Modeling the Active States of the [NiFe]- and [FeFe]-Hydrogenases

C. Matthew Whaley Final Seminar May 7, 2009

The [NiFe]- and [FeFe]-hydrogenases are members of a class of phylogenetically-distinct metalloenzymes that function in microbial metabolism to catalyze the reversible oxidation of hydrogen to protons and electrons. These enzymes are of intense interest for the roles that they play in metabolic processes in Nature. Industrially, the hydrogenases are of interest for what role they, or their small molecule mimics, could play in the hydrogen economy. They are comparable in activity to platinum for the electrocatalytic production of hydrogen while utilizing less expensive and more abundant nickel and iron, and they are significantly less susceptible to poisoning.[1] In medicine, the majority of all gastric cancers is due to the action of *Helicobacter pylori*, an anaerobic bacterium that relies on the activity of [NiFe]-hydrogenase for its metabolic processing of hydrogen as an energy source.[2]

The most widespread and well-studied of the hydrogenases is the [NiFe]-hydrogenases, whose active sites (Figure 1, right) feature an octahedral $Fe(CN)_2(CO)$ unit coordinated to a $Ni(S\text{-cysteine})_2$ unit by two bridging cysteine thiolates and a bridging hydride (in the catalytically-active Ni-R state).[3] The more recently evolved hydrogenase is the highly active [FeFe]-hydrogenase, whose active site (Figure 1, left) features an octahedral Fe(CN)(S-cysteine)(CO) unit coordinated to a Fe(CN)(CO)H unit by a bridging carbonyl and a bridging dithiolate that is proposed to be derived from bis(thiomethyl)amine.[3] Unlike the [NiFe]-hydrogenase active site, the [FeFe]-hydrogenase active site is bridged to a [4Fe-4S] cluster by the coordinated cysteine thiolate that is responsible for electron-transfer to and from the active site. The main goal of this research is to synthesize small molecule mimics of these hydride species in order to gain understanding of the way Nature processes hydrogen and to guide future efforts toward developing active hydrogen oxidation and/or proton reduction catalysts.

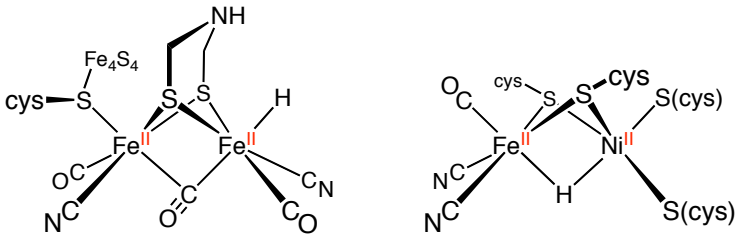

Figure 1. Active site of catalytically-active states of [FeFe]-hydrogenase (H_{red}, left) and [NiFe]-hydrogenase (Ni-R, right).

The first example of a hydride-containing ferrous cyano-carbonyl complex, $[HFe(CN)_2(CO)_3]^-$, was reported in 2002 by our group.[4] This highly electrophilic hydride complex undergoes rapid ligand substitution with monophosphorus donor ligands to give complexes of the type $[HFe(CN)_2(CO)_2L]^-$ or with the chelating diphosphine *cis*-1,2-

bis(diphenylphosphino)ethylene (dppv) to give $[HFe(CN)_2(CO)(dppv)]^-$, Figure 2.[5] This complex is a good structural model for the ferrous unit in the [NiFe]-hydrogenase active site.

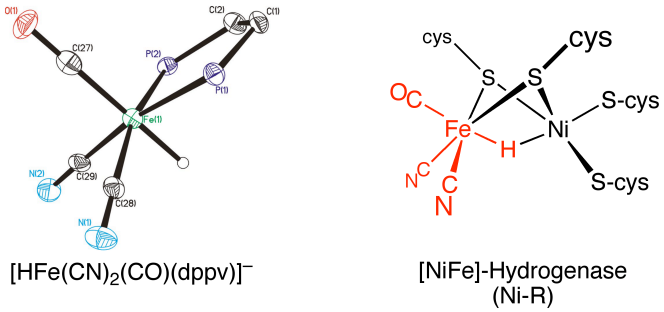

Figure 2. Comparison of the molecular structure of $[HFe(CN)_2(CO)(dppv)]^-$ and the structure of the Ni-R state of the [NiFe]-hydrogenase active site.

Attempts to substitute CO for sulfur-donor ligands on $[HFe(CN)_2(CO)_3]^-$ to prepare heterobimetallic NiFe complexes were met with no success. However, previous work on mononuclear ferrous dithiolato complexes had shown that these complexes were competent for the coordination to other metals.[6] The reaction of $Fe(S_2C_3H_6)(CO)_2(dppe)$ with $NiCl_2(dppe)$ in refluxing acetone solution generated the heterobimetallic species $[(dppe)(CO)Fe(S_2C_3H_6)(\mu\text{-}Cl)Ni(dppe)]^+$, isolated as the BF_4^- salt. This complex was fully characterized, and the molecular structure is given in Figure 3.

Reaction of a CH_2Cl_2 solution of $Fe(S_2C_3H_6)(CO)_2(dppe)$ and $NiCl_2(dppe)$ with Bu_4NBH_4 resulted in the formation of a mixture of hydride complexes as evidenced by ^{1}H-NMR spectroscopy. The target hydride complex, $[(dppe)(CO)Fe(S_2C_3H_6)(\mu\text{-}H)Ni(dppe)]^+$ was observed in the ESI-mass spectrum; however, no NiFe-hydride complexes could be isolated. This complex was later characterized and isolated utilizing a synthetic procedure that involved the photochemical substitution of two CO ligands for dppe on $[(CO)_3Fe(S_2C_3H_6)(\mu\text{-}H)Ni(dppe)]BF_4$, which was prepared from the protonation of $(CO)_3Fe(S_2C_3H_6)Ni(dppe)$ with $HBF_4 \bullet Et_2O$ in CH_2Cl_2.[7]

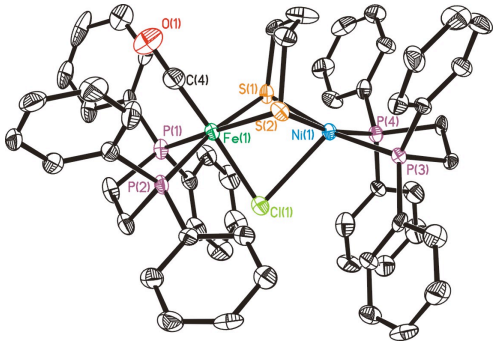

Figure 3. Molecular structure of the cation $[(dppe)(CO)Fe(S_2C_3H_6)(\mu\text{-}Cl)Ni(dppe)]BF_4$.

While the active hydride-containing species for [NiFe]-hydrogenase is a bridging hydride, the active species for [FeFe]-hydrogenase is a terminal hydride. The first terminal hydride-containing [FeFe]-hydrogenase model complex, $[HFe_2(S_2C_2H_4)(\mu\text{-}CO)(CO)(PMe_3)_4]PF_6$, was prepared upon treatment of $[Fe_2(S_2C_2H_4)(\mu\text{-}CO)(NCMe)(CO)(PMe_3)_4](PF_6)_2$ with $LiAlH_4$ at -40 °C.[8] This complex isomerizes to the bridging hydride at room temperature—even in the solid state. Protonation of the terminal hydride in MeCN liberates H_2 and regenerates the MeCN-complex.

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