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Models for the Hydrogenases Put the Focus Where It Should Be—Hydrogen

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Hydrogenase enzymes are topical because of their potential relevance to the “hydrogen economy”. Furthermore they have structurally exotic active sites, featuring carbon monoxide, cyanide, and bimetallic cores, aspects that traditionally are associated with organometallic chemistry, not biology.^[1] Two main hydrogenases are of current interest, the [NiFe] and the [FeFe] hydrogenases. A third hydrogenase has been established which also contains an {Fe(CO)₂} active site,^[2] and the community is eagerly awaiting crystallographic insights. Concerning the architecture of the [NiFe]-hydrogenase active site (Figure 1), the important information derived from X-ray crystallography, various spectroscopic methods, and theoretical modeling has been reviewed.^[3,4]

Recent work from Ogo and co-workers has described a combined structural and functional model for the [NiFe] hydrogenases,^[5] the most pervasive family of biocatalysts for the production and oxidation of H₂. In examining the active site of the [NiFe] hydrogenase, three structural criteria come to mind: a nickel–iron core, a pair of bridging thiolate ligands, and, most importantly, a bridging hydride.^[6] The biomimetics of the enzyme have been pursued even before structural data were available, with emphasis mainly on the first two structural criteria. For this reason, even the most realistic synthetic reproductions of the active site (for example, those of Tatsumi and co-workers^[7]) have not yet evolved into functional models. This situation may change in light of Ogo and co-workers’ complex that meets nearly all the structural criteria and is functional, which reacts directly with H₂ from a well-defined precursor complex **1** (Scheme 1). The results of Ogo et al.^[5] strengthen the long-held idea that the enzyme operates by a reactive {Fe^{II}(μ-SR)₂Ni^{II}} core, or a weak adduct thereof, that binds and heterolytically cleaves H₂ to give a {Fe^{II}(μ-H)(μ-SR)₂Ni^{II}} core.

To achieve and fully characterize their functional model, Ogo et al.^[5] replaced the {Fe(CN)₂(CO)} unit with {Ru(C₆Me₆)²⁺}. This was a smart move, as ruthenium forms more stable dihydrogen complexes than any other metal, whereas similar charge-neutral iron species are rare because of their intrinsic lability.^[8] The disparity between the {Fe(CO)(CN)₂} and {Ru(C₆Me₆)²⁺} moieties will no doubt be the subject of ongoing discussion, and the challenge associated with closing this gap should not be underestimated. Another difference between nature and the model is the perfectly planar environment of nickel in **1**, whereas in the protein a distorted tetrahedral (SF₄-like) geometry is clearly discernable and is most likely imposed by the conformation of the macromolecule. Some authors have concluded that owing to this geometry, the nickel atom may be the center of initial reactivity with hydrogen, since it is already well prepared for the oxidative addition of H₂.^[9]

The chemical and structural features of Ogo and co-workers' system allow planning for improved theoretical modeling of the [NiFe] hydrogenases, which can now be based more on facts than assumptions. The pseudo-octahedral Ru^{II} and square-planar Ni^{II} centers of precursor complex **1** (Scheme 1) are electronically saturated, and are thus in principle inactive. Owing to the flexible hinge of the thiolato bridges, the ruthenium-coordinated water molecule finds enough space between the two metals without perturbing the nickel center. According to Ogo and co-workers, this labile water ligand is easily substituted by a H₂ molecule, which initially anchors at ruthenium in the dihapto mode (compound **2** in Scheme 1). From this point, theory may help to determine the fate of H₂. In principle, homolysis of the H–H bond can only occur at one metal center of a dimetallic system, such as the reaction with the diruthenium complex shown in Scheme 2a,^[10] or over the two cooperating metals (as originally suggested to occur for the reactant in Scheme 2b).^{11a} Contrary to this hypothesis, oxidative addition of H₂ to an {Ir₂S₂} unit is probably not bimetallic but occurs at a single metal center with the subsequent shift of one hydride ligand.^{11b} In contrast, an analogous {Rh₂S₂} framework induces a (reversible) H₂ double heterolysis owing to the adjacency of electrophilic (the metal) and nucleophilic centers (the S bridges, see Scheme 2c).^{11c}

In the system of Ogo et al.,^[5] H₂ heterolysis is clearly indicated by a decrease in the pH value of the solution after addition of hydrogen. The polar metal–thiolato bonds do not, however, seem to directly participate. Experience shows that μ -thiolato ligands are consistently innocent, but that μ -sulfides often are not, so one must look elsewhere for the Lewis base. Ogo et al. have suggested that the actual H₂ deprotonation is affected by water, but it remains to be seen if water in fact has sufficient basicity. Moreover, the {Ru(C₆Me₆)} environment is rather hydrophobic. In this context, the triflate counterions in the solution could play a collaborative role in forming ion pairs and extracting the proton.^[12] Information on this key heterolysis step must now await the calculations.

Another open question concerns the mode of the Ni^{II} singlet–triplet conversion. In addition to the magnetism, half-populated metal–ligand antibonding orbitals ($d_{x^2-y^2}$ and d_{z^2}) of the octahedral nickel atom in **3** are confirmed by elongated Ni–S and Ni–N bonds (Scheme 3). We can guess that the ruthenium-bound hydride ligand bends closer to the nickel and, with its axial perturbation, turns on the Lewis acidic character of high-spin nickel, thus favoring the *trans*-axial H₂O coordination. It remains to be defined how gradually the transformation of the Ni^{II} center from square planar to octahedral occurs and how the intersystem crossing can be relevant to the overall function of enzyme. Also, it is intriguing to speculate that this kind of spin-switch might be incorporated into other catalysts as a means of unmasking a latent Lewis acid. Relevant examples of high-spin, octahedral nickel hydrides have been described.^[13] Ad hoc DFT calculations for the two possible spin states, also associated with the study of the MO architecture and electron distribution, promise to provide many valuable hints in this respect.

The molecular dynamics method of Car–Parrinello (MDCP) could be usefully applied to monitor the behavior of the water solvent, because during the process one H₂O ligand actually migrates from one metal to the other. Moreover, water seems to play an important role in the H₂ splitting. With respect to the DFT gas-phase modeling, the evident advantage of MDCP is to verify whether the bulk of water molecules might cooperate in abstracting a proton from H₂ even in the absence of a strong base. Moreover, a study of this type could be a prelude to a more complete investigation of the actual enzyme, where the mobility of the dihydrogen and water molecules is constrained within specific channels in the protein, eventually biasing the substrate toward one of the two metals.^[14]

Models for the two major families of dimetallic hydrogenases are usually classified on the basis of their constituent metals: complexes composed of two iron centers are considered models for the [FeFe] hydrogenases and those with nickel and iron centers are naturally called models for

the [NiFe] hydrogenases. The accumulated evidence, now reinforced by Ogo et al., suggests that a more appropriate distinction between these two families of hydrogenases may be the location of the hydride ligand. There is strong evidence for the existence of hydride bridge between the two metals in the [NiFe] hydrogenases.^[6] For the [FeFe] hydrogenases, the H_{red} state either features a terminal hydride or a vacant site on the distal iron center (Scheme 4a). Recent modeling work^[15] indicates that the [FeFe] hydrogenases convert protons into H₂ by protonation at a single iron center. Relative to the more prevalent μ -hydrido diiron complexes, which are stable toward acid, the terminal hydrido complexes evolve H₂ more readily upon protonation.^[10,16] Models for the H_{ox} state of the [FeFe] hydrogenases support the idea that the reactivity is localized at a single metal, not between two metal centers.^[17] Perhaps, therefore, it will be appropriate to classify hydrogenase models according the regiochemistry of the hydride ligands: those with bridging hydrides, such as the compound of Ogo et al. and [(CO)(PMe₃)₂Fe(μ -H)(μ -SR)₂Fe(CO)(PMe₃)₂]⁺ (see Scheme 4c) are [NiFe] hydrogenase-like, whereas those with terminal hydride ligands (Scheme 4b) are mimics of the [FeFe] hydrogenases. This dichotomy also may prove relevant to the tendency of these enzymes to oxidize or produce H₂.

In summary, both in vitro and computer modeling of hydrogen activation by {M₂S₂} systems is leading to a significantly improved understanding of the hydrogenases. The coming few years promise to be very revealing as researchers continue to focus on the biochemistry of metal hydrides.

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Figure 1. The crystallographically determined $[\text{Fe}(\text{CO})(\text{CN})_2(\mu\text{-SR})_2(\mu\text{-O})\text{Ni}(\text{SR})_2]$ active site of [NiFe] hydrogenase. S = cysteine residue.^[3]

Scheme 1.
Pathway for hydrogen heterolysis implicated by Ogo et al.^[5]

Scheme 2.

H₂ addition to a) Ru, b) Ir, and c) Rh {M₂S₂} complexes.

Scheme 3.

Significant bond lengths [Å] and {Ru₂S₂} fold angles [°] associated with the conversion of [(C₆Me₆)Ru(OH₂)(μ-SR)₂Ni-(amine)₂]²⁺ (**1**; left) into [(C₆Me₆)Ru(μ-SR)₂(μ-H)Ni(amine)₂(H₂O)]⁺ (**3**, right).

Scheme 4.

a) Structure of active site of the [FeFe] hydrogenase. X=H, H₂, or vacant site; Y = undetermined light atoms (CH₂, NH, O). b) A proposed model complex, and c) its less-reactive isomer with a bridging hydride.