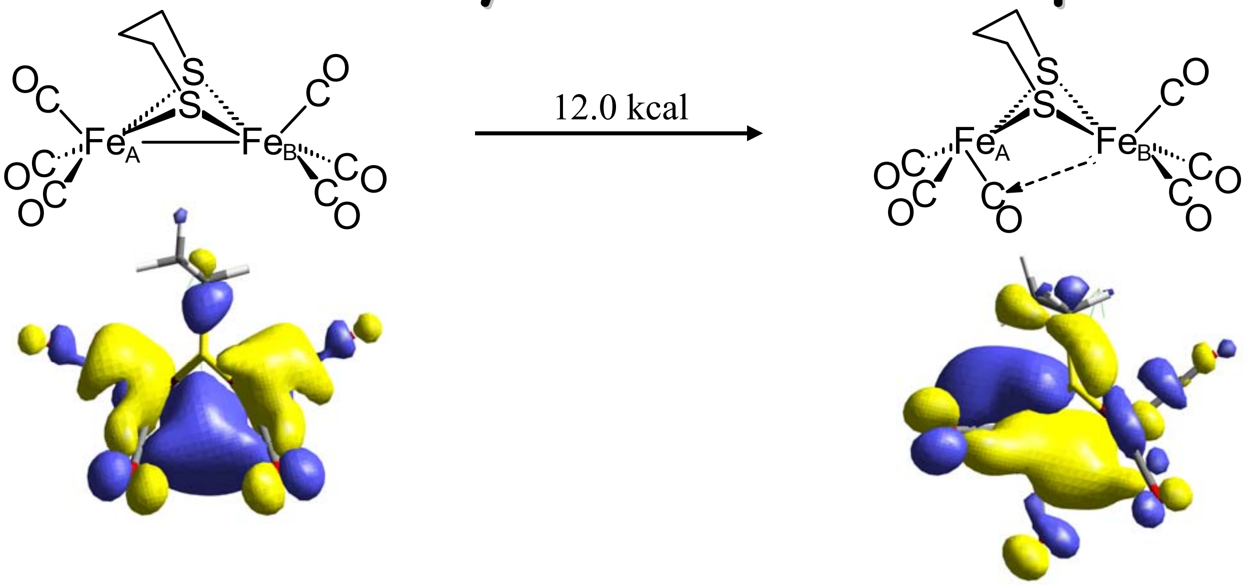
Question: Why is the enzyme so much better?

Why is the enzyme so much better?
Models are symmetric. Enzyme is rotated.





Importance of $Fe(CO)_3$ Rotation: DFT Calculations shows shift of e-density of Fe-Fe bond upon rotation

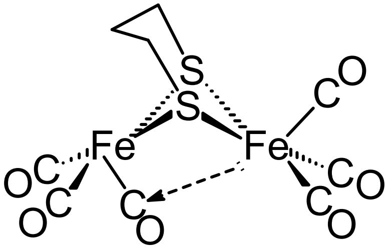


HOMO

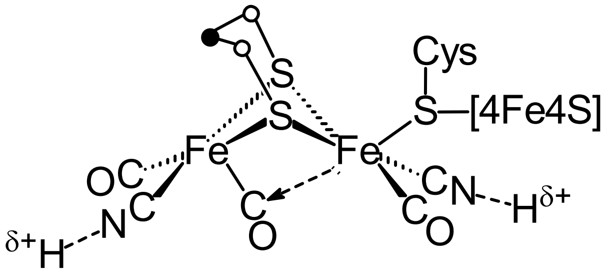
Mulliken charges: Fe_A -1.045
Fe_B -1.031

Fe_A -0.998
Fe_B -1.174

Relation to the active site structure: Entatic state



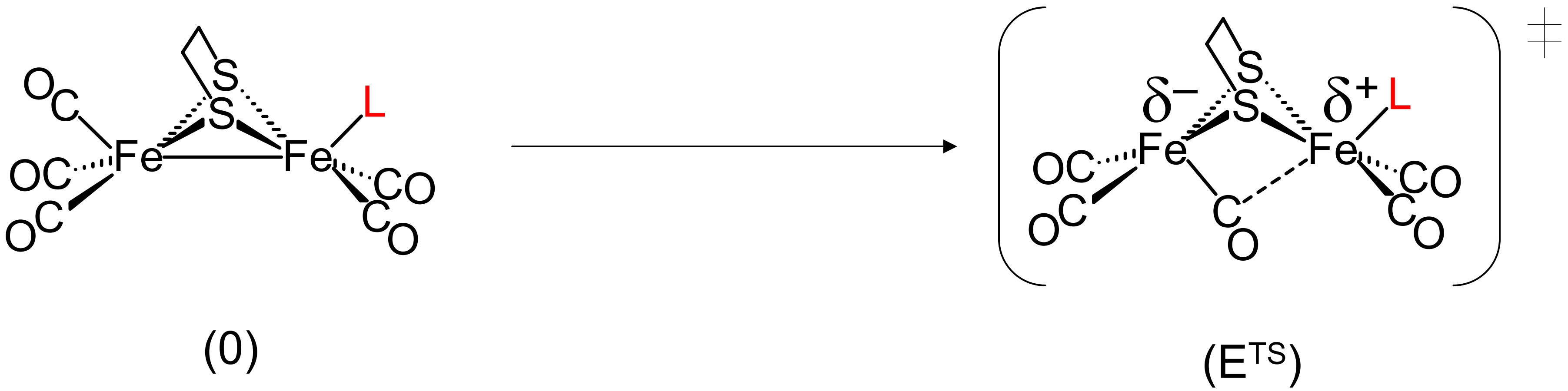
Rotated Transition State



Enzyme Active Site

⇨ **Active site construction traps high energy, reactive structure**

The Effect of the Donor Ability of L on Achieving a "Rotated" State



L	E^{TS}
NO^+	19.7
CO	14.7
PH_3	12.9
CN^-	5.4

Increasing donor ability

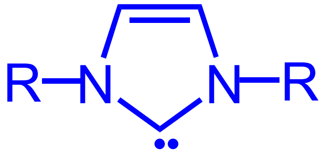
Lowers barrier to $Fe(CO)_3$ rotation

Could asymmetric complexes perform better???

Tye, Darensbourg, Hall, IC, 2006

Two Ligands Used for Asymmetric Model Complexes

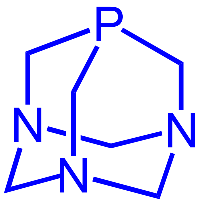
1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes)



(R = 2,4,6-trimethylphenyl)

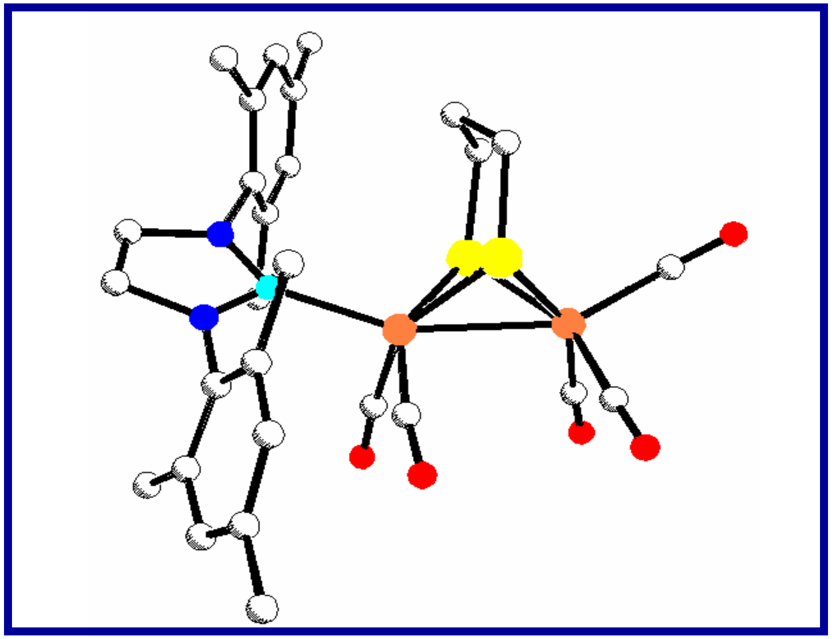
- Electron-rich donors
- Have been called “phosphine mimics”
- Unique steric characteristics
- Form strong Metal-Carbon bonds
- Bonus: analogue of cofactor for Thauer’s H_2ase

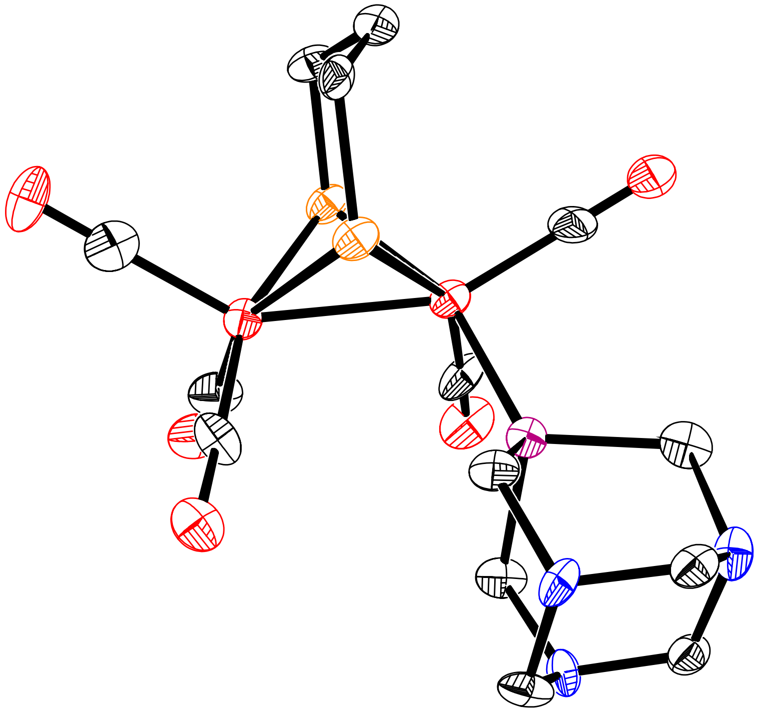
1,3,5-triaza-7-phospha-adamantane (PTA)



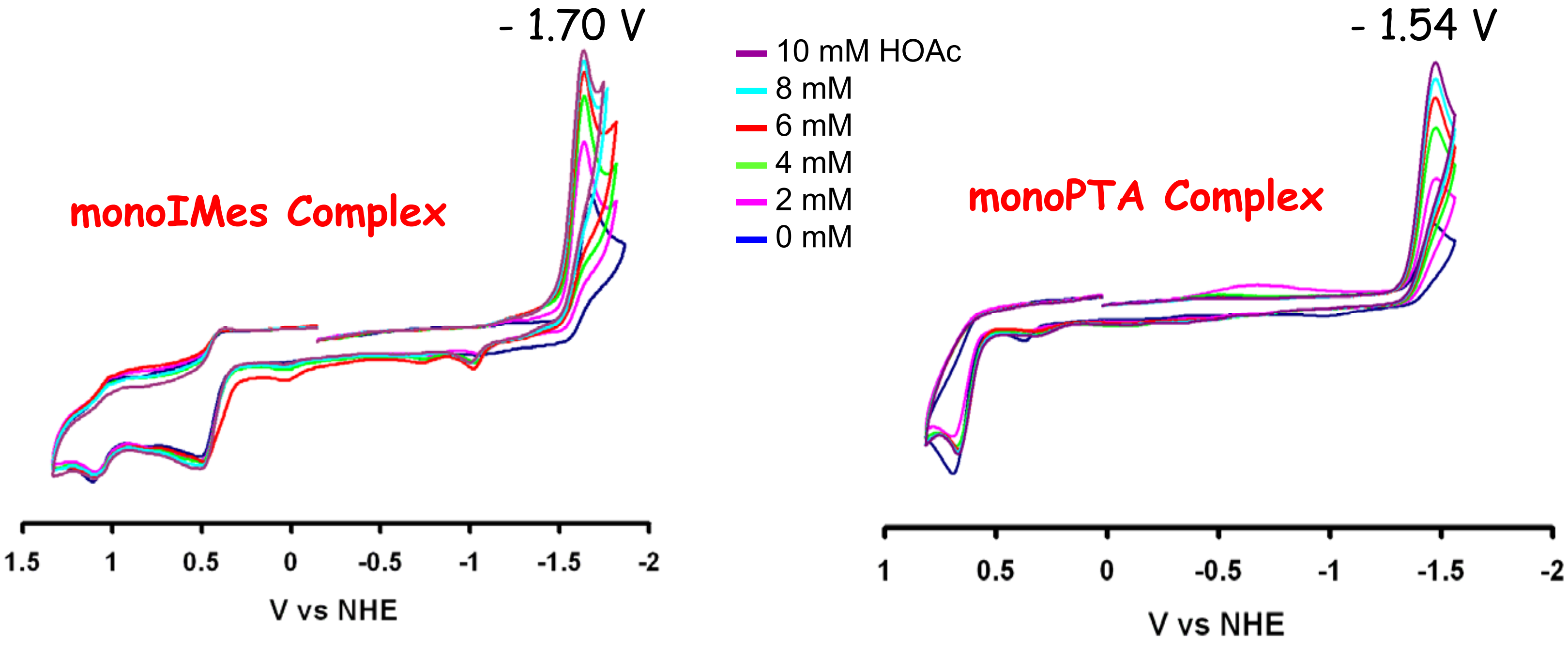
- Basicity similar to PMe_3
- Water-soluble and air-stable
- Alternative to the use of TPPTS
- Alkylation or Protonation occurs at one N to afford an Ionic ligand ⇒ Water-solubility is improved

Molecular structures of diiron-PTA and IMes complexes





Electrocatalysis of H_2 Production
Cyclic Voltammetry of (μ-pdt)[$Fe(CO)_3$][$Fe(CO)_2$IMes] and (μ-pdt)[$Fe(CO)_3$][$Fe(CO)_2$PTA] in CH_3CN with Increments of HOAc, Carbon electrode

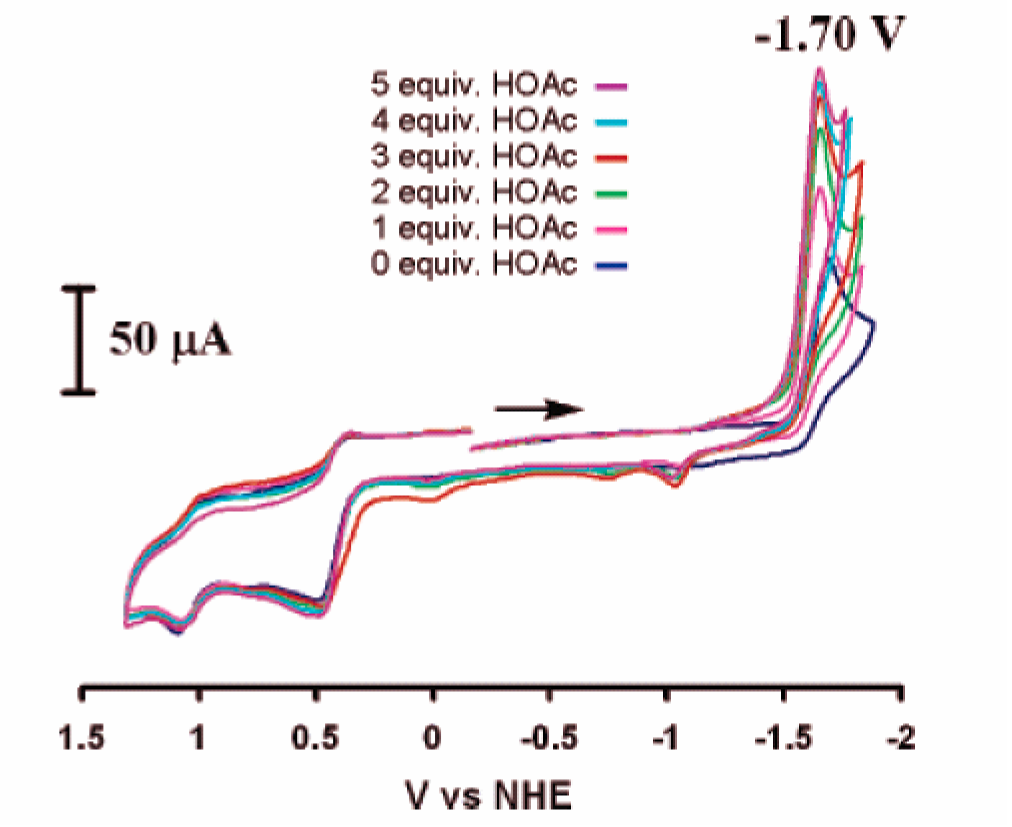


Criteria for Electrocatalysis: current α [H^+]
Positive shift in potential from non-catalyzed
HOAc reduction (-2.01 V → -1.70 V and –1.54 V)

(Note: The symmetrical (μ-pdt)[$Fe(CO)_2$PTA]$_2$ produces H_2 at –1.78 V in CH_3CN.)

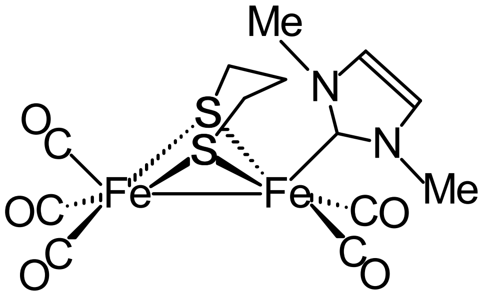
Electrocatalysis of H_2 Production
Cyclic Voltammetry of (μ-pdt)[Fe(CO)$_3$][Fe(CO)$_2$(IMes)] in CH_3CN with Increments of HOAc

A 2-electron reduction process !

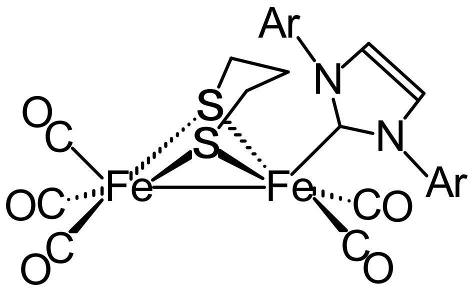


Inorg. Chem. **2005**, *44*, 5550.

Why does the IMes Complex Undergo a Two-Electron Reduction?

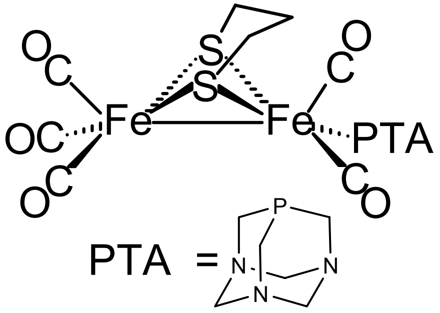


1 e⁻ reduction at
–1.66 V vs NHE



Ar = 2,4,6-trimethylphenyl

2 e⁻ reduction at
–1.70 V vs NHE

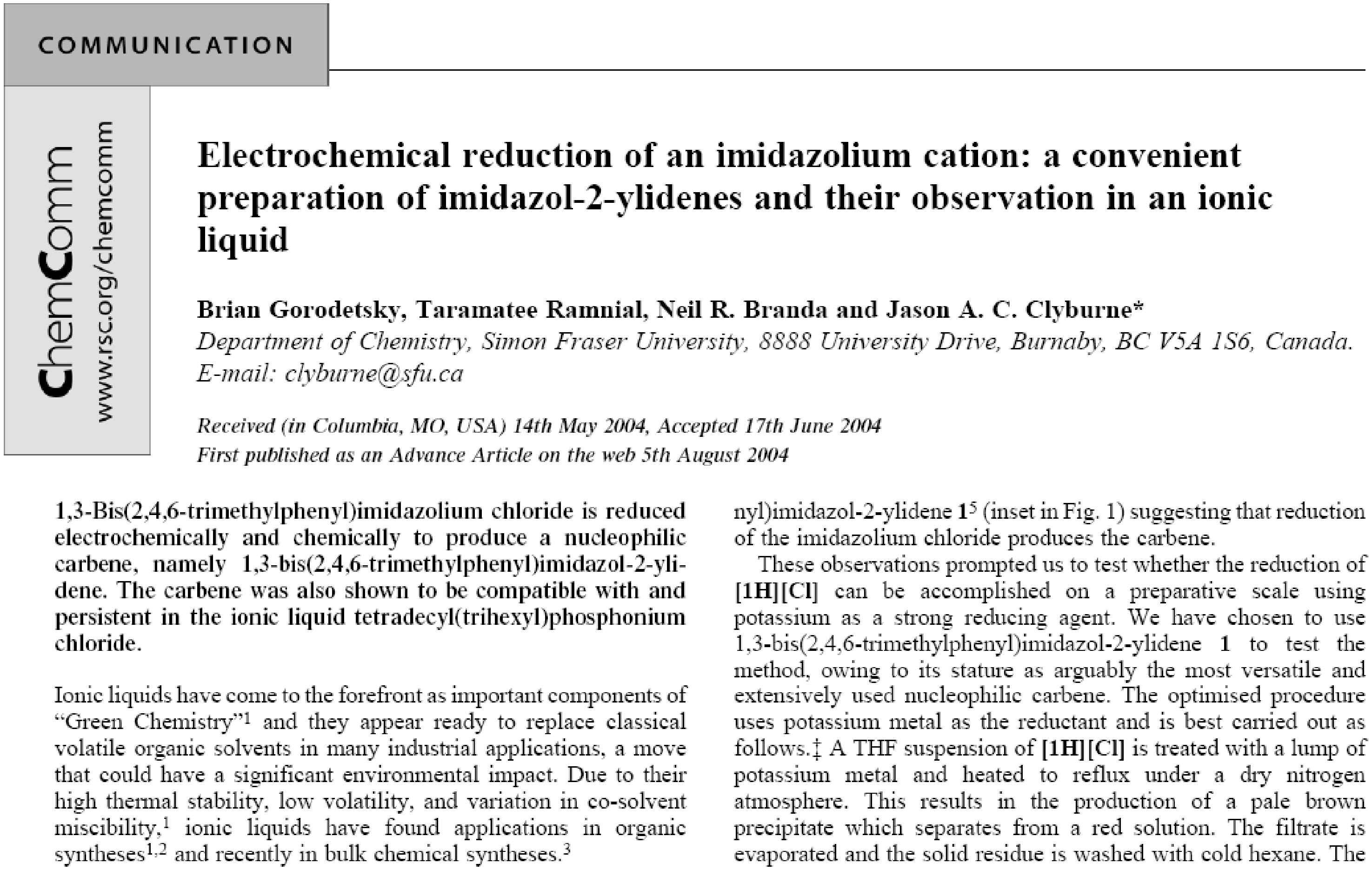


PTA =

1 e⁻ reduction at
–1.54 V vs NHE

Capon *et al. OM*, **2005**, *24*, 2020.
Tye *et al. Inorg. Chem.* **2005**, *44*, 5550.
Chong *et al. Dalton Trans.*, **2003**, *21*, 4158.

Electrochemical Reduction of the IMes Ligand



COMMUNICATION

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Electrochemical reduction of an imidazolium cation: a convenient preparation of imidazol-2-ylidenes and their observation in an ionic liquid

Brian Gorodetsky, Taramatee Ramnial, Neil R. Branda and Jason A. C. Clyburne*
Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, BC V5A 1S6, Canada.
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Received (in Columbia, MO, USA) 14th May 2004, Accepted 17th June 2004
First published as an Advance Article on the web 5th August 2004

1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride is reduced electrochemically and chemically to produce a nucleophilic carbene, namely 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. The carbene was also shown to be compatible with and persistent in the ionic liquid tetradecyl(trihexyl)phosphonium chloride.

Ionic liquids have come to the forefront as important components of "Green Chemistry"[1] and they appear ready to replace classical volatile organic solvents in many industrial applications, a move that could have a significant environmental impact. Due to their high thermal stability, low volatility, and variation in co-solvent miscibility,[1] ionic liquids have found applications in organic syntheses[1,2] and recently in bulk chemical syntheses.[3]

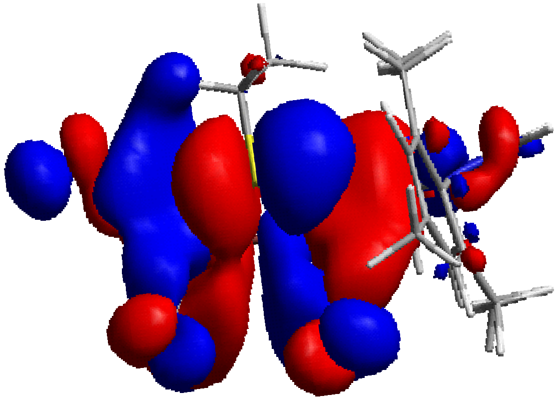
nyl)imidazol-2-ylidene **1**[5] (inset in Fig. 1) suggesting that reduction of the imidazolium chloride produces the carbene.

These observations prompted us to test whether the reduction of **[1H][Cl]** can be accomplished on a preparative scale using potassium as a strong reducing agent. We have chosen to use 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene **1** to test the method, owing to its stature as arguably the most versatile and extensively used nucleophilic carbene. The optimised procedure uses potassium metal as the reductant and is best carried out as follows.‡ A THF suspension of **[1H][Cl]** is treated with a lump of potassium metal and heated to reflux under a dry nitrogen atmosphere. This results in the production of a pale brown precipitate which separates from a red solution. The filtrate is evaporated and the solid residue is washed with cold hexane. The

Frontier Molecular Orbitals of 1-IMes

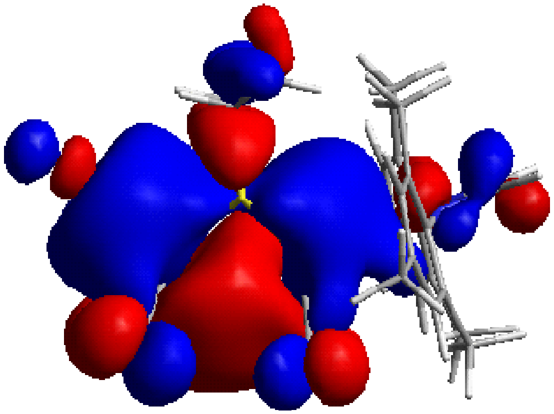
(LUMO + 1)

Fe-Fe antibonding



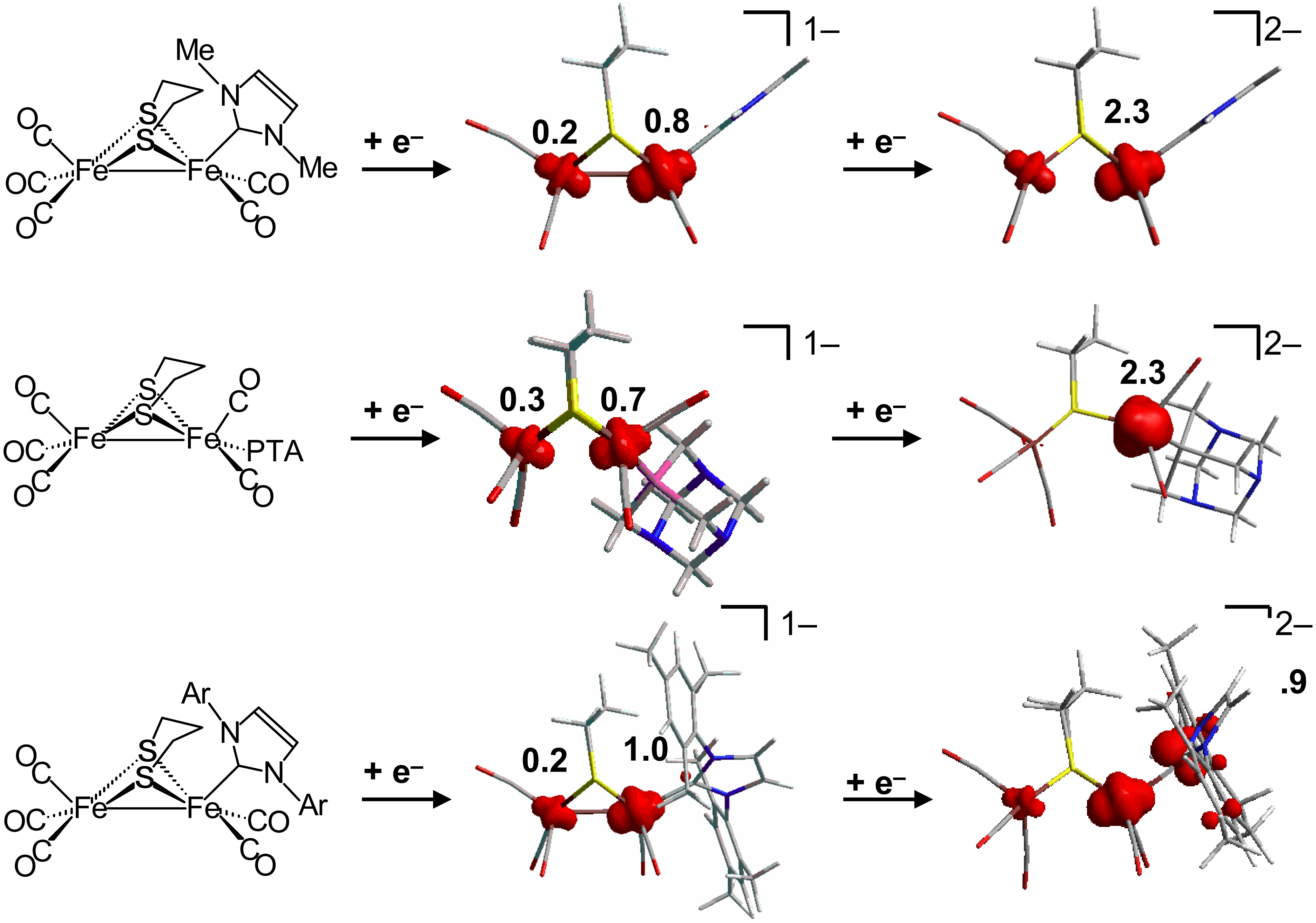
LUMO

Fe-Fe bonding

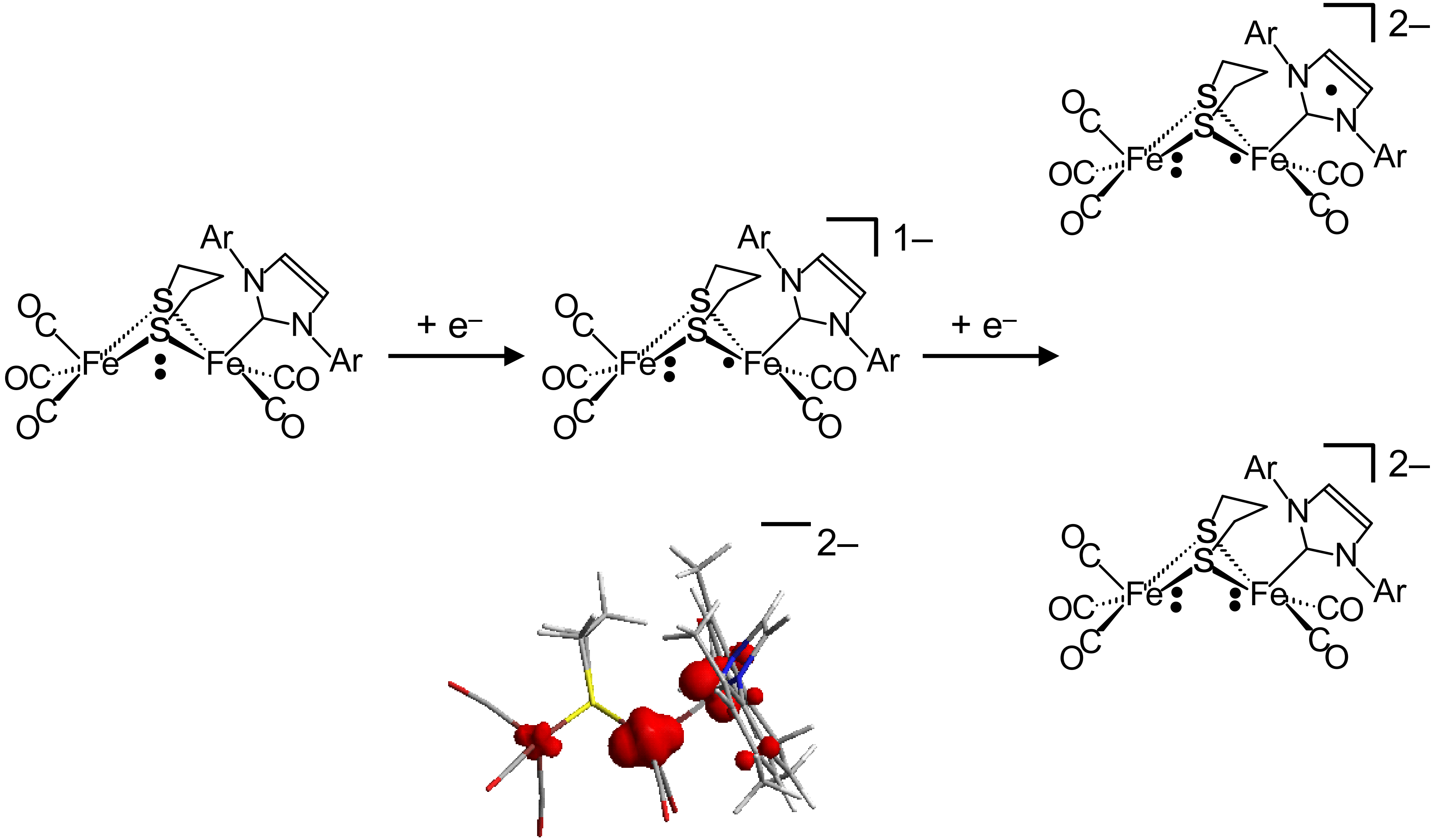


HOMO

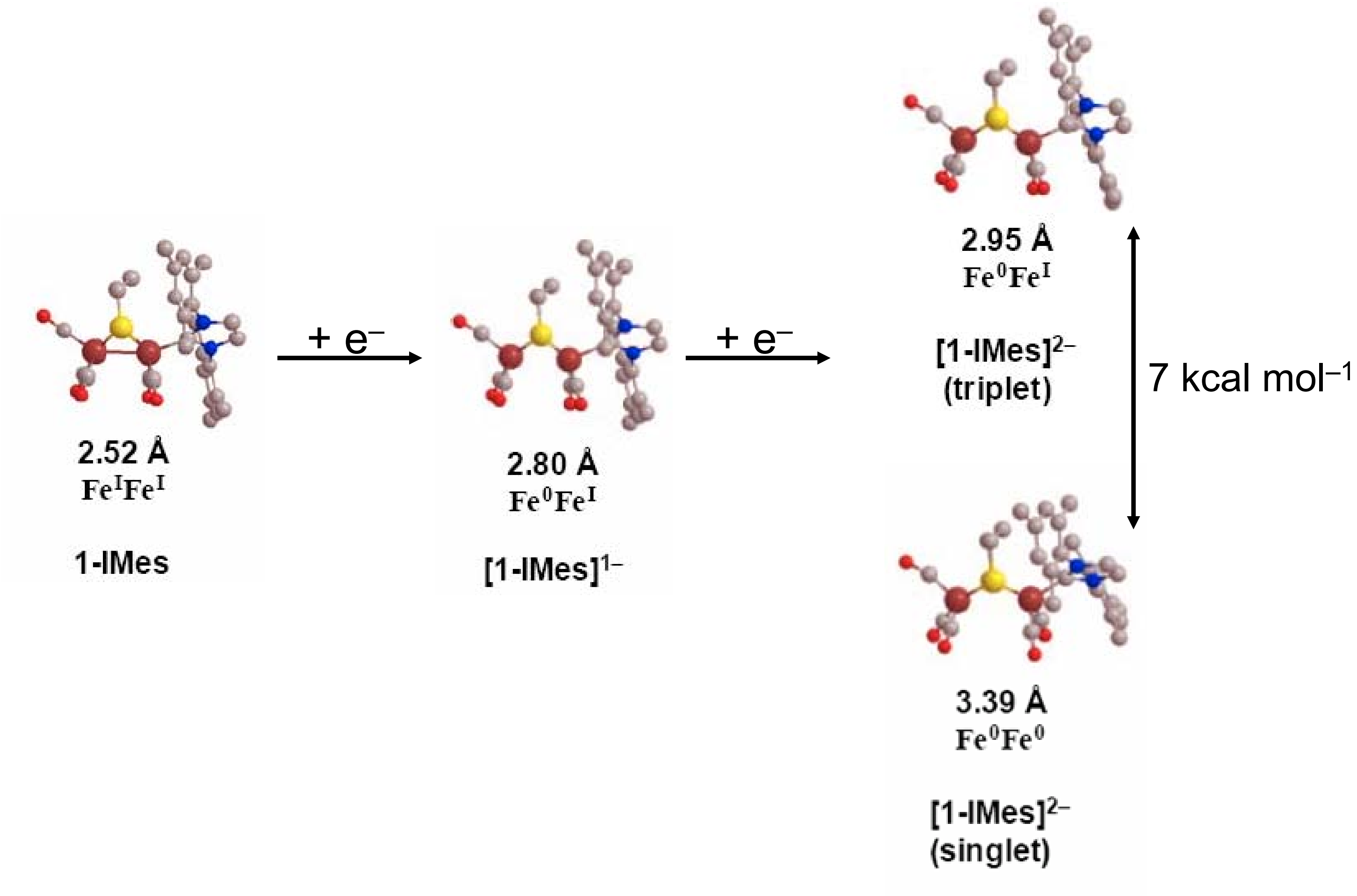
Computed Unpaired Spin Densities



Unpaired Spin Densities



Optimized Structures of the Reduced Forms



2.52 Å
$Fe^{I}Fe^{I}$

1-IMes

$\xrightarrow{+\ e^{-}}$

2.80 Å
$Fe^{0}Fe^{I}$

$[1\text{-IMes}]^{1-}$

$\xrightarrow{+\ e^{-}}$

2.95 Å
$Fe^{0}Fe^{I}$

$[1\text{-IMes}]^{2-}$
(triplet)

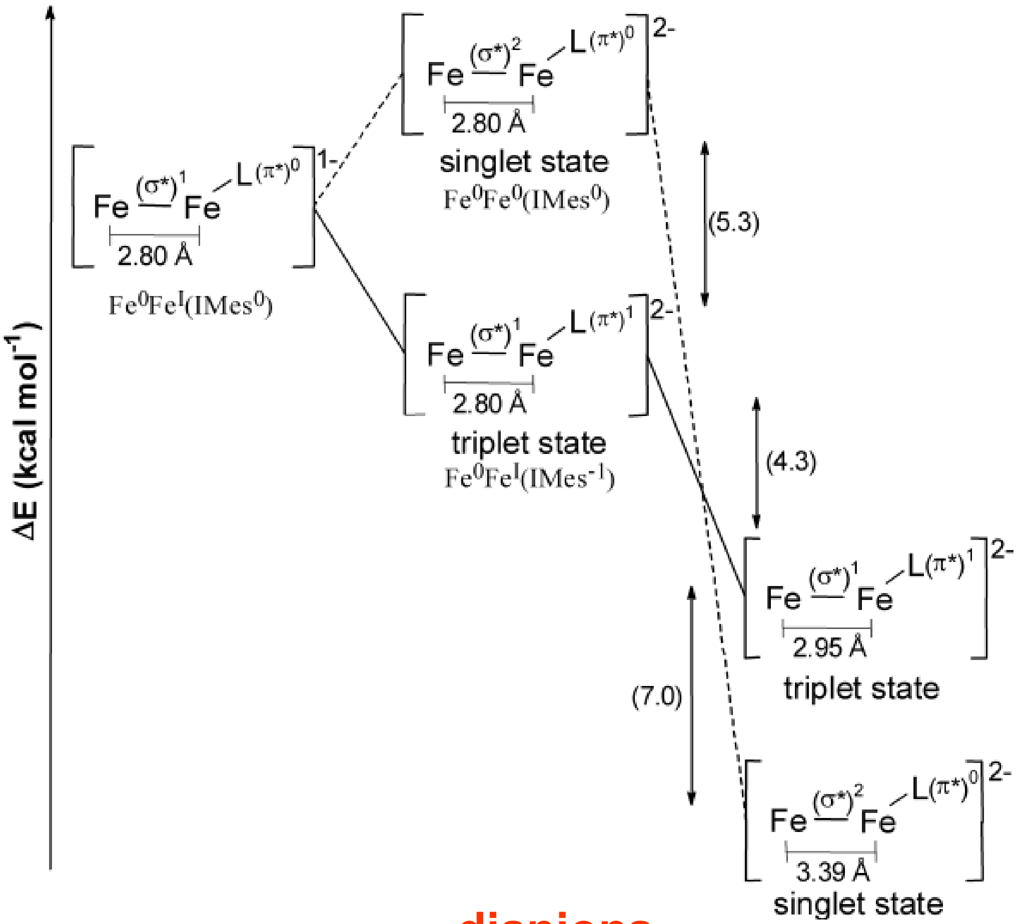
7 kcal mol^{-1}

3.39 Å
$Fe^{0}Fe^{0}$

$[1\text{-IMes}]^{2-}$
(singlet)

Tye *et al. Inorg. Chem.* **2005**, *44*, 5550.

At the electrode surface…



fully-optimized monoanion

dianions at monoanion geometry

fully-optimized dianions

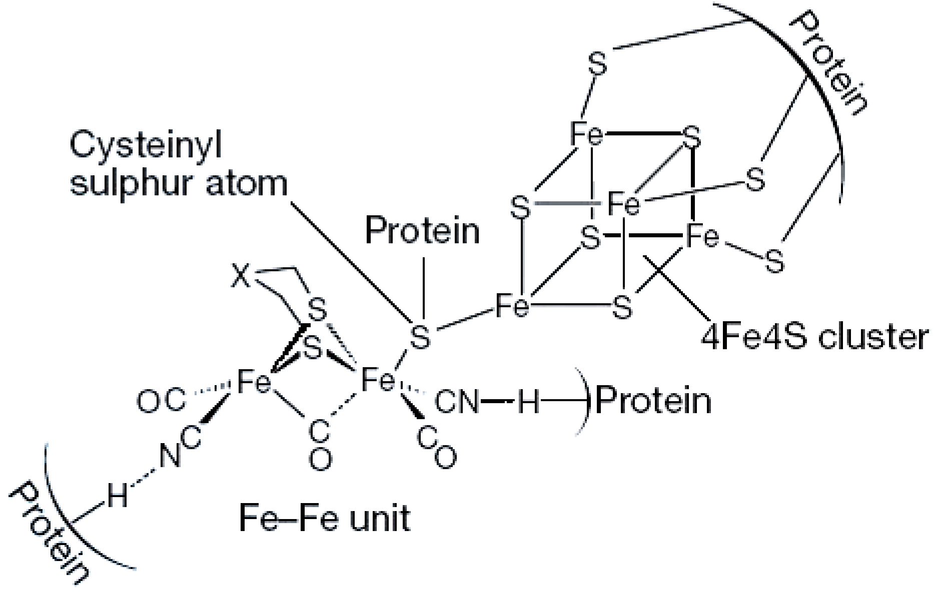
Tye *et al. Inorg. Chem.* **2005**, *44*, 5550.

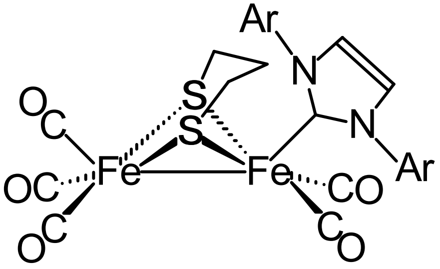
Conclusions

- The extended π system of the IMes ligand allows the 1-IMes complex to undergo a simultaneous two-electron reduction.

►The redox-active IMes ligand acts as a model of the [4Fe4S] site of the H-cluster.

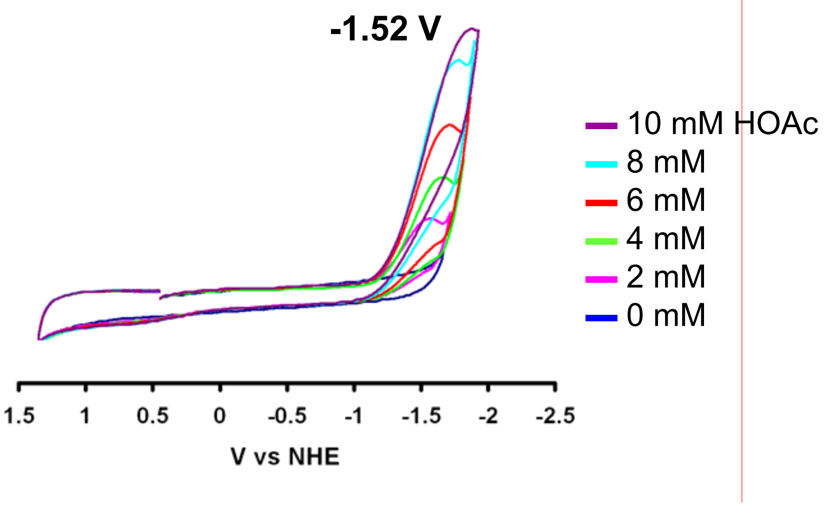
- The addition of the 1-IMes complex leads to a + 500mV positive shift for the reduction of HOAc.



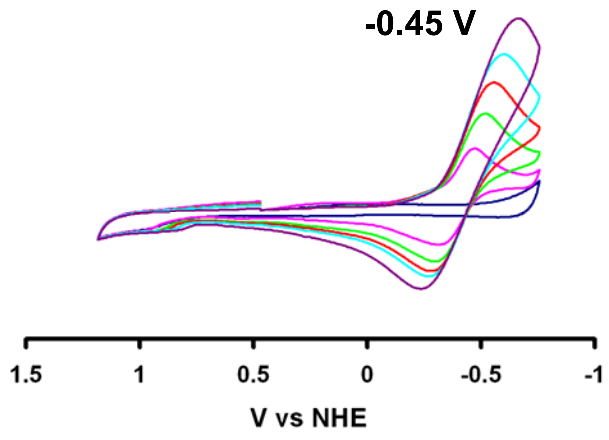


Proton Reduction Studies: $CH_3CN:H_2O$ (1:3) Comparison of Fe-monoPTA solution electrocatalyst and Pt electrode

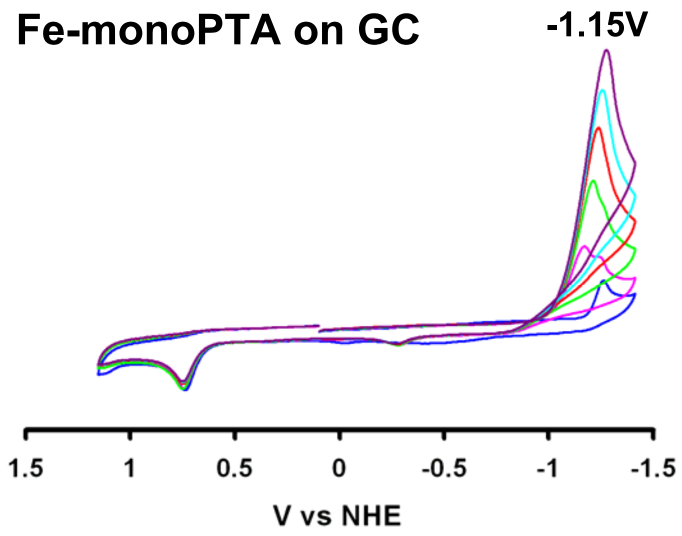
a) Glassy Carbon + HOAc



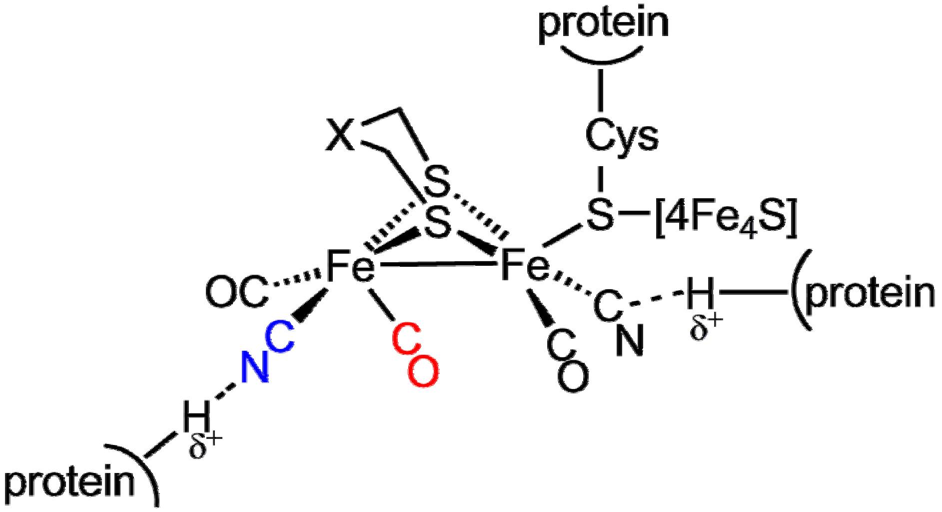
b) Pt + HOAc

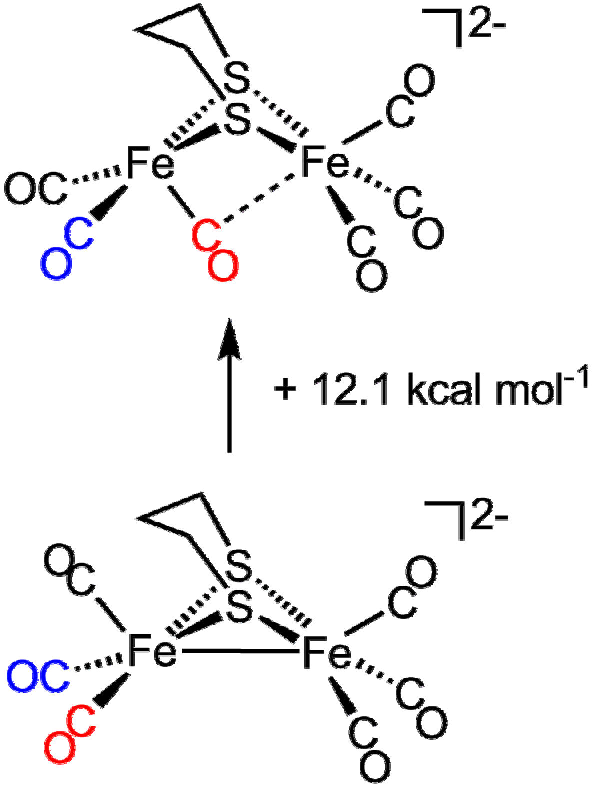


c) Fe-monoPTA on GC



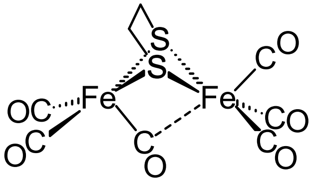
De Novo Design of Synthetic Di-Iron(I) Complexes as Structural Models of the Reduced Form of Iron-Iron Hydrogenase





Tye, et al. Inorg. Chem. **2006**, 45, 1552-1559.

Combination of Effects



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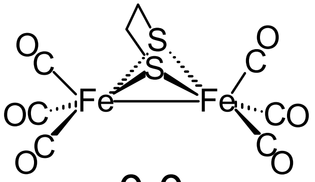

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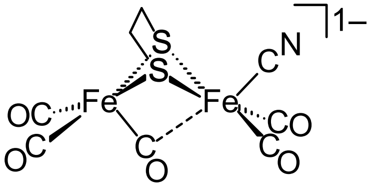

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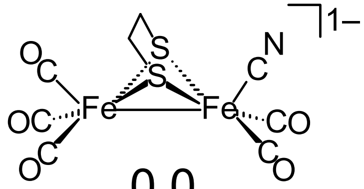

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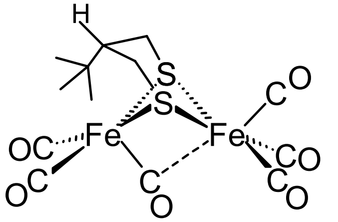

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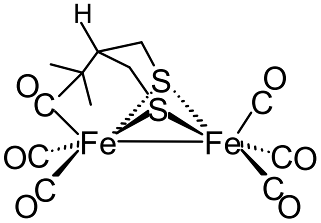

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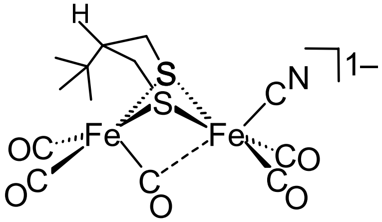
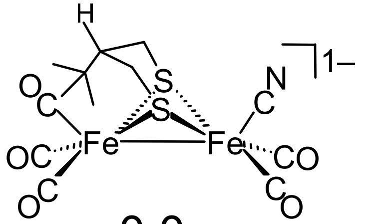


1.9



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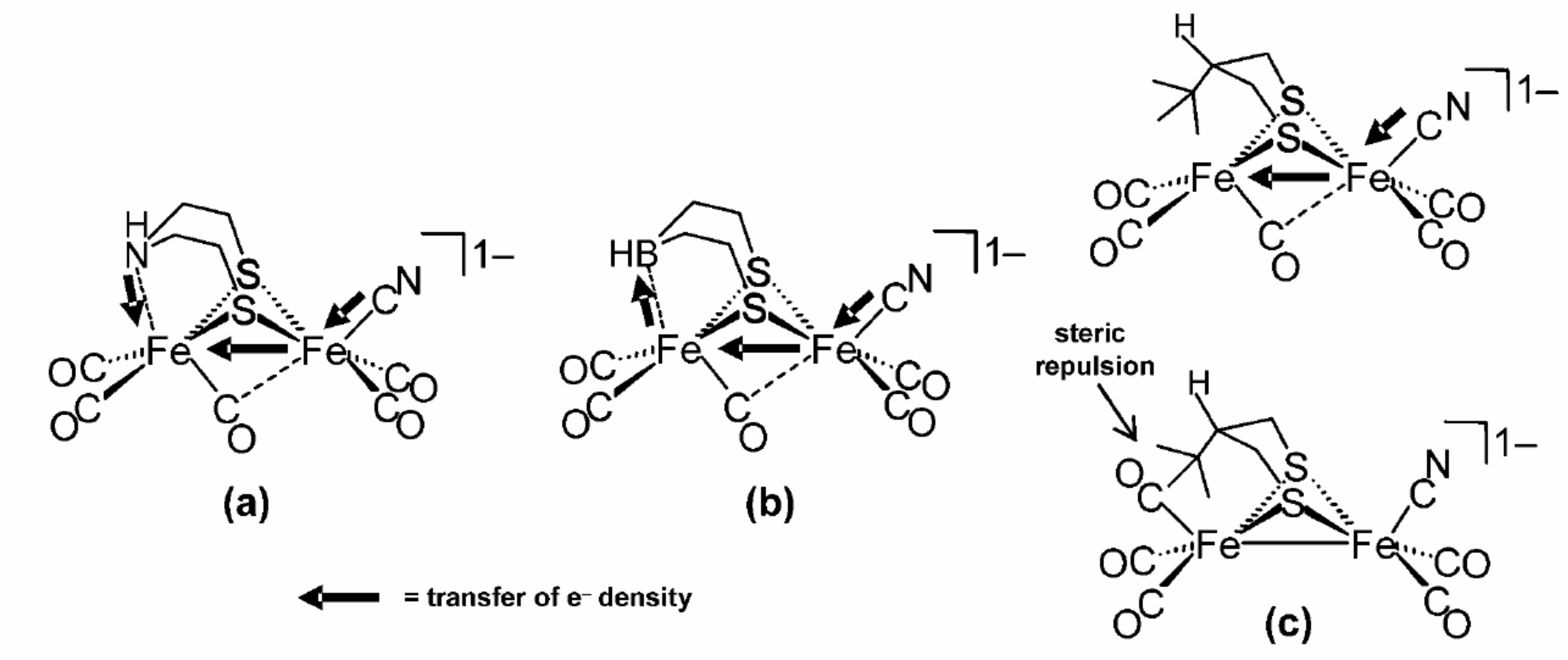
Combination of Effects: A Summary



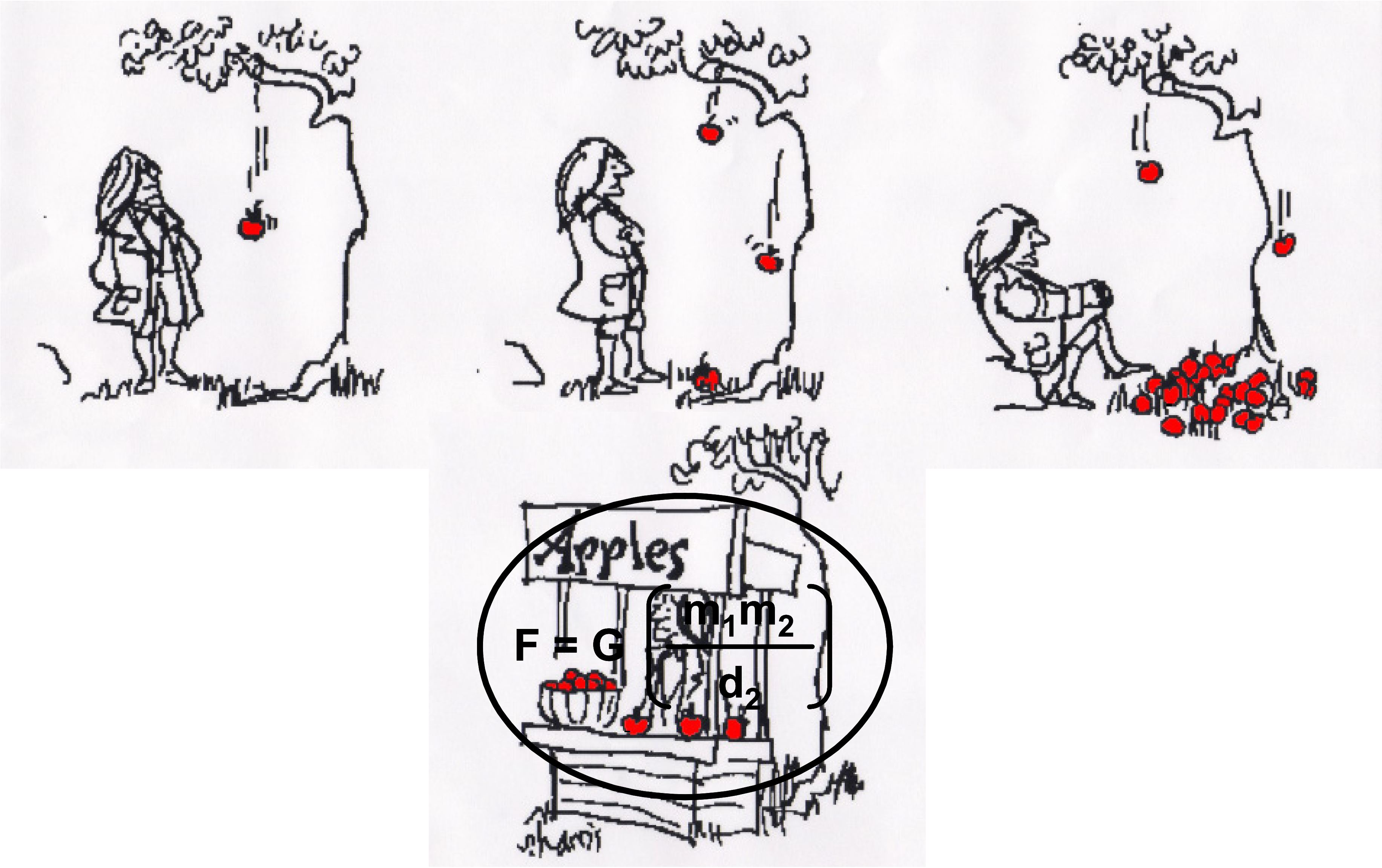
Conclusions

● Incorporation of the N or B functionalities stabilizes the rotated form, but potentially blocks the site for H^+ acceptance.

►The best method incorporates the use of steric bulk on the S-to-S linker and the use of strong donor ligand on the adjacent iron.

Acknowledgement: Jesse W. Tye and Michael B. Hall

The Future of Hydrogenase Research?



$$F = G\left(\frac{m_1 m_2}{d_2}\right)$$

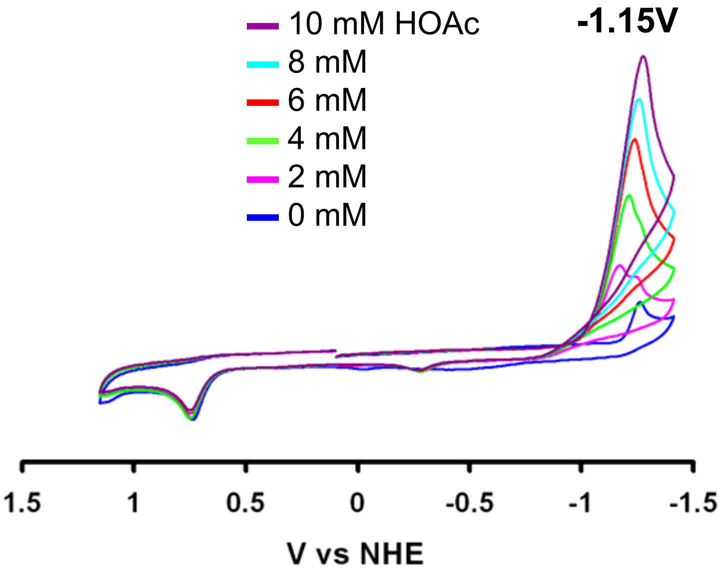
Hydrogenase 2007: The 8th International Hydrogenase Conference

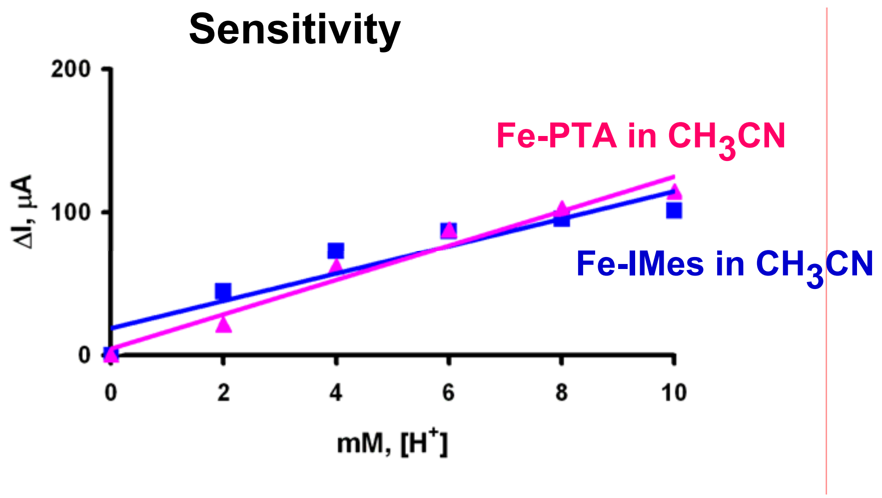
Colorado, USA
August 05-10, 2007

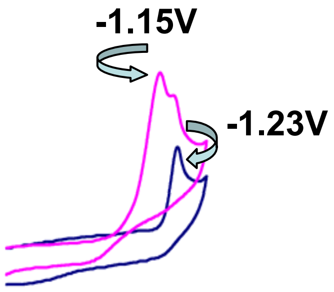
http://www.chem.tamu.edu/hydrogenase/

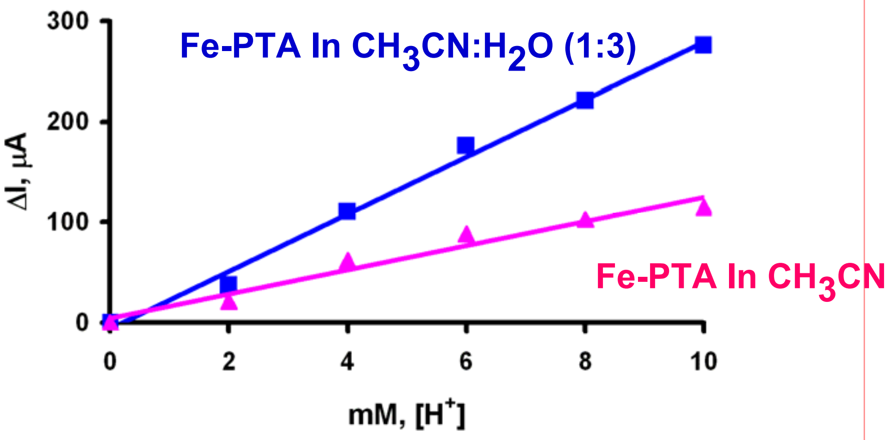
hydrogenase@mail.chem.tamu.edu

Proton Reduction Studies in the Presence of Water: $CH_3CN{:}H_2O$ (1:3) The Fe-monoPTA solution electrocatalyst with added increments of HOAc; GC electrode

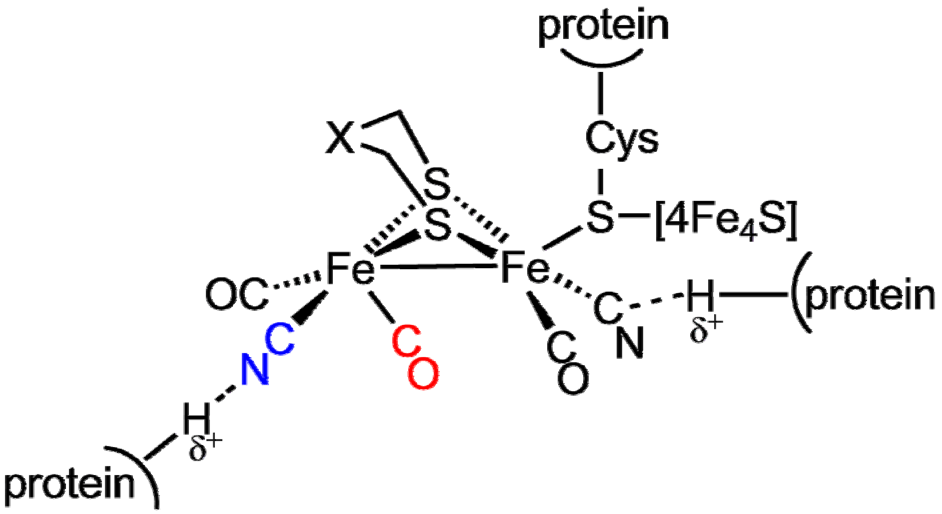


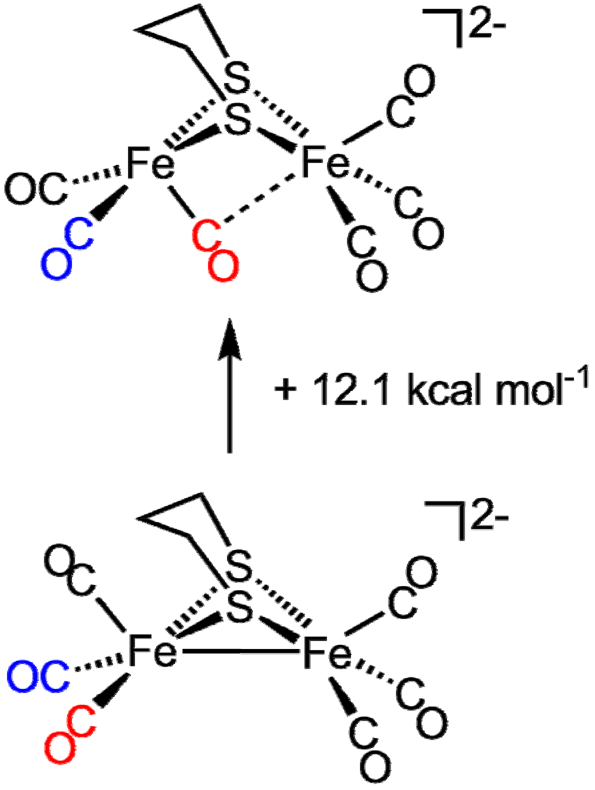






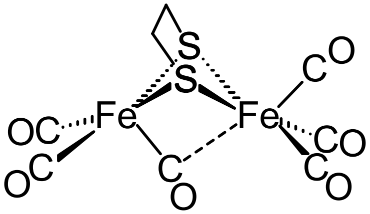
De Novo Design of Synthetic Di-Iron(I) Complexes as Structural Models of the Reduced Form of Iron-Iron Hydrogenase





Tye, et al. Inorg. Chem. **2006**, 45, 1552-1559.

Combination of Effects



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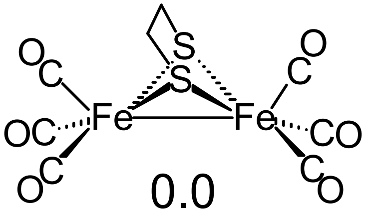

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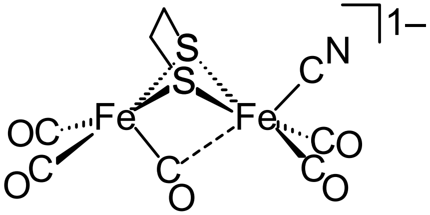

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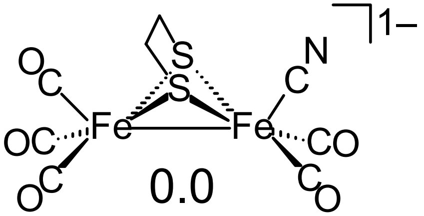

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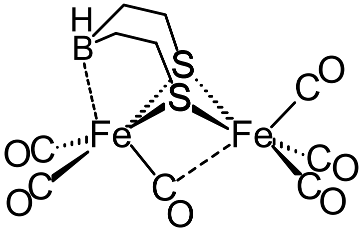

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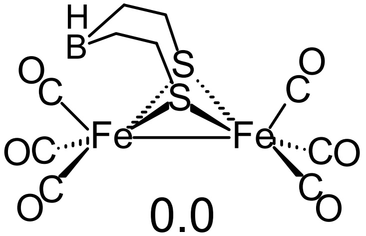

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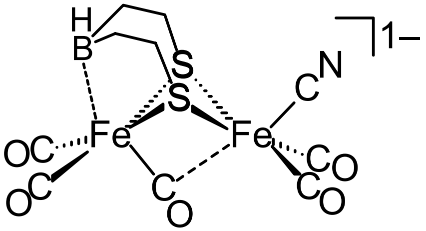

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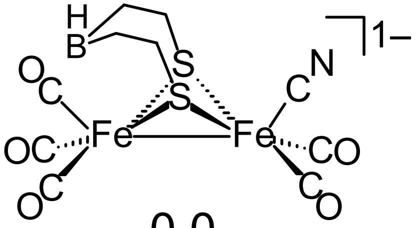

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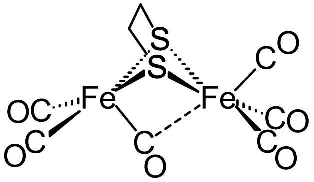
Combination of Effects



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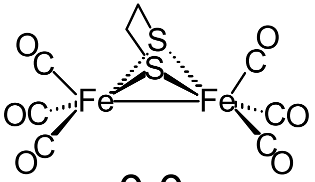

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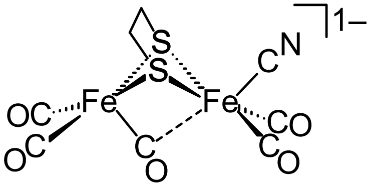

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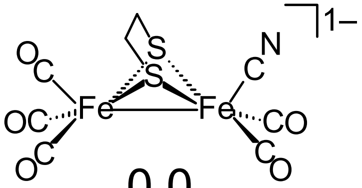

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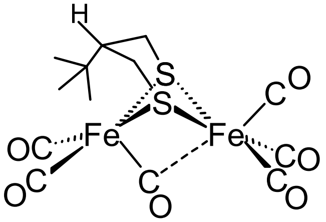

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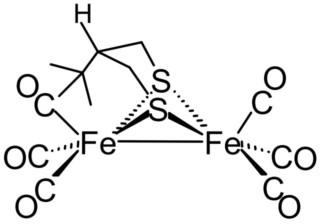

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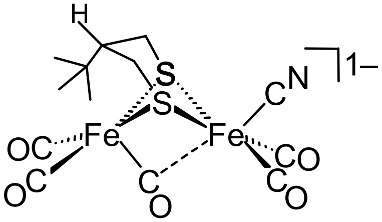

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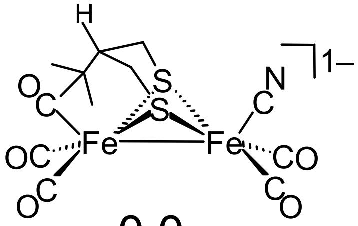

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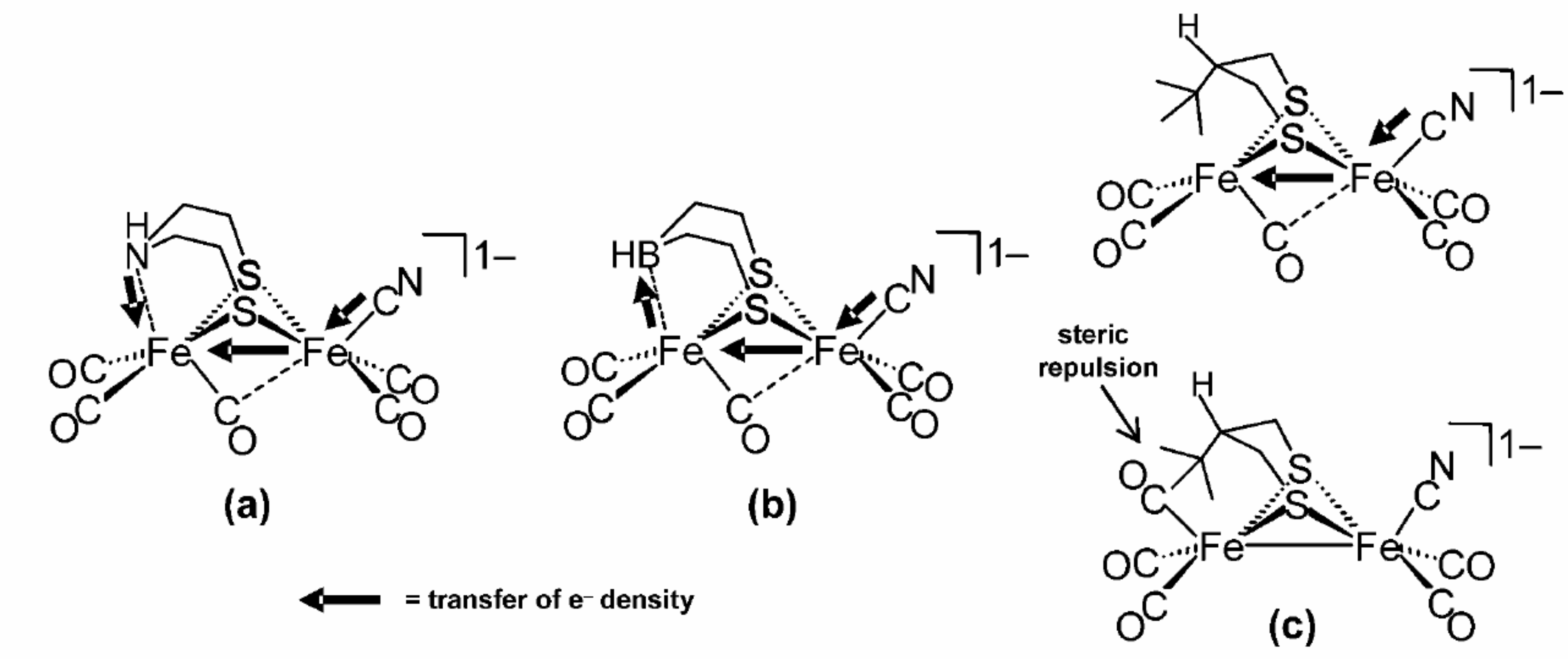
Combination of Effects: A Summary



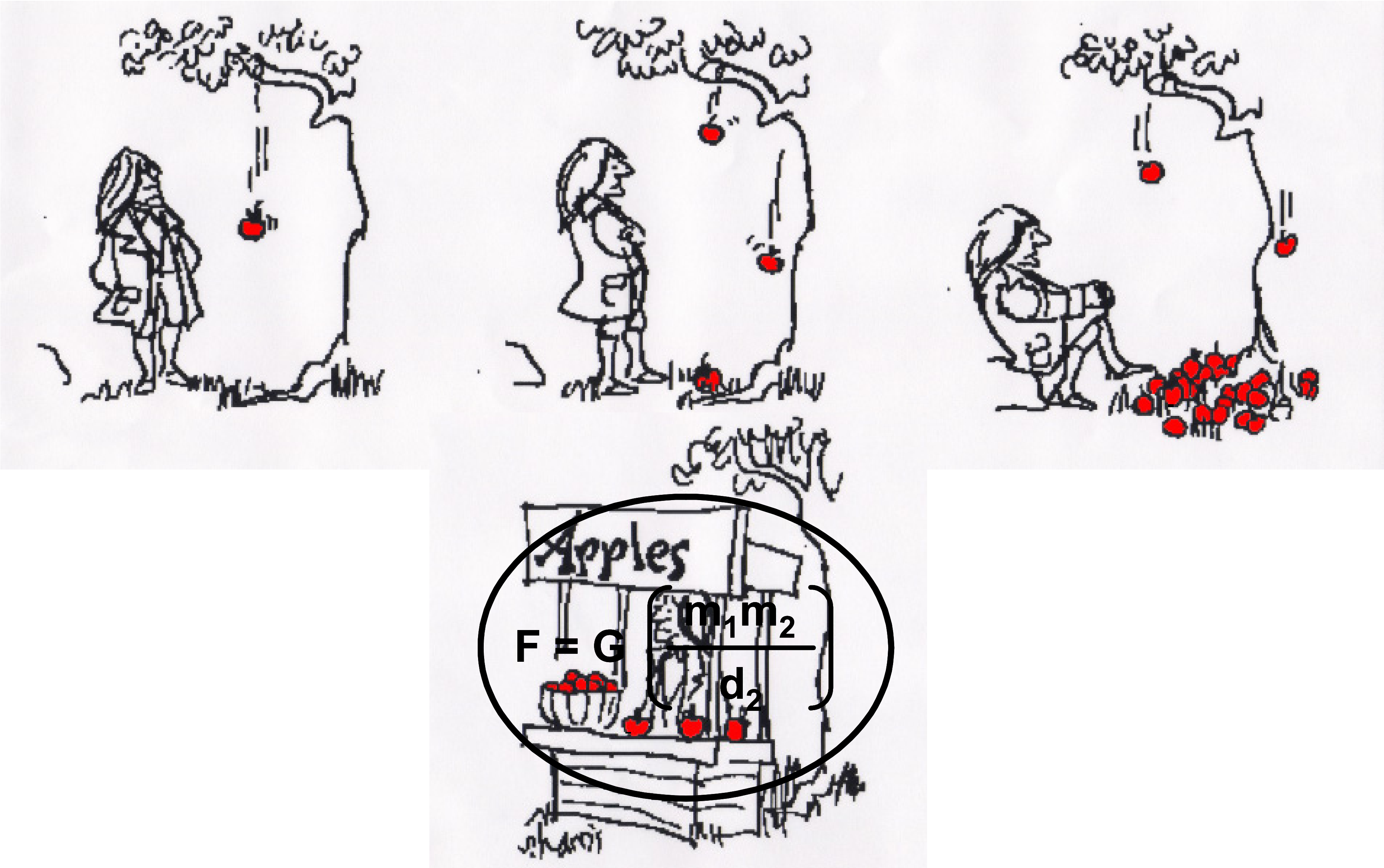
Conclusions

- Incorporation of the N or B functionalities stabilizes the rotated form, but potentially blocks the site for H^+ acceptance.

► The best method incorporates the use of steric bulk on the S-to-S linker and the use of strong donor ligand on the adjacent iron.

Acknowledgement: Jesse W. Tye and Michael B. Hall

The Future of Hydrogenase Research?



$$F = G\left(\frac{m_1m_2}{d_2}\right)$$

Hydrogenase 2007:
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