

From Structure to Function: One Hundred Years of Inadvertent Fe-only Hydrogenase Modeling

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The iron-only hydrogenase (Fe H₂-ase) enzymes are responsible for hydrogen oxidation and proton reduction in microorganisms.¹ The active site (H-cluster) contains a ferredoxin-like [Fe₄S₄] cluster bound to a unique two-iron sub-cluster with dithiolate, carbonyl, and cyanide ligands (Figure 1).² The two-iron unit is thought to be site of dihydrogen and proton binding. The dithiolate ligand probably contains a central atom capable of hydrogen bonding;² DFT calculations favor assignment of NH for X.³

A series of structural models for the H-cluster based on the dianion [Fe₂(S₂C₃H₆)(CN)₂(CO)₄]²⁻, initially reported by Schmidt, Contakes, and Rauchfuss,⁴ were prepared in an attempt to fully explore the characteristics of the mixed cyano-carbonyl compounds. Of special interest were the details of the cyanide substitution reaction.^{5,6} Treatment of MeCN solutions of Fe₂(S₂C₃H₆)(CO)₆^{7,8} with two equiv of CN⁻ gave [Fe₂(S₂C₃H₆)(CN)₂(CO)₄]²⁻ compounds; furthermore, treatment of Fe₂(S₂C₃H₆)(CO)₆ compounds with less than two equiv of CN⁻ gave predominantly [Fe₂(S₂C₃H₆)(CN)₂(CO)₄]²⁻ and unreacted Fe₂(S₂C₃H₆)(CO)₆. The mechanism of the CN⁻-for-CO substitution was probed as follows: (i) excess CN⁻ with a 1:1 mixture of Fe₂(SMe)₂(CO)₆ and Fe₂(SC₆H₄Me)₂(CO)₆ gave no mixed thiolates, (ii) treatment of Fe₂(S₂C₃H₆)(CO)₆ with Me₃NO followed by CN⁻ gave [Fe₂(S₂C₃H₆)(CN)(CO)₅]⁻, (iii) treatment of Fe₂(S₂C₃H₆)(CO)₆ with CN⁻ in the presence of excess PMe₃ gave [Fe₂(S₂C₃H₆)(CN)(CO)₄(PMe₃)]⁻ much more rapidly than the reaction of PMe₃ with [Fe₂(S₂C₃H₆)(CN)(CO)₅]⁻, and (iv) a competition experiment showed that CN⁻ reacted with Fe₂(S₂C₃H₆)(CO)₆ more rapidly than with [Fe₂(S₂C₃H₆)(CN)(CO)₅]⁻.

A new functional model for the proton reduction activity of the H-cluster was obtained as a result of the above mechanistic study. Early models for the H-cluster of the Fe H₂ase enzymes, [Fe₂(SR)₂(CN)₂(CO)₄]²⁻ compounds, were unstable in the presence of excess acid, and therefore could not be utilized for catalytic proton reduction.^{4,9,10} Electrolysis of a solution of (Et₄N)[Fe₂(S₂C₃H₆)(CN)(CO)₄(PMe₃)] (Figure 2) and sulfuric acids in MeCN produced H₂ in ca. 100% Faradaic yield, corresponding to six turnovers for the bulk solution. The activity of this compound was comparable to other proton reduction catalysts^{11,12} and it exhibited a significantly lower overpotential than many of such systems.¹³ The anion [Fe₂(S₂C₃H₆)(CN)(CO)₄(PMe₃)]⁻ was protonated by sulfuric or toluenesulfonic acid to give HFe₂(S₂C₃H₆)(CN)(CO)₄(PMe₃).^{14,15} Spectroscopic and electrochemical measurements indicated that HFe₂(S₂C₃H₆)(CN)(CO)₄(PMe₃) could be further protonated at nitrogen to give [HFe₂(S₂C₃H₆)(CNH)(CO)₄(PMe₃)]⁺. Electrochemical and analytical data showed that reduction of [HFe₂(S₂C₃H₆)(CNH)(CO)₄(PMe₃)]⁺ gave H₂ and [Fe₂(S₂C₃H₆)(CN)(CO)₄(PMe₃)]⁻. Parallel electrochemical studies on [HFe₂(S₂C₃H₆)(CO)₄(PMe₃)₂]⁺ in acidic solutions led also to catalytic proton reduction.

The $[\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CO})_4(\text{PMe}_3)_2]^+ / [\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CO})_4(\text{PMe}_3)_2]$ couple is reversible, whereas the $[\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CNH})(\text{CO})_4(\text{PMe}_3)]^+ / [\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CNH})(\text{CO})_4(\text{PMe}_3)]$ couple is not, due to the efficiency of the latter as a proton reduction catalyst. Experimental studies in conjunction with DFT calculations establish that the regiochemistry of protonation was subtly dependent on the co-ligands.

While $[\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CNH})(\text{CO})_4(\text{PMe}_3)]^+$ is an active catalyst for proton reduction, it is not sufficiently stable in its oxidized form to bind H_2 . Therefore, new structural models for the H_2 -oxidizing state of the H-cluster are being investigated. Our most recent success in synthesizing Fe-Fe bonded model complexes with 2 e⁻ bridging ligands will be presented (Figure 3).

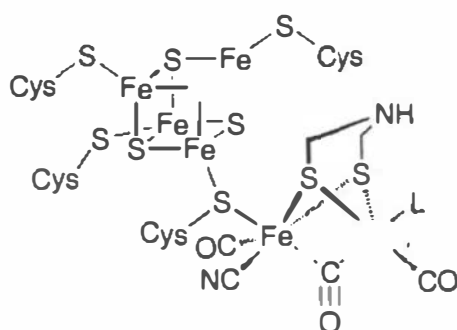


Figure 1

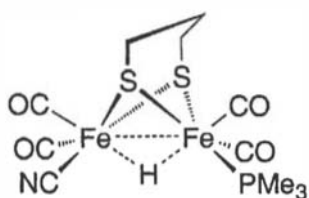


Figure 2

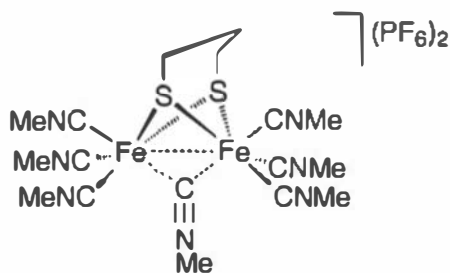


Figure 3

References

1. Adams, M. W. W.; Mortenson, L. E.; Chen, J. S. "Hydrogenases" *Biochim. Biophys. Acta* **1981**, *594*, 105-176.
2. Frey, M. "Hydrogenases: Hydrogen-Activating Enzymes" *ChemBioChem* **2002**, *3*, 153-160.
3. Liu, Z.-P.; Hu, P. "Mechanism of H_2 Metabolism on Fe-Only Hydrogenases" *J. Chem. Phys.* **2002**, *117*, 8177-8180.

4. Schmidt, M.; Contakes, S. M.; Rauchfuss, T. B. "First Generation Analogues of the Binuclear Site in the Fe-Only Hydrogenases: $\text{Fe}_2(\mu\text{-SR})_2(\text{CO})_4(\text{CN})_2^{2-}$ " *J. Am. Chem. Soc.* **1999**, *121*, 9736-9737.
5. Ellgen, P. C.; Gerlach, J. N. "Kinetics and Mechanism of the Substitution Reactions of Bis(mercaptopotricarbonyliron) Complexes" *Inorg. Chem.* **1973**, *12*, 2526-2532.
6. Lyon, E. J.; Georgakaki, I. P.; Reibenspies, J. H.; Darensbourg, M. Y. "Coordination Sphere Flexibility of Active-Site Models for Fe-Only Hydrogenase: Studies in Intra- and Internuclear Diatomic Ligand Exchange" *J. Am. Chem. Soc.* **2001**, *123*, 3268-3278.
7. Markó, L.; Markó-Monostory, B. "[Organoiron] complexes with sulfur-containing ligands" *Org. Chem. Iron* **1981**, *2*, 283-232.
8. King, R. B.; Bitterwolf, T. E. "Metal carbonyl analogues of iron-sulfur clusters found in metalloenzyme chemistry" *Coord. Chem. Rev.* **2000**, *206-207*, 563-579.
9. Lyon, E. J.; Georgakaki, I. P.; Reibenspies, J. H.; Darensbourg, M. Y. "Carbon monoxide and cyanide ligands in a classical organometallic complex model for Fe-only hydrogenase" *Angew. Chem., Int. Ed.* **1999**, *38*, 3178-3180.
10. Le Cloirec, A.; Best, S. P.; Borg, S.; Davies, S. C.; Evans, D. J.; Hughes, D. L.; Pickett, C. J. "A Di-iron Dithiolate Possessing Structural Elements of the Carbonyl/Cyanide sub-Site of the H-Centre of Fe-Only Hydrogenase" *Chem. Commun.* **1999**, 2285-2286.
11. Koelle, U.; Paul, S. "Electrochemical Reduction of Protonated Cyclopentadienylcobalt Phosphine Complexes" *Inorg. Chem.* **1986**, *25*, 2689-2694.
13. Le Gall, T.; Ibrahim, S. K.; Gormal, C. A.; Smith, B. E.; Pickett, C. J. "The Isolated Iron-Molybdenum Cofactor of Nitrogenase Catalyzes Hydrogen Evolution at High Potential" *Chem. Commun.* **1999**, 773-774.
14. Bhugun, I.; Lexa, D.; Savéant, J.-M. "Homogeneous Catalysis of Electrochemical Hydrogen Evolution by Iron(0) Porphyrins" *J. Am. Chem. Soc.* **1996**, *118*, 3982-3983.
15. Bianchini, C.; Laschi, F.; Ottaviani, M. F.; Peruzzini, M.; Zanello, P.; Zanobini, F. "Nucleophilic Properties and Electrochemistry of Five-Coordinate Rhodium(I) σ -Cyanide Complexes. Synthesis and Characterization of Stable *cis* Hydride Cyanide Complexes of Rhodium(III)" *Organometallics* **1989**, *8*, 893-899.
16. Nataro, C.; Chen, J.; Angelici, R. J. "Cyanide Ligand Basicities in $\text{Cp}'\text{M}(\text{L})_2\text{CN}$ Complexes (M = Ru, Fe). Correlation between Heats of Protonation and ν_{CN} " *Inorg. Chem.* **1998**, *37*, 1868-1875.

