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ORGANOMETALLICS
Review

Perspectives on How Nature Employs the Principles of Organometallic Chemistry in Dihydrogen Activation in Hydrogenases†

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Relatively recent developments in metalloenzyme and organometallic chemistry have targeted a growing link between these outwardly incongruous fields, giving birth to a merger now popularly termed "bio-organometallic" chemistry. The astonishing discovery of CO and CN ligands bound to dinuclear iron sites in billion-year-old hydrogenase enzymes has led to a new paradigm and triggered an explosion of research on bioinspired chemistry. The article will focus on the impressive array of organometallic chemistry principles that work in concert in the structure and function of H_2ases. Molecular H_2 is at the forefront of bioinspired energy, and its production and storage are critical for renewable energy systems. Biomimetic inorganic chemistry and photochemistry involving water splitting for H_2 production has erupted in the past decade and will also be reflected upon here.

I. Introduction

At the macroscopic level, nature displays dazzling beauty and surprises on a regular basis. On the molecular level, its mystique is even more fascinating to biologists and chemists in all their subfields. The admiration engendered here is now more true than ever for organometallic chemists: the revelation of the architecture of the organometallic active sites of hydrogenase (H_2ase) enzymes was as stunning to this profession as the discovery of the double helix was to a molecular biologist. It is further astonishing (and indeed humbling) how long nature kept hidden its exquisite use of classic organometallic ligands such as CO and CN in activation of dihydrogen by H_2ases! By the same token, until relatively recently in organometallic chemistry no one would have expected the H_2 molecule (and two decades before that, N_2), to have a stable, rich coordination chemistry. On the basis of these discoveries, it is therefore not surprising that bioinspired inorganic chemistry involving H_2 has become so fashionable in the past decade, particularly its critical importance in future energy. It turns out there are prominent relationships between the biological and classical organometallic chemistry here, the major theme of this article.

Relatively recent developments in metalloenzyme and organometallic chemistry have targeted a growing link between these outwardly incongruous fields, giving birth to a merger now popularly termed "bio-organometallic" chemistry.[1] Organometallic systems are typically characterized by abiological and generally toxic ligands (e.g., CO, PR_3) coordinated to reactive, air-sensitive transition-metal complexes that would seemingly be despised and avoided by nature. This view was shattered by the relatively recent discovery, initially spectroscopically[2,3] then crystallographically,[4] of CO and CN ligands bound to dinuclear iron sites in hydrogenase (H_2ase) enzymes that have existed in numerous microorganisms for over a billion years. It is now ironic that use of such organometallic functionalities would have previously been disparaged as being biologically irrelevant if used in attempts to model metalloenzymes, e.g. the synthetic analogue approach[5] to the metal sites in iron−sulfur proteins such as ferredoxins that was initiated in the early 1970s by Holm.

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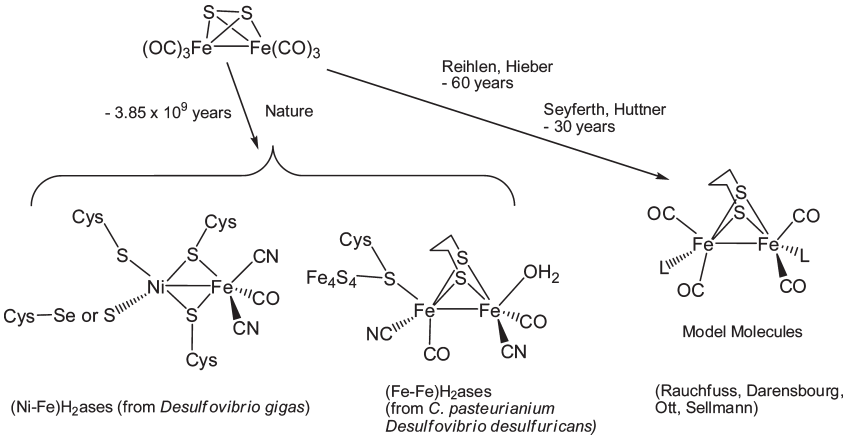
Scheme 1



The transformational discovery of organometallic centers in H_2ases has released a torrent of investigations into modeling both experimentally and computationally the structure and function of these remarkable biocenters for critical future energy applications, as detailed in numerous reviews and thematic journal issues.[6] The review by Darensbourg entitled "The Bio-organometallic Chemistry of Active Site Iron in Hydrogenases" brought particular initial attention to this area.[6o] The focus has now been greatly broadened to areas well beyond traditional organometallic chemistry to include artificial photosynthesis, bioinspired catalysis, and related renewable energy ("solar fuels"), the themes of recent volumes of *Accounts of Chemical Research*, *Chemical Society Reviews*, *Chemical Reviews, Dalton Transactions, and Comptes Rendus Chimie*, where efficient water splitting to produce hydrogen is a key goal.[6e,7,8] Nocera has often stated that developing new methodologies for carbon-neutral energy is primarily a *chemistry* problem.[8] It should be further emphasized that *synthetic* organometallic and inorganic chemistry lie at the heart of these efforts and should thrive. Nature's primordial synthesis and use of transition-metal-based active sites of enzymes is fascinating as well, particularly in comprehending and speculating upon the "how and why" aspects.

The ultimate antecedent of the markedly organometallic active sites of H_2ases is diiron hexacarbonyl disulfide, a fragment of the mineral iron sulfide that nature apparently evolved to be molecular with the aid of carbon monoxide (Scheme 1, from Jaouen[1a]), as hypothesized by Darensbourg[6n] and others.[9]

This simple organometallic complex has been monumental in the evolution of modeling key aspects of both primordial biology and modern inorganic chemistry. It is a superb example of one of the sublime traits of nature: efficient, minimal use of base elements such as iron, sulfur, and carbon (even CO). The synthesis is facile: reaction of $Fe(CO)_5$ in alkaline solution (KOH in methanol) with aqueous polysulfide (Na_2S + elemental sulfur). Like many carbonyl complexes, $Fe_2(\mu\text{-}S_2)(CO)_6$ is slightly volatile and is readily purified by sublimation, forming air-stable (but light-sensitive) bright red-orange crystals, as recalled by this author (G.J.K.) in early efforts[10] to model ferredoxins. Dietmar Seyferth, to whom this special volume is dedicated, has played an important role in the development of the chemistry of this complex and its derivatives.[11] Notably, he published his initial studies in the first issue of *Organometallics* in 1982.[11a] Dietmar clarified here that, although Hieber is generally given credit for the synthesis of this complex, it was initially correctly identified by Brendel[12] as described in his 1956 Ph.D. thesis. This work was then later published in 1958 by Hieber and Gruber from the same laboratory (wherein Brendel's thesis was mentioned in a footnote).[13] The crystal structure was reported in 1965 by Dahl,[14] a luminary in establishing the structure and bonding of Fe−S and other polymetallic clusters. Seyferth reduced this neutral complex containing a bridging disulfide to its dianion, which then allowed the synthesis of many new thiolate derivatives of the type $Fe_2(\mu\text{-}SR)_2(CO)_6$,[11a] including those now used as models for the active sites of [FeFe] H_2ases (Scheme 1). Hieber[13b] had earlier reported a simple parent species (R = Et), but now model complexes containing the more sophisticated *propanedithiolate* type linkers contained

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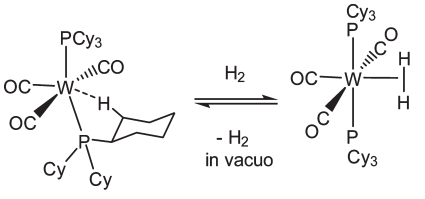
in *C. Pasteurianum* became readily accessible. Rauchfuss showed that $Fe_2[(\mu\text{-}SCH_2)_2NR)_2](CO)_6$ could be easily synthesized by condensation of $Fe_2(\mu\text{-}SH)_2(CO)_6$, formaldehyde, and amines.[15]

From a more general viewpoint, nature is also remarkably adept at binding and activating other small molecules such as O_2, N_2, and even inert hydrocarbons, including methane. The trends of inorganic and organometallic chemistry have taken inspiration from this for many decades, particularly because the coordination chemistry of several of these molecules that nature easily activates on metalloenzymes has been challenging to study in the laboratory. N_2 coordination and the epic half-century effort to comprehend how nitrogenases (N_2ases) function to produce ammonia are probably the most luminous examples of this. Oxygenases are well-known to selectively oxidize methane and other hydrocarbons to alcohols, but in contrast to stable H_2 and N_2 coordination, alkane complexes are unstable at ambient temperature. A transition metal−CH_4 complex, $[(PONOP)Rh(CH_4)]^+$ (PONOP = 2,6-($^tBu_2PO)_2C_5H_3N$), has only just now been definitively observed at −110 °C with the use of solution NMR spectroscopy by Brookhart and co-workers.[16]

The bioactivation field is now very extensive, and the focus of this article will be limited to perspectives on the impressive array of organometallic chemistry principles that perform in beautiful harmony in the structure and function of H_2ases. Molecular H_2 is at the forefront of bioinspired energy, and its production and storage is of course important for fuels and for reaction with N_2 for agriculture: ammonia production via the energy-intensive Haber−Bosch process supports much of the world's population. As mentioned above, biomimetic (more broadly, "bio-inspired") inorganic chemistry and photochemistry for renewable energy has erupted on the scene in the past decade and will also be reflected upon here.

II. Dihydrogen Coordination Chemistry and Hydrogenases

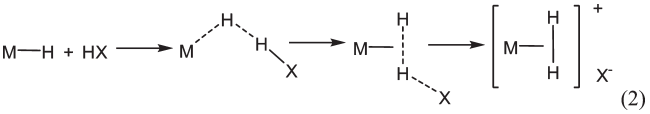
Dihydrogen Coordination. Dihydrogen is the simplest molecule, but until relatively recently it did not have any metal coordination chemistry. H_2 and the similarly "inert" methane molecule have very strong σ bonds (ca. 102 kcal/mol) without any nonbonded electrons to grasp onto metals and had not been envisioned to form a stable complex. This view dramatically changed upon the unexpected discovery in 1984 of H_2 coordination to an organometallic complex containing zerovalent tungsten supported by three CO and two organophosphine groups (eq 1).[6f,17]



(1)

The side-on-bonded H_2 ligand remained largely intact, except that the H−H bond was elongated about 20% from 0.75 to 0.89 Å, as determined by neutron diffraction and solid-state ^1H NMR spectroscopy. Many new H_2 and other complexes that coordinate X−H bonds (X = H, C, B, Si, etc.) have since been found and have been termed σ *complexes*.[6f,17b,18] Importantly the H_2 ligand in eq 1 can easily be reversibly removed, e.g. in vacuo, to restore the unsaturated precursor that in this case has an *intramolecular* agostic C−H interaction. Such facile molecular binding and loss of H_2 is presumed to occur in H_2ases and would be highly advantageous in such extremely rapid enzymatic processes. Coordination of other σ bonds such as C−H in organic molecules would appear to be possible in metalloenzymes via either intra- or intermolecular C−H coordination as in the methane complex above.[16] However, this type of interaction is enthalpically too weak (~10 kcal/mol vs > 20 kcal/mol in H_2 complexes) for it to be observable under ambient conditions: e.g., in regard to the mechanism of methane monooxygenase. Methane C−H bond activation may not even occur at the dinuclear Fe sites in the latter but rather at the bridging oxo ligands, involving either radical or concerted mechanisms, as suggested computationally.[19]

Several methods exist to prepare H_2 complexes,[6f] the simplest being reaction of H_2 gas with a coordinatively unsaturated complex or one that is effectively unsaturated such as $W(CO)_3(PR_3)_2$ (eq 1). Displacement of a weakly bound "solvento" ligand such as dichloromethane or, more biologically relevant, H_2O, can be facile also. By far the most common method is *protonation* of metal hydride complexes, a reaction of obvious importance in both enzymatic systems and efforts to produce hydrogen fuel. The detailed protonation mechanism is however quite subtle, involving multistep reactions, diverse intermediates, and high sensitivity to the nature of the proton donor, transition-metal complex, solvent, and even the eventual counteranions (eq 2).[20]



(2)

The reaction can proceed via observable[20b] hydrogen bonding of the acid (which can be as weak as alcohols) to the basic hydride. This method is widely applicable because it does not require an unsaturated precursor that often either does not exist or is difficult to prepare. The H_2 ligand formed in this manner is often quite labile and easily dissociates to release H_2 gas, of obvious importance to generation of H_2 both inorganically as well as biomimetically. Double protonation of a metal complex was found to directly produce H_2, presumably via a monohydride and an unstable H_2 complex (eq 3; M = Ni).[21]

$$M(dppe)_2 \xrightarrow{HClO_4} \underset{\text{unobserved}}{[MH(dppe)_2][ClO_4]} \xrightarrow{HClO_4} [M(H_2)(dppe)_2][ClO_4]_2 \xrightarrow{-H_2} [M(dppe)_2][ClO_4]_2 \quad (3)$$

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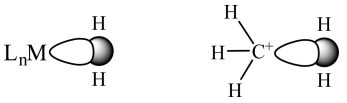
Scheme 2



It is important to recognize that H_2 complexes are nearly universally involved in metal-mediated hydrogen production, even if only as fleeting intermediates. Distinguishing between molecular H_2 versus classical hydride binding is most easily accomplished by solution proton NMR methods, particularly by measuring J_{HD} of the isotopomer containing HD, and of interest here, Morris has tabulated the NMR properties of all the iron-group H_2 complexes.[18c]

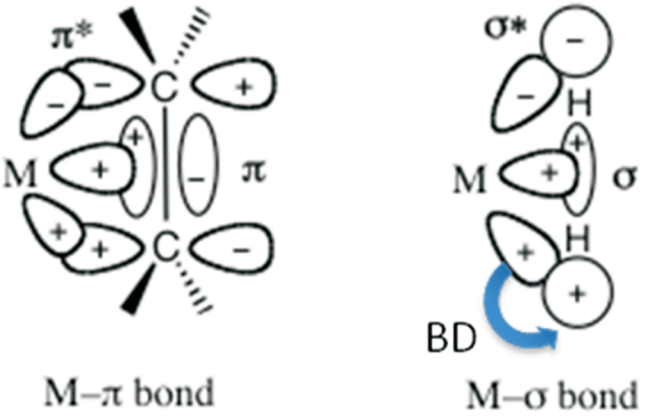
Bonding and Splitting of Dihydrogen. As Scheme 2 illustrates, the σ-bond-coordinated H_2 complexes feature nonclassical three-center, two-electron bonding somewhat analogous (isolobal) to that in, for example, carbocations (now viewed as highly dynamic $CH_3(H_2)^+$ species[22]).

However, unlike in the far less robust main-group topologies, in metal complexes $M_{d\pi}\rightarrow H_2$ *back-bonding* from filled d orbitals to the H_2 σ^* orbital is present that greatly strengthens the coordination (Scheme 3) by adding a second, separate component to the bonding interaction in addition to the relatively weak σ-donation component.

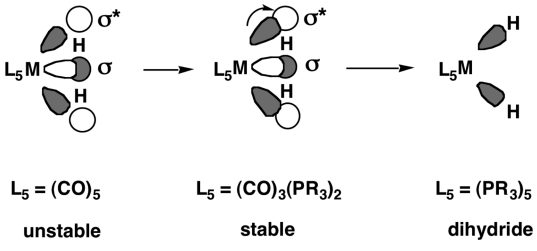
The back-donation component (abbreviated BD) is quite analogous[17c] to that in metal−olefin π coordination in the classic Dewar−Chatt−Duncanson model,[23] a cornerstone of organometallic chemistry bonding concepts. The amount of back-donation is critical: H_2 does not stably bind to highly Lewis acidic d^6 metal centers (e.g., cationic systems with electron-withdrawing ligands) or to d^9 or d^{10} Lewis acids because the BD is much weaker (electron-poor metal centers) than in electron-rich metal centers. Later transition metals such as Ni(II) have a higher nuclear charge and are poor back-bonders, and a stable Ni−H_2 complex has not yet been isolated, an important consideration in the [NiFe] H_2ases (an unstable complex has just been identified by low-temperature NMR spectroscopy,[24] as will be discussed later).

However, BD is a two-edged sword: *too much* BD can lead to H−H bond splitting and oxidative addition to form a dihydride complex (Scheme 4). This is critical in the promotion of chemical reactions of H_2, particularly catalytic homogeneous hydrogenation processes. The nature of the L_5M ligand set is crucial: electron-donating L ligands (e.g., all phosphines; M = W) increase the back-bonding, which eventually ruptures the H−H bond as a result of overpopulation of the H_2 σ^* orbitals.[17b,c] However, strongly electron-withdrawing CO ligands compete for back-bonding, especially when trans to the ligand of interest (i.e., H_2), a fundamental tenet of organometallic chemistry. This limits $M_{d\pi}\rightarrow H_2$ back-bonding and favors molecular H_2 coordination over cleavage to dihydride moieties. Charge is also important: more Lewis acidic *cationic* complexes disfavor *homolytic* H_2 splitting but favor *heterolytic* splitting (see below). However, if all ligands are CO, the complexes are thermally unstable. For such electron-poor centers, loss in BD is offset to some extent by increased donation from H_2 to

Scheme 3



Scheme 4



the electron-poor center, but a near-perfect balance is struck for $L_5 = (CO)_3(PR_3)_2$ where one of the CO ligands is trans to H_2. The back-bonding stabilizes the H_2 binding (accounting for about half of the bond strength of H_2 to the metal according to computations[25]) yet is not quite strong enough to cause H−H bond scission.

As will be discussed below in bioactivation of H_2 by H_2ases, the finely tuned stabilization of *molecular* H_2 *coordination* rather than dihydride formation is crucial to the function of the enzyme. Here the unprecedented biological presence of CO ligands in the active site of H_2ases is a key organometallic chemistry feature utilized by nature to ensure that the activation of H_2 involves reversible molecular bonding instead of irreversible oxidative addition to a dihydride.[6f,26] Molecular binding of H_2 is beneficial in H_2ases for several reasons. It is a surprisingly *versatile* ligand because it is effectively amphoteric like CO, binding to (or oxidatively adding to) virtually every unsaturated metal fragment (and even *main group* Lewis acids and bases).[6f,17b] Hoffmann asserts that the reason CO is an excellent, ubiquitous ligand is the balance between its good donor/acceptor capabilities and its innate stability.[27] The H_2 ligand has the same advantages, albeit on a lesser binding-energy scale. H_2 also can have steric (small size) and entropic advantages over other ligands, as will be shown. Lastly, H_2 binding can be completely reversible, and H_2 ligands formed by protonation steps (e.g., eqs 2 and 3) can readily eliminate as free H_2. All are important in understanding the activation of H_2 in

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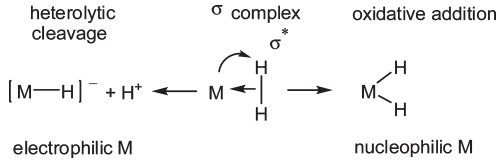
(26) Huhmann-Vincent, J.; L. Scott, B. L.; Kubas, G. J. *Inorg. Chim. Acta* **1999**, *294*, 240.
(27) Radius, U.; Bickelhaupt, F. M.; Ehlers, A. W.; Goldberg, N.; Hoffmann, R. *Inorg. Chem.* **1998**, *37*, 1080.

Scheme 5



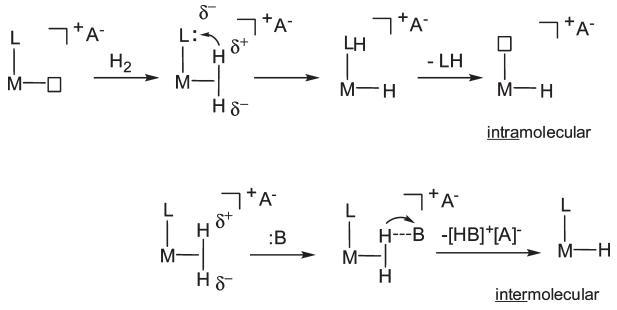
metalloenzymes and are among the many organometallic principles relevant to the structure and function of H_2ases.

More relevant to biological activation of H_2 than the above homolytic splitting of H_2 to hydrides is *heterolytic* cleavage of H_2 (Scheme 5).[28,29] The H−H bond can be effectively split into H^+ and H^- fragments, and this is one of the oldest, most significant and widespread reactions of coordinated H_2. Importantly *neither the metal oxidation state nor the coordination number changes*, whereas in homolytic splitting, the oxidation state of the metal increases by 2 and the coordination number also increases. Heterolytic cleavage is an important pathway in certain industrial catalytic processes and is critical to the mechanism of hydrogenases described below. Several mechanisms are possible (Scheme 6) that essentially involve deprotonation of bound H_2, usually on electrophilic metal centers (often cationic complexes where positive charge aids polarizing the bound H_2 fragment).

In effect, the binding of H_2 to such complexes tremendously increases the acidity of H_2 gas, up to 42 orders of magnitude![28] The pK_a of H_2 falls from 37 in the free molecule to as low as −5 when bound. The hydrogen in L_nM-H_2 thus can become more acidic than sulfuric acid and can transfer one of its protons as H^+ to weakly basic external molecules (*inter*molecular heterolytic splitting) or internal sites (*intra*molecular heterolytic splitting).[28,29] Charge is a critical factor in the acidity of the H_2. In the isoelectronic series $Mo(CO)(H_2)(PP)_2$, $[Mn(CO)(H_2)(PP)_2]^+$, and $[Fe(CO)(H_2)(PP)_2]^{2+}$ (PP = diphosphine), the H_2 in the dicationic complex is the most acidic and is the lowest in the neutral species.[17b] Intermolecular heterolysis gives a metal hydride (H^- fragment) and the conjugate acid of the base, HB^+: i.e., the reverse of the protonation reactions that are commonly used to synthesize H_2 complexes.[20] Intramolecular heterolysis of H_2 can lead to elimination of L (=H, halide, etc.) as HL and formation of a monohydride. These proton transfers are important in the function of H_2ases, as will be shown below.

All of the H_2 heterolysis reactions can be reversible, an important feature in designing molecular catalysts for hydrogen production by, for example, mimicking biological H_2 activation. As pointed out by DuBois, the heterolytic cleavage of H_2 should be at or near equilibrium to avoid high-energy intermediates.[6g,30] This implies the hydride (H^-) acceptor ability of the metal and the proton (H^+) acceptor ability of the base (either external or internal) must be

Scheme 6



energetically matched to provide enough energy to drive the heterolysis of H_2, but this reaction should not be strongly exergonic. These vital features of H_2 coordination chemistry and their relevance to bioactivation of H_2 will be discussed in detail below.

Binding of H_2 versus H_2O and N_2. Another important facet of the coordination properties of H_2 is its surprising ability to compete with bonding of traditional ligands, particularly H_2O, the archetypal lone-pair donor in classical coordination chemistry. How can H_2 compete in enzymatic active sites with seemingly "stronger" classical ligands such as water or even atmospheric dinitrogen that are present? It is illuminating to compare the binding energy of H_2 versus that of H_2O, since one of the early H_2 complexes, $[IrH(H_2)(PPh_3)_2(bq)]^+$, was prepared by displacement of H_2O under 1 atm of H_2 in organic solvents.[31] Thermodynamic data for a reverse reaction, displacement of H_2 by H_2O on the organometallic $W(CO)_3(P^iPr_3)_2$ center, were determined in THF (eq 4).[32]

$$W(CO)_3(P^iPr_3)_2(H_2) + H_2O + THF \longrightarrow W(CO)_3(P^iPr_3)_2(H_2O)\cdot THF + H_2 \qquad (4)$$

$$\Delta H = -4.5 \pm 0.2 \text{ kcal/mol};$$

$$\Delta S = -18.8 \pm 2.0 \text{ cal/(mol K)}$$

The enthalpy of displacement of H_2 by water is exothermic by only 3−4 kcal/mol, showing that these ligands can be competitive. Indeed, it was suggested that H_2 can displace water bound to iron in the active site of H_2ases as the initial step, as will be discussed below.[26] In rare cases H_2 complexes can even be soluble in water, and H_2 coordination chemistry relevant to reactivity in aqueous solution, including biomimetic aspects, has been reviewed.[33]

Hydrogen-bonding interactions between coordinated H_2O and THF solvent are significant in the thermodynamics in eq 4, and the surprisingly high negative entropy change no doubt reflects free THF becoming bound (three particles converting to two). ΔG_{298} can be calculated to be 1.1 kcal/mol: i.e., favoring the left side of eq 4, thus showing that H_2 is the slightly better ligand (the enthalpy of binding of H_2 to $W(CO)_3(P^iPr_3)_2$ is -11.2 ± 0.5 kcal/mol in toluene). *Entropic*

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and solvation factors can thus be critical in competition between weak ligands for binding sites, as will be seen below for N_2 versus H_2 binding. Binding of H_2 versus H_2O should then be favored on hydrophobic metalloenzyme sites where the effective H_2O concentration is low.

Binding a gaseous ligand such as H_2 increases the total entropy of $ML_n(H_2)$ relative to ML_n but does so by a relatively minor amount compared to the entropy lost by the free ligand.[34] On this basis the total entropy of exchange for eq 5 should depend primarily on the differences in absolute entropies for $N_2(g)$ and $H_2(g)$.

$$ML_n(N_2)(soln) + H_2(g) \longrightarrow ML_n(H_2)(soln) + N_2(g) \quad (5)$$

The third-law entropies, S^o, of the two gases can be calculated by using standard formulas of statistical thermodynamics.[34] Due to its lower mass and moment of inertia, the absolute entropy (S^o) of H_2 (31.2 cal/(mol K)) is 14.6 cal/(mol K) lower than that for N_2. In eq 5, if the total entropies of the complexes in solution exactly canceled, the predicted entropy change would be 14.6 cal/(mol K), favoring the right side of eq 5, i.e. H_2 binding, since $\Delta G = \Delta H - T\Delta S$. Thus, because H_2 has the smallest S^o value of any diatomic gas, H_2 will be more competitive in binding relative to N_2 or other small molecules, which may be important in the biological activation of H_2.

Other factors include the electron richness of the metal center, which is particularly dependent on overall charge. As the electrophilicity of M increases and M→L back-donation decreases, H_2 actually becomes an increasingly better ligand than N_2. The disparity here apparently stems from N_2 being a poor σ donor,[35−39] weaker than even H_2, although from theoretical analysis N_2 is a good π-acceptor like H_2.[25a] This is corroborated experimentally by comparison of their interactions with the strongly electrophilic, poorly back-bonding complex $[Mn(CO)_3(PCy_3)_2]^+$, which binds H_2 reversibly but not N_2, even at low temperature.[40] The above considerations may also be relevant in the function of N_2ases.

Binding of H_2 versus CO is another significant consideration, particularly in fuel cells, because low levels of CO can be present that could inhibit catalytic function. Normally CO is a much stronger ligand but not always: Dubois' $[Ni(P_2N_2)_2]^{2+}$ systems coordinate H_2 20 times more strongly than CO.[30a,c]

III. Activation of H_2 in Hydrogenases and the Need for CO Ligands

Biological activation and production of small molecules such as H_2 and CH_4 have been known for many decades, but the mechanism was shrouded in mystery until relatively recently (although several questions still exist). The remarkable H_2ases are redox enzymes that evolved billions of years ago in micro-organisms and catalyze *completely reversible* interconversion of H_2 and protons/electrons to either utilize H_2 as an energy source or dispose excess electrons as H_2 (eq 6) at very high rates (10^4 turnovers/s).[2−4,5c,6a,h,i,k,l,n,o,41−49]

$$H_2 \rightleftharpoons 2H^+ + 2e^- \quad (6)$$

This is a rare true equilibrium process much like that in the hydrogen electrode: e.g., there is a fine dependence on H_2 pressure whether H_2 is produced or consumed by the microorganism. The active sites of the three known types of H_2ases are shown in Figure 1. A series of Fe−S cluster "stepping stones" are also involved in electron transport in and out of many of the enzymes.

Until being unexpectedly disclosed by IR spectroscopy[2,3] and crystallographically confirmed in the [Fe−Fe] H_2ases from *Clostridium pasteurianum*[4a] and *Desulfovibrio desulfuricans*,[4b] CO and CN ligands had never been found as intrinsic constituents of a prosthetic group in biology. Not only does nature cope with these nearly universal poisons but, as will be shown, profits from them as well. The reactions of most of these enzymes in nature usually occur under anaerobic conditions, which is the case for most organometallic reactions. Somewhat surprising is that H_2ases (and other Fe−S metalloenzymes) feature a sulfur-rich core, because sulfur compounds poison most industrial catalysts, although complexes with sulfur ligands can be active catalysts in homogeneous reactions.[50] Thus, there are vital lessons to be learned here for the development of both sulfur-tolerant and inexpensive nonprecious metal industrial catalysts for hydrogen-related (e.g., fuel cells and biomimetic water splitting) and other transformations.

As originally noted by Crabtree,[51] reaction mechanisms involving binding of η^2-H_2 ligands must be considered in relation to the structure and function of enzymes such as H_2ases and N_2ases. Several properties of coordinated H_2 such as its acidity and ability to compete with N_2 and aquo ligands (as discussed above) clearly conform to the requirements for bioactivation that was later judged to occur at the Fe sites (and possibly Ni in the [NiFe] H_2ases) by a plethora of theoretical calculations.[52−55] The enzymes, for example, catalyze H/D exchange between H_2O and D_2, which an acidic H_2 ligand coordinated to the above active sites can

(34) Based on the use of the Sackur−Tetrode equation for translational entropy; see: Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969. For approximate application to reactions in solution see: Page, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 449.
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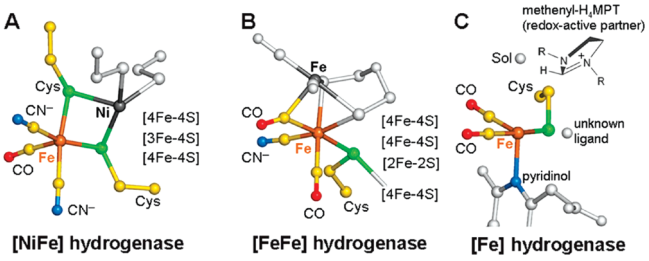

Figure 1. Three types of H_2ases.

easily promote. Although there is yet no observable evidence for H_2 coordination in any form of the H_2ase enzymes, an H_2 complex of a rudimentary model for a H_2ase active site, $[Ru_2(\mu\text{-}H)(\mu\text{-}S_2C_3H_6)_2(H_2)(CO)_3(PCy_3)_2]^+$, has been synthesized, albeit with Ru instead of Fe and with phosphine ligands that do not occur in enzymes.[56] The NMR J(HD) value for the HD complex is 31 Hz, indicative of $d_{HH} = 0.90$ Å: i.e., a true H_2 complex.[6f,17b,18c] Solutions catalyze H_2/D_2 exchange, which is characteristic of H_2ases.

An "organometallic" biologically active site with a mix of donor and acceptor ligands such as CO is advantageous here. Nature has found extremely efficient ways to use first-row metals such as Fe and Ni rather than the precious metals widely used as industrial catalysts, and intense efforts to utilize base metals (and even main-group systems) for biomimetic catalysis are underway.[6−9] Although H_2ases often contain Ni, *Fe* appears to be the site of small-molecule binding and activation, and enzymes that contain only Fe are known. The presence of bimetallic active sites on H_2, producing H_2ases, is also intriguing because H_2 is most often activated on mononuclear organometallic sites, i.e. $L_nM-(H_2)$, without the need for a second metal.[6f,17,18,28,29] Indeed, polynuclear H_2 complexes are quite rare. Hall has examined by density functional theory the role of two-state reactivity at the enzyme active site with respect to binding of molecular H_2 for the high- and low-spin forms of [NiFe]-hydrogenase (Ni−SI forms).[55b] Binding of a single H_2 molecule at either the Ni or Fe of the active site and also possible simultaneous binding of H_2 at each metal center were examined. Concurrent binding of two molecules of H_2 suggested a potential hydrogen bottleneck in which high concentrations might lead to a decrease in the rate of hydrogen oxidation. In addition to these considerations, the presence of M−M bonding interactions in H_2ases may play a critical role in electron transfer and possibly protonation reactions, and the rationale for this will be discussed in more detail later.

Recent single-crystal diffraction studies revealed that a *mononuclear* iron site is present in the [Fe] H_2ase (referred to as Hmd; Figure 1).[57] It is octahedrally ligated by two *cis*-CO molecules, a cysteic sulfur atom, a pyridone nitrogen atom originating from the organic skeleton of the Hmd cofactor, an unknown ligand trans to a CO, and a hydrogen-bonded water trans to the pyridone.[57a] However, Hmd is phylogenetically unrelated to the other H_2ases, and the activity of this enzyme is not reversible and does not function to produce H_2.

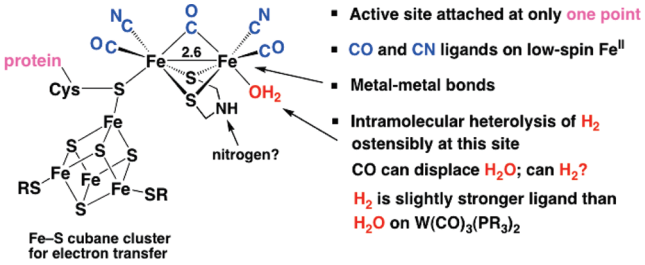

Figure 2. Structure and mechanism of the active site of *Clostridium pasteurianum*, incorporating several common features of organometallic chemistry that may occur in metalloenzyme activity.

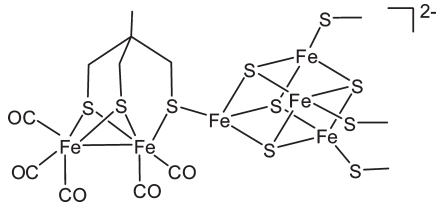

Figure 3. Structure of the model complex for [FeFe] H_2ase containing a cubane cluster.

Rather, it converts the pterin, methenyl-H_4MPT^+, to methylene-H_4MPT and involves a ternary complex catalytic mechanism requiring the presence of all three components (pterin, H_2, and Hmd) for enzymatic activity to occur. The crystal structure of a binary complex of Hmd with methylene-H_4MPT has been reported and supports this mechanism for H_2 activation.[57b] Since the structure of the active site has been known for only a short time, there are few reports of synthetic analogues,[58,59] in contrast to the vast literature on models for the bimetallic H_2ases.

The above features common to organometallic chemistry are numerous, especially in the [FeFe] H_2ases, as partially summarized in Figure 2. CO, a mainstay ligand in organometallic chemistry, binds to two iron atoms spaced ~2.6 Å apart and connected by a two-electron bond, forming the backbone of the active site.[4] The Fe site is unusual in being low spin with most of the ligands exogenous, the only strong attachment to the protein being through the cysteinyl sulfur bridging to the Fe_4S_4 cluster (the cyanide ligands are hydrogen-bonded to the protein backbone; further aspects of CN coordination will be discussed later). The cubane cluster is involved in electron transfer steps, and some enzymes feature channels that relay reagents (H^+, H_2) into and out of the

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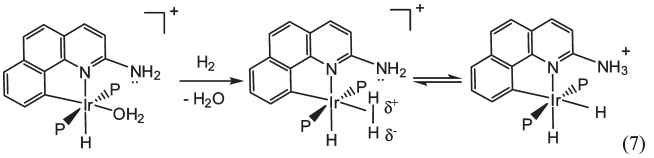
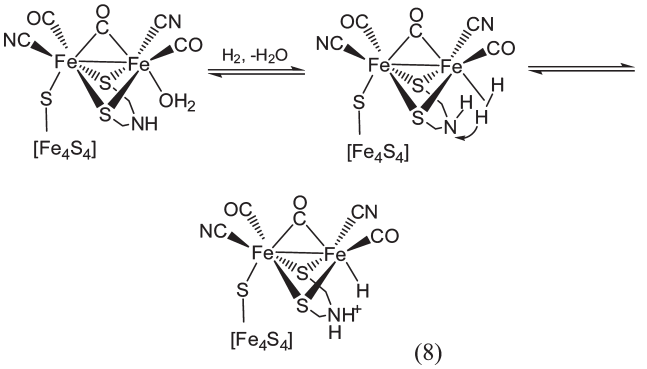
active site, as well as a chain of electron-transporting Fe−S clusters. Thus far the only model complex containing a cubane cluster was elegantly synthesized by Pickett (Figure 3).[60]

It should be first noted that reversible activation of H_2 via *molecular* binding is critical as opposed to pathways involving oxidative addition to dihydride, where subsequent elimination of H_2 usually is irreversible (a "dead-end" process) or is less facile. Reversible binding must occur for rapid activation or production of H_2 in H_2ases, where H_2 can be either produced or consumed in the same micro-organism (eq 6). Such highly labile H_2 binding is favored on relatively low-valent metal centers, e.g. Fe(II), particularly with low-spin d^6 configurations. Virtually all inorganic H_2 complexes are of this type (paramagnetic species are extremely rare), and the metal sites in H_2ases that bind and activate H_2 would be expected to have similar properties, as is generally observed experimentally and computationally. The biologically unconventional π-acceptor CO ligands in H_2ases serve to increase the electrophilicity (Lewis acidity) of the binding site by withdrawing electrons from the metal, a well-established principle in organometallic chemistry.[61] This favors facile reversible molecular binding[6f,26] of H_2 critical to the extremely high reaction rates (10^4 turnovers/s) in these enzymes and also promotes highly selective binding of H_2 over atmospheric N_2.[40] As will also be shown, the elevated Lewis acidity of the active site also supports heterolytic cleavage of H_2 vital to the reaction mechanism. Cleavage of the strong H−H bond into protons is critical to the enzyme function, and coordinated H_2 can readily be split heterolytically on electrophilic metal complexes by proton transfer to a basic ligand,[28−30] as well exemplified by Crabtree in a cationic iridium complex (eq 7).[62]



(7)

H_2 displaces an H_2O ligand (as discussed above), and the now acidic H_2 ligand is split heterolytically, transferring a proton to a pendant amine. Although the Ir complex does not have a CO, heterolysis is aided here by the positive charge, whereas it may be needed in H_2ases because nature has a limited menu of ligands that can increase the electrophilicity of metal centers. The process in eq 7 is similar to what is generally proposed to occur in [FeFe] H_2ases that also feature a water ligand on one metal. The CO-containing ligand set on H_2ases may tune the acidity of bound H_2 (possibly to more physiological pH values) to facilitate proton transfer between bound H_2 to e.g. a basic site (possibly NH) on the three-membered unit bridging the sulfur donors (eq 8).



(8)

The nature of the dithiolate ligand has been much discussed. It was originally tentatively assigned as $CH_2(CH_2S^-)$,[4a,b] but several groups suggested that $NH(CH_2S^-)_2$ is more likely,[6a,p,63] because the amine group could act as a proton acceptor during the catalytic cycle.[6a,p] A new crystal structure combined with density functional theory (DFT) calculations indicated that this was possible but $O(CH_2S^-)_2$ might be even more plausible.[4c] However, recent quantum refinement calculations do not support the latter and indicate $NH(CH_2S^-)_2$ is more likely.[63d]

The redox states of the sites that are active in the H_2 splitting process may possess positive charge to further increase metal electrophilicity, and cationic organometallic Fe−H_2 complexes with CN or CO are known: e.g., $[Fe(H_2)(CN/CO)(L)_2]^{+/2+}$ (L = diphosphine).[64] The protons presumably migrate from the protonated amine (or other site such as cysteine) to the protein, while electrons flow away from the site via the attached $[Fe_4S_4]$ cluster. In some H_2ases, this can be easily reversed to *generate* H_2 on the same site, and this is why H_2ases and their organometallic models are receiving intense scrutiny for biomimetic H_2 production.

IV. Why Are the Active Sites Bimetallic? Iron−Sulfur Clusters in Enzymes

An obvious question is this: why are two metals commonly employed by H_2ases to split H_2 when one could work? In organometallic and inorganic systems, binding and activation of H_2 on dinuclear metal centers is actually very rare.[6f] One rationale is that there are many more facile mechanistic options at such a structurally as well as electronically flexible dinuclear site. Furthermore, iron−sulfur clusters have been well-known to mediate numerous electron transfer and reduction/oxidation (redox) processes in nature.[5,47,65] In the [FeFe]-hydrogenase enzymes, [4Fe4S] cluster cubanes transfer electrons through a cysteinyl sulfur to a [2Fe2S] cluster that is in a butterfly arrangement (Figure 1).[66−68] The [2Fe2S] cluster then serves as the active site for reversible reduction of protons to molecular hydrogen.[6o,69,70] Fluxionality of the [2Fe2S] core may play a critical role here. For example, as will be discussed below,

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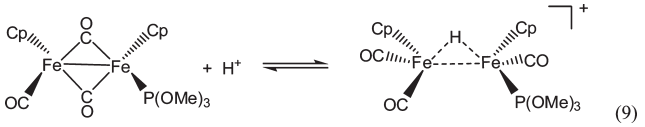
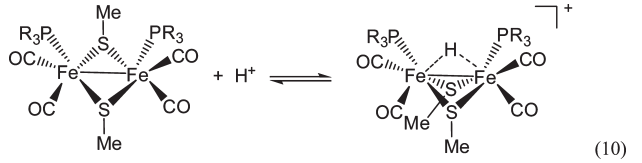
the CO ligand can possibly convert from bridging to terminal (or semibridging), a common feature in polynuclear metal carbonyl chemistry. Also, proton transfer processes could involve the M−M bonds. The most basic site for initial protonation in the enzyme active sites may be the electrons in the M−M bonds, which in organometallic chemistry can readily be reversibly protonated to form hydride-bridged species, an important principle.[71] The Fe−Fe bonds in $[CpFe(CO)(PR_3)(\mu\text{-CO})]_2$ are as basic as weak amines (pK_b around 6), and a concomitant shift of μ-CO to terminal positions occurs on protonation (eq 9).[72] Protonation of the Fe−Fe bond in $[Fe(CO)_2(PR_3)(\mu\text{-SR}')]_2$ occurs in preference to protonation of the sulfur ligands (eq 10).[73,74]



(9)



(10)

The hydride ligand could reversibly shift back and forth between terminal and bridging positions and, when situated terminally, be readily protonated to a dissociable H_2 ligand, leading to a cyclic process for either H_2 consumption or production. Indeed, protonation of iron hydrogenase active site mimics to form bridging hydride complexes and related computational and kinetic studies have been reported.[75−80] Depending on acid strength, protonation of the adt (*N*-benzylazadithiolate)-bridged complex (Figure 4) occurs at the bridging nitrogen to give $[Fe_2(\mu\text{-Hadt})(CO)_4(PMe_3)_2]^+$, the Fe−Fe bond to give $[Fe_2(\mu\text{-adt})(\mu\text{-H})(CO)_4(PMe_3)_2]^+$, or both sites simultaneously to give $[Fe_2(\mu\text{-Hadt})(\mu\text{-H})(CO)_4(PMe_3)_2]^{2+}$.[77a] Reaction with strong acids, e.g. perchloric acid, gives nitrogen protonation, but reaction with hydrochloric acid ($pK_a = 8$) results ultimately in the metal-protonated

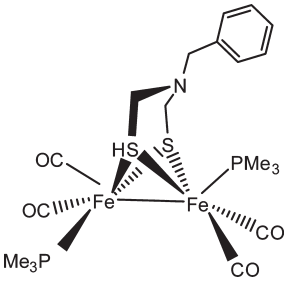
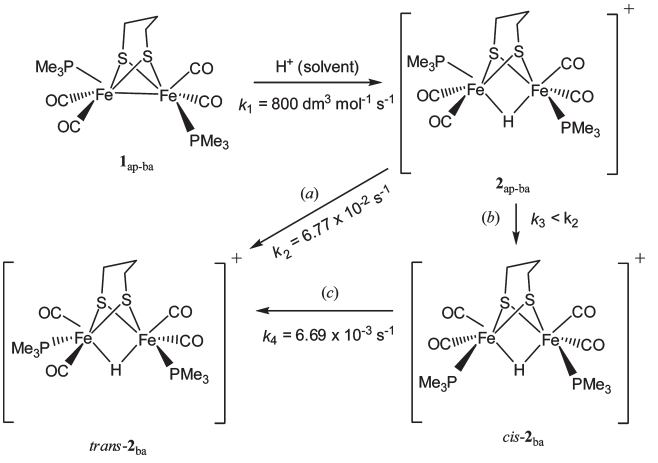


Figure 4. Structure of $Fe_2(\mu\text{-adt})(CO)_4(PMe_3)_2$.

Scheme 7



complex, which indicates that the Fe−Fe bond is more basic than the adt nitrogen.

As shown in Scheme 7, a combination of stop-flow UV−visible and IR studies with variable-temperature NMR spectroscopy established that protonation of **1**, an electron-rich Fe^IFe^I model, occurs via a two-step mechanism.[75]

The mechanistic role of isomer interconversion and how this critically relates to steric access to the diiron bridge were revealed. No direct evidence of a terminal hydride was seen by NMR spectroscopy, although a semibridging hydride was implicated in the interchange reaction.

The synthesis of the diferrous terminal hydride analogue $[Fe(H)(PMe_3)_2(\mu\text{-CO})\{\mu\text{-S(CH}_2)_2\text{S}\}Fe(CO)(PMe_3)_2](PF_6)$ has been reported; its proton NMR spectrum exhibits a signal at −4.6 ppm, which has been assigned to the terminal hydrido ligand.[78] The corresponding μ-hydride compound $[Fe_2\{\mu\text{-S(CH}_2)_2\text{S}\}(\mu\text{-H})(CO)_2(PMe_3)_4](PF_6)$ displays a signal at −20.6 ppm attributable to the bridging hydride. In the system $[HFe_2(SR)_2(PR_3)_x(CO)_{6-x}]^+$ ($x = 2-4$), terminal/bridging isomerization of the hydride complexes was again found to be relevant to the active site models for the [FeFe]-hydrogenases.[79] Related studies showed that the terminal hydride is thermodynamically more easily reduced and more readily protonated than the bridging isomer but is not necessarily poised for hydrogenesis.[80] The hydridic character of the terminal isomer is, however, enhanced upon one-electron reduction.

Such bridging/terminal shifts involving CO as well as H would be especially likely to occur in the [FeFe] H_2ase sites, which are attached to the protein only via the 4Fe−4S cluster. Early DFT calculations on $[(MeS)(CO)(CN)Fe(\mu\text{-S})_2(\mu\text{-CO})Fe(CO(CN)]^z$ ($z = 0$ to -2) models show that the

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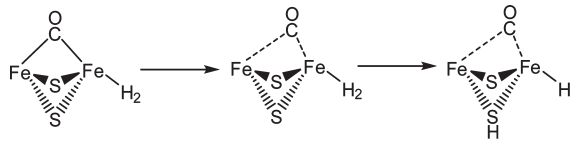
μ-CO can easily shift like a gate (eq 11), where the O atom moves little but the carbon swings left or right to form *semibridging* CO ligands that are well-known in organometallic chemistry.[81]



(11)

The active site of bimetallic H_2ases possess a relatively flat potential energy surface for geometrical changes at Fe, CO, S, and bound H, which is consistent with the extremely rapid rates of H_2 production in the enzymes. H_2 can weakly bind to Fe by displacing the H_2O ligand in *C. Pasteurianum* (eq 8), and calculations indicate the H_2 complex is stabilized by a CO gate shift to the right. In the reduced dianionic states of these models, transfer of one H atom from Fe−H_2 to form SH is essentially barrierless, and a low barrier would similarly be expected if the proton transferred to the amine functionality in the dithiolate bridge in H_2ases.

More recently in regard to the above, the groups of Pickett, Darensbourg, Hall, Rauchfuss, and De Gioia examined experimentally and theoretically the coordination of a bridging CO to models, thus mimicking the "CO-inhibited form" of the H_2ases.[82−84] The CO movements and overall coordination-sphere "rotations" about the Fe centers were studied in structurally characterized mixed-valent Fe(II)Fe(I) dithiolato complexes that featured semibridging CO ligands, e.g. (μ-pdt)[Fe(CO)$_2$(PMe$_3$)]$_2$, (μ-pdt)[Fe(CO)$_2$(IMes)]$_2^+$ (pdt = propanedithiolate; Imes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene),[83a] and [Fe$_2$(S$_2$C$_2$H$_4$)(CO)$_2$(μ-CO)((PMe$_3$)-(dppv)][BF$_4$] (dppv = *cis*-1,2-C$_2$H$_2$(PPh$_2$)$_2$).[84] A protected open site with structural similarity to the active site of [FeFe] H_2ases for possible H_2 binding and activation was found in these complexes, Darensbourg found that CO uptake takes place at the vacant coordination site on the rotated Fe center, as in H_{ox}-CO of [FeFe] H_2ase. Moreover, CO binding results in substantial electron reorganization, with the unpaired spin distributed over both Fe centers and on the bridging CO ligand.[83] Addition of steric bulk to the S to S bridging ligand in these types of complexes enforced a significant twist in the solid structure, leading to the first structurally characterized model complex that has a bridging CO and does not require bulky ligands.[83b] For the dppv complex addition of CO gave a concomitant shift of the semibridging CO to a normal bridging position.[84] Two isomeric forms existed: a kinetically favored unsymmetrical derivative and a thermodynamically favored symmetric species. It was also found that CO binding to the parent Fe^IFe^{II} complex gave rise to a spin delocalization over both Fe centers. De Gioia's calculations showed that CO affinity depends on the redox state of the model and the nature of its ligands.[82c] Fe^IFe^{II} species favor forming the CO adducts over the reduced Fe^IFe^I species. The computed energetics for CO addition to Fe$_2$(pdt)(CO)$_5$L models showed that CO affinity follows the ligand sequence L = $SCH_3^- > CN^- > PPh_3 >$ CO (Fe^IFe^I) and L = CO > $CN^- > PPh_3 > SCH_3^-$ (Fe^IFe^{II}). For the Fe^IFe^{II} systems, the spin density was initially localized on the rotated Fe but became delocalized on addition of the CO, and irons are best described as containing averaged +1.5 oxidation states, in agreement with Rauchfuss's findings.

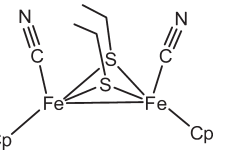


Figure 5. Structure of [CpFe(CN)(μ-SEt)]$_2$.

A metal−metal-bonded active site in H_2ases can be advantageous for the necessary electron transfer processes, because in organometallic chemistry metal−metal-bonded complexes can easily undergo reversible redox behavior (eq 12).

$$\underset{\text{2e bond}}{[M-M]} \overset{-e^-}{\leftrightarrow} \underset{\text{1e bond}}{[M\cdots M]^+} \overset{-e^-}{\leftrightarrow} \underset{\text{no bond}}{[M\ M]^{2+}} \qquad (12)$$

The dithiolate-bridged iron dimer [CpFe(CO)(μ-SCH$_3$)]$_2$, studied by Dahl, is a classic example,[85] as is Cp$_2$Fe$_2$(μ-SEt)$_2$(μ-S$_2$).[10b,86] Here Fe−Fe separations are ~2.6 Å for a normal two-electron bond in the neutral complex and ~3.0 Å for a *one-electron bond* in the mono-oxidized cationic complex,[85] while bond distances are > 3.4 Å when no bond is present: e.g., in dicationic analogues.[86a] These interactions permit complexes to exist in multiple oxidation states that can be interconvertible by reversible one-electron-transfer steps. Mixed metal oxidation states can readily exist and be accessible by a one-electron process, e.g. $Fe^{II}Fe^{II} \leftrightarrow Fe^{II}Fe^I \leftrightarrow Fe^IFe^I$. Computations on the model (μ-1,2-ethanedithiolato)-diiron hexacarbonyl support this assessment.[87] Upon an initial one-electron reduction, the inherent fluxionality of the [2Fe2S] complex anion allows for a second one-electron reduction at a less negative potential to form a dianionic species. The structure of this dianion is characterized by a rotated iron center, a bridging carbonyl ligand, and, most significantly, a dissociated Fe−S bond. This fluxionality of the [2Fe2S] core upon reduction has direct implications for the chemistry of [FeFe]-hydrogenase mimics and for iron−sulfur cluster chemistry in general.

One notable organometallic example of a two-electron Fe−Fe-bonded complex relevant to H_2ases is shown in Figure 5, a rare example of this type of moiety containing terminal CN and bridging dithiolate ligands.[86] The ν(CN) IR stretch for this *Fe(III)* complex (2102 cm^{-1}) is similar in position to those in the various [FeFe]-H_2ases that range from 2072 to 2107 cm^{-1} (depending on redox level), although here the oxidation states are lower (Fe(I−II)).[88] The similarity

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of the ν(CN) values is consistent with the electron-withdrawing CO ligands in H_2ases functioning to reduce the electron richness of the low-valent Fe centers here (hence raising ν(CN) to values similar to those in the Fe(III) species). This favors η^2-H_2 coordination over oxidative addition to dihydride.

Polynuclear metal−sulfido clusters are ubiquitous in biology, particularly in anaerobic organisms in which H_2ases and N_2ases are found as well as ferredoxins and other biomolecules.[5,47,65] These clusters facilitate electron transfer, influence protein structure, and can act as catalysts and sensors.[89] Although cyclopentadienyl ligands are of course abiological, much of the original research on Fe_2S_2, Fe_3S_4, and Fe_4S_4 clusters containing Fe−Fe bonds was performed on organometallic complexes such as the well-known cubane cluster $[CpFeS]_4$ as models for the nonheme groups in biology. The extensive bodies of work of Dahl[90] on the latter as well as Holm[5] on clusters of the type $[Fe_4S_4X_4]^{n-}$ and $[Fe_2S_2X_4]^{n-}$ with X = thiolate ligands instead of organometallic Cp ligands have been iconic here. All of these metal−metal-bonded cluster cores can exist in a variety of redox states (n = 0−4) readily accessible by reversible one-electron-transfer processes and are indispensible in many enzymatic systems. It is significant that the synthesis of these clusters from simple precursors such as iron salts and thiols can be remarkably facile (eqs 13 and 14); this is perhaps a key aspect of why nature utilizes them.

$$FeCl_2 + 4RS^- \longrightarrow 2[Fe(SR)_4]^{2-} \xrightarrow{6S} [Fe_2S_2(SR)_4]^{2-} + RSSR + 2RS^- \quad (13)$$

$$4FeCl_3 + 6RS^- + 4HS^- + 4OMe^- \longrightarrow [Fe_4S_4(SR)_4]^{2-} + RSSR + 12Cl^- + 4MeOH \quad (14)$$

Holm has characterized many of the syntheses as "self-assembly" and states that "no two metal and non-metal elements in combination have ever generated as large a number of structure types as those encompassed by iron−sulfur clusters, the majority of which are not known to occur naturally".[5b] Cubane clusters can, for example, contain both sulfide and disulfide ligands: e.g., $Cp_4Fe_4(\mu\text{-}S)_2(\mu\text{-}S_2)_2$.[86a]

Nature has well exploited the archaic abundance of iron and sulfur to its best advantage here. In the N_2ases, changes in Fe−Fe bonding by electron addition to the $MoFe_7NS_9$ cofactor and/or P cluster may be crucial to the binding and activation of N_2.[91−93] A designed synthesis of the FeMo−cofactor cluster with its newly recognized interstitial atom, possibly nitride,[92b] poses a challenge to the analogue chemist no less imposing than that of any other complex natural product.[5b]

V. Why Cyanide Ligands? Ligand Field Strengths and the Need for a Low-Spin State in H_2ases

Although nature can employ extremely sophisticated ligands such as macrocycles, its palette for simple inorganometallic ligands is quite limited, and perhaps this is why the curious combination of CN and CO (with thiolates) evolved for H_2ases. Ligands potentially useful for H_2 activation such as cyclopentadienyl and phosphines are absent in biology (even halide ligands are rare). However, cyanide and the CO ligands can be made biochemically,[94] as recently highlighted by both Rauchfuss and Darensbourg in their discussions of the biosynthesis of H_2ases.[94f,g] Biosynthesis of the H cluster at the active site of the [FeFe]-hydrogenase requires three accessory proteins, two of which are radical AdoMet enzymes (HydE, HydG) and one of which is a GTPase (HydF).[94a,b] Both CN and CO were found to be products of HydG-catalyzed tyrosine cleavage, and CO production was detected by using deoxyhemoglobin as a reporter and monitoring the appearance of the characteristic visible spectroscopic features of carboxyhemoglobin.[94b] This was the first report of the enzymatic synthesis of CO in hydrogenase maturation. As noted by Koch, one of the earliest organometallic complexes, $[Fe(CN)_5(CO)]^{3-}$, first reported 123 years ago by Muller, possessed CO and CN ligands coordinated to Fe(II).[95] A major advance in the chemistry of model systems for H_2ases was the demonstration in 1999 that two CO ligands of a propanedithiolate hexacarbonyl (e.g., **1** in Scheme 7, without the phosphines) could be replaced by cyanide, to give water-soluble dianions.[96]

Although the role of CO ligands in reversible H_2 binding and activation is clear, why biology utilizes toxic CN ligands in the dimetallic hydrogenases can only be subject to conjecture. The cyanides are known to be involved in hydrogen-bonding interactions of the active site with protein components, but surely there are other rationales for their presence. One possible role that will be discussed first relates to the *low-spin* configurations of the metal centers in all redox states. As detailed below, this is essential for preservation of CO coordination and indeed the integrity of the metal−ligand core. In accord with principles of transition-metal chemistry, the overall ligand field strength strongly influences the spin state of the metal active sites: e.g., strong-field ligands such as CO and CN favor low-spin configurations.[97,98] The peculiar presence of *cyanides* could then be related to the general deep

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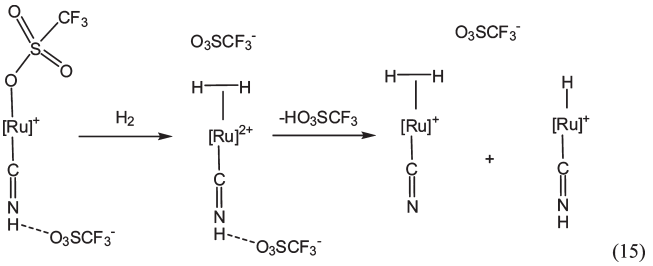
conviction that they are strong-field ligands,[99] thus reinforcing the low-spin states of H_2ases as previously conjectured by us.[6f] There is a vast contrast between the organometallic-like sites of the H_2ases and the iron sites in ferredoxins and related Fe−S proteins exemplified by the electron-transfer Fe_4S_4 cuboidal cluster found in the [FeFe]-H_2ase itself. According to Holm,[5b] nearly all properties of the latter clusters and the complexes designed to model them can be attributed to their *weak-field* nature: (a) tetrahedral site stereochemistry and attendant high-spin $d^{5,6}$ electron configurations in two readily accessible oxidation states ($Fe^{II,III}$), (b) kinetic lability to substitution of terminal ligands, and (c) facile structural conversions not encountered elsewhere. These features derive from the weak-field properties of thiolate and sulfide ligands and the propensity of sulfide to maintain the effective S^{2-} oxidation state even in the presence of one or more Fe^{III} interactions. A further advantage here is the nucleophilicity of coordinated thiolate, facilitating various types of substitution reactions. These weak-field properties, particularly the latter, are however precisely what would *not* be advantageous for hydrogen activation in H_2ases. Ligand lability, especially for the CO and CN groups, would be deadly here, certainly in terms of the integrity of the core site. A "secure" active site is essential for reversible H_2 activation, although fluxional behavior such as bridging/terminal ligand isomerization would be tolerable and even advantageous.

While the function of the CN ligands to increase the ligand field (LF) strength may still be a proper rationale, some controversy has recently arisen whether CN is truly a strong-field ligand.[100,101] For example, Scheidt found that coordination of a single axial cyanide does not generate a sufficiently strong LF to ensure a low-spin complex under all conditions in [Fe(tetraphenylporphyrinate)(CN)].[101a] This is in contrast to the analogous CO complex that is at all times low-spin, and 3 years prior to this finding, Gray had established from computations that CO is indeed a stronger field ligand than CN (and even stronger than previously believed).[98a] Furthermore, unlike CO, CN^- derives most of its LF strength from strong σ donation and not as much from back-donation, especially for Fe(II) complexes, where there is very little back-bonding from CN. The debate over this matter is thus ironic in that this article scrutinizes how seemingly well-established, half-century-old principles of organometallic chemistry are linked to biology, yet this and other scientific "dogmas" continue to evolve. Nonetheless, cyanide is clearly *not a weak-field ligand* and is stronger than other biological anionic ligands such as thiolate.

There is one other important feature to consider: although CN ligands can be protonated to CNH,[102] this species is not susceptible to elimination as HCN. Halides and other ligands such as hydroxide can be protonated off metal centers in intramolecular heterolytic H_2 splitting processes (Scheme 6, top). Remarkably, Morris showed that one of the strongest acids known, *triflic acid* (CF_3SO_3H) rather than HCN is eliminated from a dicationic H_2 complex that contains CNH ligands (eq 15).[103]



(15)

Finally, new computations show that there is functionally relevant electronic interplay between CN and the Fe_4S_4 cluster in the [FeFe]-H_2ases.[104] The CN groups help maintain the frontier orbitals to be close in energy and to be localized on the two subclusters ($Fe_2S_2$and Fe_4S_4), allowing facile electron transfer between them. Other recent calculations by DeGioia show that CN helps "freeze" the dinuclear cluster in a functionally competent inverted pyramidal structure.[77c] Darensbourg had speculated that an anionic cyanide would help stabilize a bridging CO ligand.[82] Another possible role for a strongly electron-donating cyanide ligand is its influence on the redox potentials: e.g., lowering the electrochemical potential for H_2 production.

The low-spin configuration of the metal centers is closely coupled to the presence of the CO ligands that both promote this spin state (aided by CN) and also benefit from it. If one assumes that CO coordination is critical for proper H_2 activation, the binding to iron must be very strong to both maintain the integrity of the active site and prevent possible poisoning of the host organism by release of CO. Strong CO binding to iron in Fe-heme systems with attendant spin-state change (spin crossover) from high-spin Fe^{II} ($S = 2$) to low-spin Fe^{II} ($S = 0$) is, of course, particularly notorious here.[95,105−108] However, CO is not always a powerful ligand, and spin crossover is much less facile in inorganic and organometallic complexes than may generally be appreciated, and CO binding to high-spin metal systems can be anomalously weak as in $Cp_2VI(CO)$ and $Cp_2Cr(CO)$, as noted independently by Calderazzo[109] and Brintzinger.[110] They rationalized that spin pairing has to take place upon carbonylation of the high-spin fragments. In his review article on such effects of spin state, Poli[96b] notes that "in spite of this early work, the importance of electron pairing in organometallic stability and reactivity has remained essentially unappreciated". Nature has designed the hydrogenases to possess low-spin Fe centers that powerfully and purposefully

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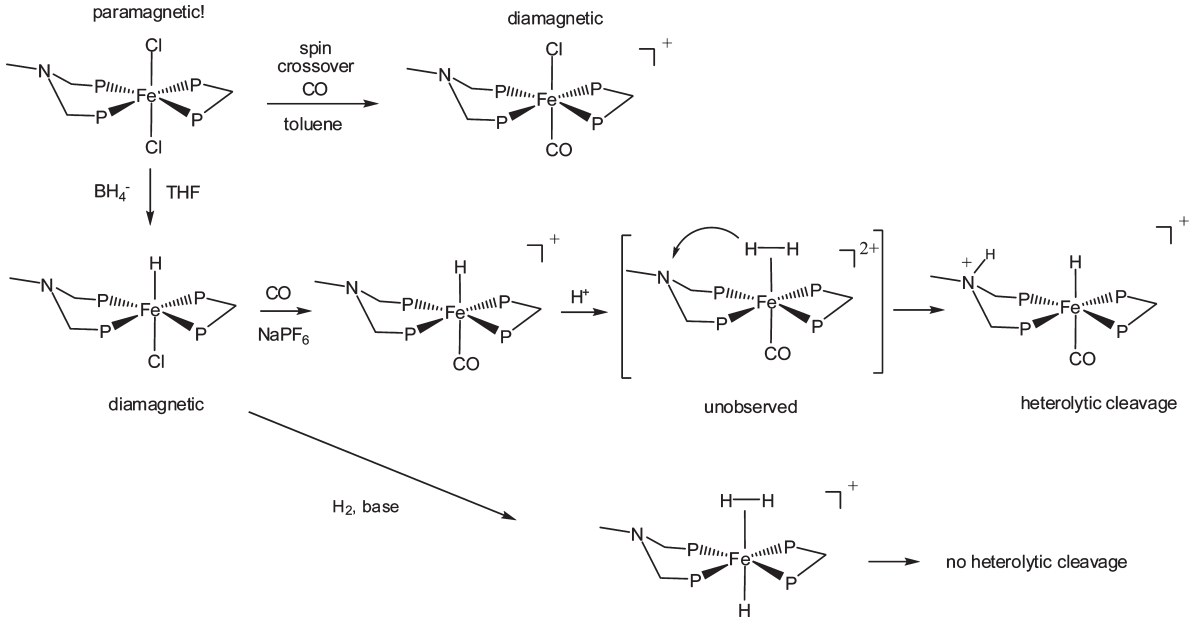
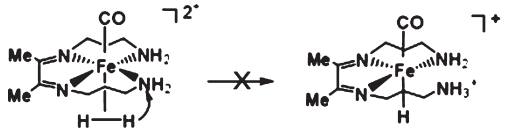
Scheme 8



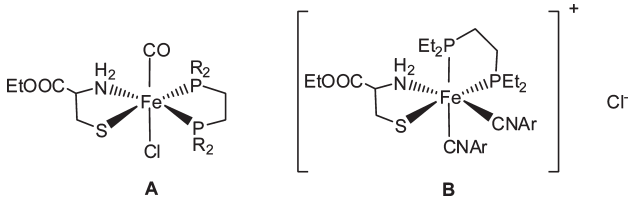
bind CO. It is important to note here that stable *coordination of H_2 to high-spin metals is extremely rare*.[6f] The enzymes must possess enough electron density at iron to strongly bind CO while maintaining with it a fine balance of electrophilic character to reversibly bind and heterolytically cleave H_2.

The above low-spin-state requirement was fully realized in unsuccessful attempts by Kubas to synthesize *mononuclear* Fe(II) complexes for H_2 activation that could be capable of H_2 activation in the same manner as the *dinuclear* H_2ase systems.[111,112] The intent was to situate a CO ligand trans to a potential H_2 binding site in order to promote intramolecular heterolysis of H_2 resulting in proton transfer from the bound H_2 to a basic N-donor located located cis to it: e.g., eq 16.



(16)

However, the target CO complex in eq 16 could not be synthesized. Metal−diimine systems such as this *rejected* all attempts to bind CO, much less add H_2 in a subsequent step.[111] The apparent reason was that the Fe(II) was in a high-spin state due to the weak-field N-donor ligand set and did not undergo spin crossover to a low-spin state necessary for robust CO binding, as supported computationally. Modified systems with cysteine-based ligands proved to be similarly difficult to synthesize and could only be made to bind CO (or CNR) by incorporating strong-field phosphines into the metal−ligand sphere to give low-spin complexes (**A** and **B**).[112]



A **B**

However, attempts to bind H_2 to **A** by chloride abstraction failed, possibly because of ligand lability and/or decomposition due to attendant heterolysis of H_2. Nevertheless, while our initial work[111] in this arena was in progress, DuBois[113,114] did succeed in heterolytically splitting H_2 in a related *phosphine* system, *trans*-$[Fe(X)(Y)(PNP)(dmpm)]^+$ (dmpm = dimethylphospinomethane), which contained a proximal basic amine group in the chelating PNP ligand analogous to that proposed in the dithiolate in [FeFe]-H_2ases (Scheme 8).

Although the precursor dichloro complex was high spin, spin crossover to low-spin complexes occurred on CO addition or replacement of Cl by H. Protonation of $[FeH(CO)(PNP)(dmpm)]^+$ gave a complex with the proton residing on the basic N atom of the PNP ligand, implying that an incipient unobserved H_2 ligand, if formed, would heterolytically cleave. However, when a hydride is placed trans to H_2 rather than a CO, H_2 does bind but does *not* heterolyze to protonate the amine. Thus, heterolysis of η^2-H_2 is much more effective when CO is trans to it, in concert with the principles previously discussed that outline how nature was opportunistic in employing CO ligands for this purpose.

So, why was DuBois' system successful versus ours? The inability of the diimine and indeed most all Fe^{II} high-spin systems to undergo carbonylation was initially thought to be symptomatic of a "spin-blocked" reaction, where a barrier may exist due to the crossing between reactant quintet and product singlet surfaces. This has been a decades-old debate and was shown computationally by Harvey and Poli to be highly dependent on the system.[115,116] However, this and

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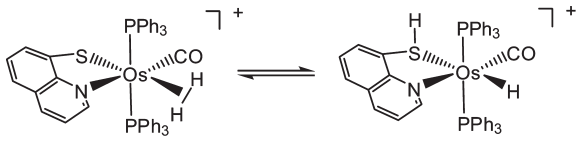
other recent work indicate that the term "spin-block" (or "spin-forbidden") should be reserved for *kinetic* effects. Indeed, a theoretical study of CO interaction with model Fe^{II}−diimine centers demonstrated that the lack of CO binding is *thermodynamic* in origin: addition of CO was essentially thermoneutral.[111] Thus, in the failed N-donor system (eq 16) versus the successful phosphine donor system (Scheme 8), the much higher ligand field strength of the P-donor ligands was key to strong CO binding.

Summarizing, the peculiar presence of *cyanide* ligands might relate to their substantial ligand-field strength, even if more moderate than originally believed. This would assist in maintaining the low-spin configuration for Fe needed to securely bind CO throughout the large known array of redox state changes[6n,o,117−119] that occur during the function of H_2ases. Weaker field ligand sets such as those typically found in enzymes (histidine, cysteine, etc.) would not fulfill this function, since N-donor ligand sets as in eq 5 give high-spin complexes incapable of even weak CO binding. In the above context, Rauchfuss also demonstrated the positive influence of CN on binding of CO to Fe^{II} and facilitating carbonylation of Fe^{II} thiolate complexes.[120] Cyanide might have other utilities, including assisting electron transfer, optimizing redox potentials, and resisting elimination upon protonation.

VI. Heterolytic Splitting of H_2 and Its Microscopic Reverse for Bioinspired Production of H_2

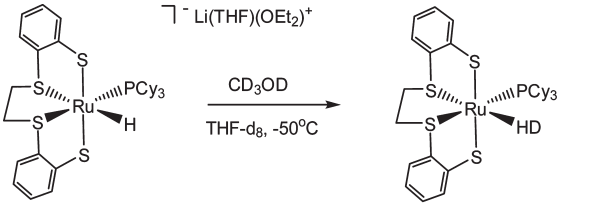
One of the oldest, most important, and widespread reactions of H_2 on metal centers is heterolytic cleavage, which effectively breaks the H−H bond into H^+ and H^- fragments.[121] The hydride ligates to the metal and the proton migrates to either an external Lewis base or an ancillary ligand or anion, as shown in Scheme 6. Initially heterogeneous processes were predominant in catalytic hydrogenation reactions, and few documented examples of homogeneous catalytic activation of H_2 by metal complexes were reported prior to 1953 when Halpern began his seminal studies.[122] It may be surprising to organometallic chemists that metal−hydride bonds were not well-characterized or even generally accepted until about 1955 (and dihydrogen complexes were not discovered for another 28 years after this!). The growth in hydride chemistry has since been exponential, and in the past decade the number and variety of reactions involving heterolysis of H_2 on metal and now even nonmetal centers ("frustrated Lewis pairs"[123]) has been dramatic as well. Heterolytic splitting of H_2 on metal centers was reviewed by Kubas in 2004[124] and featured in excellent recent articles by Ogo[6q] ("Electrons from Hydrogen") and Kuwata and Ikariya.[6r] Thus, it will not be discussed in great detail here except to highlight reactions relevant to the function of H_2ases. Importantly, the reverse reaction leads to H_2 production and will be a major focus of discussion below. Heterolytic cleavage of H_2 is also relevant in the function of nitrogenases and has been shown to occur on a Mo(III) complex that binds and reduces N_2 to ammonia.[125]

Heterolysis of Coordinated H_2 Involving Sulfur. The first direct observation of equilibrium between an acidic H_2 complex and a corresponding hydride complex with a protonated ancillary ligand resulting from heterolysis of the H_2 ligand is shown in eq 17.[126]



(17)

Several other cases of η^2-H_2 ligands (observed or implied) reacting intramolecularly with thiolate and sulfide ligands are known or believed to be intermediate steps in, for example, SH ligand formation from reaction of sulfides with H_2 and are relevant to biological systems.[28a,127−130] In order for proton transfer from η^2-H_2 to a coordinated base to occur, the pK_a values of the H_2 ligand and the protonated base must be similar. Morris has estimated that coordinated alkanethiol ligands have pK_a values between 5 and 10, which matches well with the acidity of many H_2 ligands.[129b] The extensive studies by Sellmann in this regard relate to the function of both H_2ases and N_2ases, albeit on second-row metals.[130] Protonation of an anionic Ru hydride using CD_3OD gives an unstable HD complex (eq 18; S_4 = tetradentate S-donor).[130c]



(18)

This reaction can effectively be reversed by displacing the HD by DMSO to give Ru(DMSO)(PCy_3)(S_4), which then yields $Na^+[RuH(PCy_3)(S_4)]^-$ and MeOH when treated with

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(122) For a retrospective account of homogenous catalytic hydrogenation, see: Halpern, J. *J. Organomet. Chem.* **1980**, *200*, 133.
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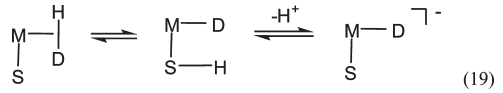
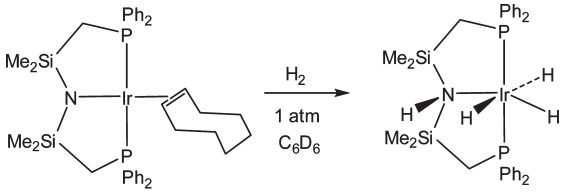
H_2 in the presence of NaOMe. This shows that H_2 can be heterolytically cleaved at M−S sites, and a mechanism was elucidated for an analogous neutral Rh−hydride system wherein the electrophilic metal and the basic thiolate donors attack the η^2-H_2 in a concerted fashion to give a thiol hydride species, $[RhH(PCy_3)(^{bu}S_4\text{-}H)]^+$.[130a,b] The similarity between the Ru and Rh systems suggests that intramolecular splitting of the HD (or a D_2) ligand in eq 18 is responsible for the D_2/H^+ exchange between $D_2$and EtOH that these complexes are known to catalyze (eq 19).



(19)

$[IrH_2(HS(CH_2)_3SH)(PCy_3)_2]^+$ had previously been shown to similarly catalyze D_2/H^+ exchange, but the H_2 complex was not observed and was assumed to be a transient.[28a] A related system, $Ni(NHP^nPr_3)(S_3)$, clearly showed that heterolysis of H_2 can also occur at nickel sites, which may be relevant to H_2 activation in the [NiFe]-hydrogenases,[130d] and this topic will be discussed further below. Although H_2 heterolysis is not believed to occur at sulfur in the [FeFe]-H_2ases, it remains a possibility. Computations do suggest that it occurs in the [Fe]-H_2ase (Figure 1), in a dual pathway involving proton transfer to the cysteine sulfur and the proximal oxygen of the 2-pyridinol ligand to form a resting state with an $Fe{-}H^{\sigma-}\cdots H^{\sigma+}{-}O$ dihydrogen bond.[131]

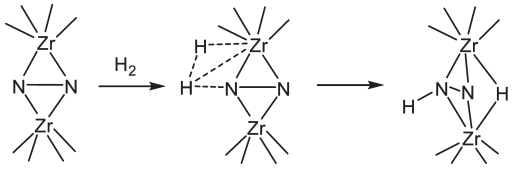
Heterolysis Involving Nitrogen Donors. The above seminal work and Crabtree's heterolysis reaction involving a pendant amine (eq 7) provided inspiration for the many dozens of new systems developed in the past decade that involve heterolysis at sites other than S-donors. The conversion in eq 7 is completely reversible by removing the H_2 gas from solution and is remarkably sensitive to phosphine size and ion-pairing effects. A similar proton transfer occurs to a Ru-bound NH_2 (amido) ligand on heterolysis of H_2 on $(PCP)Ru(CO)(NH_2)$ (PCP = $2,6\text{-}(CH_2PBu_2)_2C_6H_3$).[132] An ammonia ligand is formed, which then dissociates to give (PCP)RuH(CO). On a historic note, Fryzuk had much earlier discovered a reaction of the type M−amide + H_2 → H−M−amine and used the term "ligand-assisted heterolytic splitting of H_2" to describe it (eq 20, where attendant displacement of cyclooctene by H_2 occurs to give hydrides).[133,134]



(20)

However, this work was initially published in 1983 just before M−H_2 complexes were discovered; hence, intermediate H_2 coordination was not proposed to be a part of the mechanism of such processes. These "bifunctional" sites, including the type M/NH prominently exemplified in Noyori's ruthenium diamine hydrogenation catalysts,[135] can be readily exploited for H_2 heterolysis in an ever-expanding variety of possible pathways, even on the same complex, as described in the recent review by Kuwata and Ikariya.[6r] The most prominent H_2ase-related findings on heterolysis at N-donors have been made by DuBois in his "proton relay" systems (e.g. Scheme 8).[6c,g,30,113,114] These have a direct analogy to the proposed mechanism for H_2 cleavage involving the bridging N-donor in [FeFe]-H_2ases (eq 8). The metal centers in the DuBois systems include nickel as well as iron and in some cases feature multiple N-donor sites. Manganese(I) analogues, e.g. $[trans\text{-}Mn(CO)(H_2)(P{-}N{-}P)(PP)]^+$, have also been prepared, but here the H_2 ligand was not acidic enough to be deprotonated by the pendant amine functionality on the diphosphines.[114b] Charge is a critical factor here, and as discussed previously, in the $[M(CO)(H_2)(PP)_2]^{n+}$ series (M = Mo, Mn^+, Fe^{2+}) the H_2 in the dicationic Fe complex is the most acidic and is the least in the neutral Mo species, while that in monocationic Mn must fall in between.[17b] Most of DuBois' work has been well publicized and reviewed[6c,g] and will not be discussed further here. In general, the initial intent of incorporation of the pendant amines in these systems was to facilitate intramolecular and intermolecular proton transfer reactions, but it has become clear that pendant amines also provide additional advantages. These include stabilizing the binding of H_2 or CO ligands to a metal, lowering the barrier for heterolytic cleavage of H_2, facilitating proton-coupled electron transfer reactions, and lowering overpotentials in electrocatalytic reactions.

Several other systems show H_2 heterolysis with transfer of protons to nitrogen donors,[136] including the bridging nitride $L_3Fe(\mu\text{-}N)FeL_3$ to give $L_3Fe(\mu\text{-}NH)(\mu\text{-}H)FeL_3$.[137] Earlier Fryzuk found heterolysis could even involve a N_2 ligand, where only a very limited number of reactions are known: e.g., eq 21 for a dinuclear Zr complex capped by macrocyclic ligands with N and P donor atoms. The reaction stopped at the stage of N_2H formation and no NH_3 was formed.[138]

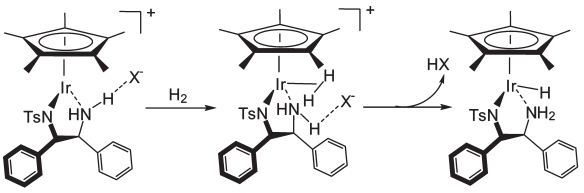


(21)

Activation of H_2 can be assisted by protons and even solvent (see below), and Rauchfuss has investigated the

(131) Yang, X.; Hall, M. B. *J. Am. Chem. Soc.* **2009**, *131*, 10901.
(132) Conner, D.; Jajaprakash, K. N.; Cundari, T. R.; Gunnoe, T. B. *Organometallics* **2004**, *23*, 272460.
(133) Fryzuk, M. D.; MacNeil, P. A. *Organometallics* **1983**, *2*, 682.
(134) Fryzuk, M. D.; MacNeil, P. A.; Rettig, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2803.
(135) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, 41.
(136) (a) Hedberg, C.; Kallstrom, K.; Arvidsson, P. I.; Brandt, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 15083. (b) Friedrich, A.; Drees, M.; Schmedt, J.; Schneider, S. *J. Am. Chem. Soc.* **2009**, *131*, 17552.
(137) Brown, S. D.; Mehn, M. P.; Peters, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 13146.
(138) (a) Fryzuk, M. D.; Love, J. B.; Rettig, S. J.; Young, V. G. *Science* **1997**, *275*, 1445. (b) Basch, H.; Muaev, D. G.; Morokuma, K.; Fryzuk, M. D.; Love, J. B.; Seidel, W. W.; Albinati, A.; Koetzle, T. F.; Klooster, W. T.; Mason, S. A.; Eckert, J. *J. Am. Chem. Soc.* **1999**, *121*, 523. See also: (c) Pool, J. A.; Lobkovsky, E.; Chirik, P. J. *Nature* **2004**, *427*, 527.

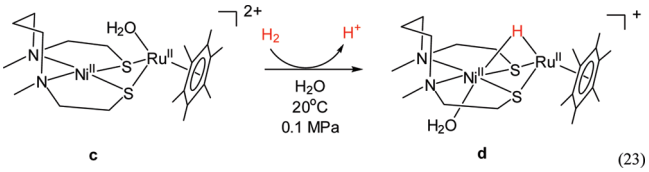
mechanistic aspects of proton-catalyzed addition of H_2 to Ru and Ir amido complexes (eq 22).[139]



(22)

The hydride product inserts O_2 without formal redox of the metal center to form an −OOH ligand, resulting in a catalytic cycle for H_2 oxidation to water. Multiple basic sites were also featured in reversible heterolysis of H_2 on CpRuH-[PPh_2(pyridine)]$_2$ that initially occurs via dihydrogen bonding involving a protonated pyridine group (Figure 6).[140] Additional intramolecular proton transfer is proposed to occur between the nitrogens on adjacent ligands, i.e. DFT calculations show that a proton can be "handed off" from one ring to another via a symmetrical proton-bridged transition state.

Of major importance, Ogo and co-workers[6q,141] developed an innovative combined structural *and functional* model for the [NiFe]-hydrogenases. Although relatively realistic synthetic reproductions of the active site have been accomplished, e.g. those of Tatsumi,[142] they have not yet evolved into functional models for H_2 activation. Ogo's work exemplifies a new way of thinking in catalysis, termed "*concerto* catalysis,"[143] in this case the successful merging of the chemical properties of a natural [NiFe]-H_2ase and a [NiRu] mimic model complex. Remarkably, the activities of these two "different" catalysts proved to be almost identical. His complex (**c** in eq 23) pairs nickel with *ruthenium* rather than iron and binds and heterolytically cleaves H_2 in *aqueous* solution (a rarity) to give a {$Ru^{II}(\mu$-H)(μ-$SR)_2Ni^{II}$} core (**d**).



c **d** (23)

The replacement of the {$Fe(CN)_2(CO)$} unit with {$Ru(C_6Me_6)$}$^{2+}$ was a brilliant application of organometallic chemistry principles: d^6 Ru^{II} forms H_2 complexes more stable than those for any other metal, whereas similar Fe systems are rare because of their higher lability and tendency to be high-spin. Significantly, the hydride complex **d** is proposed to activate a *second* hydrogen molecule, a major difference from conventional thinking on the H_2ase cycle, and this is crucial because a transient dihydride species is believed to form. Thus, two molecules of H_2 were activated and a total of four electrons were collected; there is no evidence from studies on H_2ase that two molecules of H_2 are required for enzymatic turnover. In the next step of an intricate catalytic cycle, reductive elimination liberates the hydrido ligands of the dihydride as H_2 gas. This regeneration of H_2, taking with it two of the four electrons, leaves the remaining two electrons in a Ni^IRu^I bond in an unusual low-valent species. This effectively stores the two electrons liberated from the two molecules of H_2 and can be used to catalyze reductions, e.g. copper sulfate to copper in water under ambient conditions to regenerate **c** and complete a catalytic cycle. The NiRu model complexes thus mimic the major features of H_2ases, i.e. heterolytic hydrogen activation, electron extraction, and simultaneous isotope exchange. Another surprise is that the complex is also an efficient hydrogenation catalyst, including reduction of benzaldehyde to the corresponding alcohol.

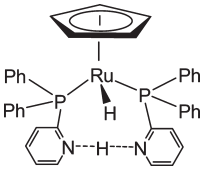
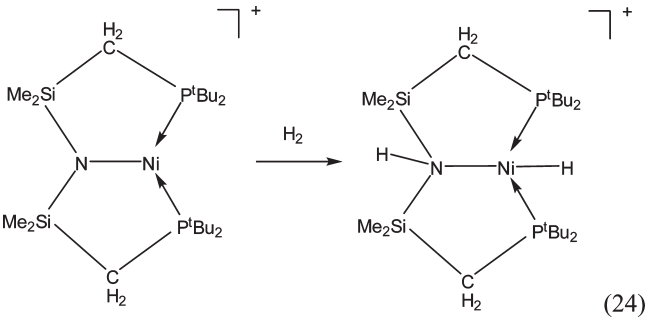


Figure 6. Product of heterolysis of H_2 on CpRuH[PPh_2-(pyridine)]$_2$.

The first example of H_2 binding and heterolysis at a Ni center has just been reported by Caulton to occur (eq 24).[144] H_2 rapidly reacted with $(PNP)Ni^+$ to give a very weak H_2 complex ($\Delta G^0_{298} \approx 0$), confirmed by a J_{HD} value of 33 Hz for $(PNP)Ni(HD)^+$. The mechanism was viewed as involving this H_2 complex as the only detected intermediate, but migration of one of these H atoms to the amide nitrogen would appear to traverse a long distance (trans mutual positioning of N and the H_2 ligand). A transition state (TS) was identified by DFT for this intramolecular migration, where the H−H bond distance is very long (1.76 Å) with short Ni−H distances characteristic of nickel hydrides: i.e., full oxidative addition to Ni^{IV}. However, it is not a minimum, and hence the mechanism does not involve a tetravalent *intermediate*, although it does appear to involve a Ni^{IV} species with the high energy characteristic of a TS. It should be noted that DuBois has observed a Ni(IV) dihydride as a true intermediate in his diphosphine systems containing pendant amine groups.[114c]

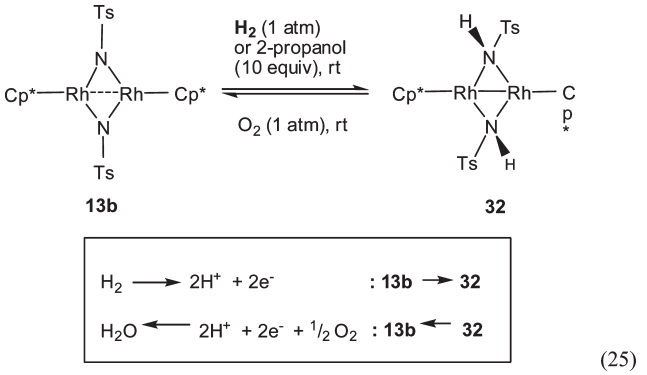


(24)

Heterolysis Involving Oxygen. A good example of multiple possible sites for heterolysis is the bis(sulfonyl*imido*)-bridged Rh(III) complex **13b**, which readily reacts with 1 atm of H_2 under mild conditions to generate the bis(sulfonyl*amido*)

(139) Heiden, Z. M.; Rauchfuss, T. B. *J. Am. Chem. Soc.* **2009**, *131*, 3593.
(140) Jalon, F. A.; Manzano, B. R.; Caballero, A.; Carrion, M. C.; Santos, L.; Espino, G.; Moreno, M. *J. Am. Chem. Soc.* **2005**, *127*, 15364.
(141) Ogo, S.; Kabe, T.; Uehara, K.; Kure, B.; Nishimura, T.; Menon, S. C.; Harada, R.; Fukuzumi, S. *Science* **2007**, *316*, 585. See also: Mealli, C.; Rauchfuss, T. B. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 8942.
(142) Li, Z.; Ohki, Y.; Tatsumi, K. *J. Am. Chem. Soc.* **2005**, *127*, 8950.
(143) Ichikawa, K.; Nonaka, K.; Matsumoto, T.; Kure, B.; Yoon, K.-S.; Higuchi, Y.; Yagi, T.; Ogo, S. *Dalton Trans.* **2010**, *39*, 2993.
(144) He, T.; Tsvetkov, P.; Andino, J. G.; Gao, X.; Fullmer, B. C.; Caulton, K. G. *J. Am. Chem. Soc.* **2010**, *132*, 910.

Rh(II) complex **32** (eq 25).[6r,145] This reaction represents a functional mimic of H_2ases because it involves formal conversion of H_2 into two amido protons and two electrons for the reduction of the dinuclear Rh(III) core in **13b**.



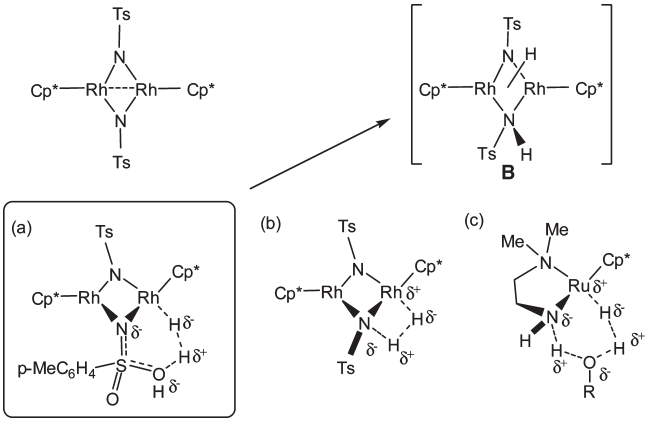
(25)

DFT calculations revealed that the hydrogenation of **13b** takes place via initial heterolytic cleavage of H_2 assisted by a *sulfonyl oxygen atom* (Scheme 9, intermediate a) rather than the direct addition of H_2 to the metal−imido bond (intermediate b) or oxidative addition of H_2 to rhodium.

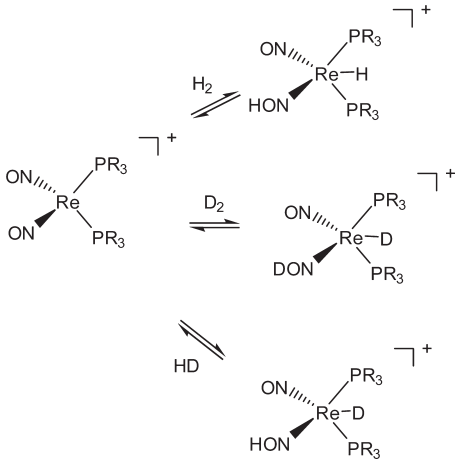
Intermediate b is related to that proposed by Morris to result from heterolysis of H_2 in the Noyori-type Ru systems.[146] An additional fourth possible path for H_2 splitting existed here: assistance by a solvent alcohol molecule in a six-membered pericyclic transition state (Scheme 9, intermediate c). The importance of alcohol and even water in promoting such base-assisted heterolysis of H_2 in metal bifunctional catalysis (e.g., Noyori-type Ru catalysts) has been reported,[136,137] including a hydroxycyclopentadienylruthenium(II) system involving the OH substituent.[147] As an aside, it is noteworthy that H_2 *heterolysis can be assisted by both bases and acids* (see above[139]). However, in this system (Scheme 9, intermediate a) the sulfonyl oxygen atom appears to be key in H_2 splitting rather than nitrogen, and the proton generated on it is relayed to the imido nitrogen atom to afford the hydride−amide intermediate **B**, which was experimentally observed using another synthetic route. Spontaneous hydride migration in **B** led to the formation of the amido complex **32** shown in eq 25. Remarkably, the "reverse" reaction of **32** with O_2 regenerated **13b** and water (eq 25). Although the precise mechanism remains unclear, the reaction was speculated to possibly occur via initial insertion of O_2 into the Rh(II)−Rh(II) bond followed by a proton shift from the bridging amide to the μ-peroxo ligand and several subsequent steps. This single system illustrates well the rich structural and mechanistic chemistry that encompasses both H_2 splitting and the much less studied area of oxidation of protons by O_2 to water on metals, the reverse of biomimetic water splitting reactions now under intense investigation for H_2 production.

Heterolysis of H_2/D_2 can even involve the oxygen on NO ligands, leading to isotopic scrambling (Scheme 10).[148] Although the protonated NO ligands were not observed, analogous heterolysis of a silane did give a complex with a

Scheme 9



Scheme 10



silylated nitrosyl ligand, Et_3SiON. This is a notable example of *parallel heterolysis of H−H and Si−H bonds* that often can occur in unsaturated 16e complexes,[124] a feature to keep in mind for the design of potential H_2 production schemes.

VII. Bioinspired Production and Electrocatalysis of H_2

As eminently expressed by prominent researchers in the field, chiefly Nocera,[8] "the supply of secure, clean, sustainable energy is arguably the most important scientific and technical challenge facing humanity in the 21st century". He has often stated that this is primarily a *chemistry* problem (rather then engineering or materials), and it can be assumed that inorganic/organometallic chemistry will play an important role. Hydrogen is, of course, the ideal energy carrier, but its massive-scale economic production is a demanding challenge. Furthermore, vast quantities of hydrogen are also vital in chemical processes: catalytic hydrogenations are the largest volume human-made chemical reactions in the world. All crude oil is treated with H_2 to remove sulfur and nitrogen, and 10^8 tons/year of ammonia are produced from H_2/N_2 by the Haber process. Ultimately, *water* must be the source of H_2, rather than its current production principally from natural gas. Schemes involving use of solar and other alternate energy to split water are currently of high interest, and several excellent reviews have now been published on this subject.[6e,7,8] Determining precisely how biological systems use cheap and abundant metals to accomplish this and

(145) Ishiwata, K.; Kuwata, S.; Ikariya, T. *J. Am. Chem. Soc.* **2009**, *131*, 5001.
(146) Abdur-Rashid, K.; Clapham, S. E.; Hadzovic, A.; Harvey, J. N.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 15104.
(147) Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, *127*, 3100.
(148) Llamazares, A.; Schmalle, H. W.; Berke, H. *Organometallics* **2001**, *20*, 5277.

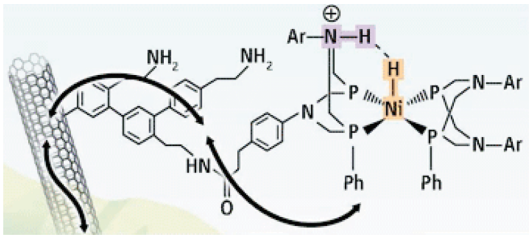
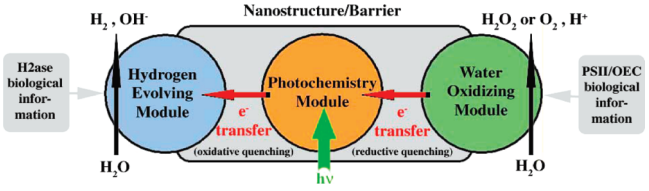


Figure 7. Ni complex attached to multiwalled carbon nanotubes in a high-surface area cathode material by Le Goff, from the Perspective by Hambourger et al. in ref 149. Reprinted with permission from the AAAS.

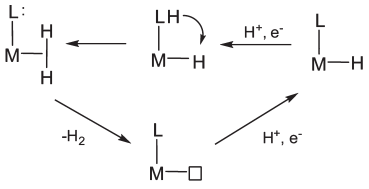
Scheme 11



designing an efficient artificial system for it would be a historic achievement. Current functional man-made water-splitting catalysts rely on precious metals that would not be abundant enough to fulfill future world energy demand. Thus, the catalyst systems being developed for H_2 production focus on first-row transition metals, particularly Fe, Co, and Ni. A prime example is Nocera's self-healing cobalt phosphate catalyst that splits water into hydrogen and oxygen more efficiently and cheaply than other materials and is getting much attention for "personalized solar energy".[8b] However, this is a very broad area and, due to space limitations, only those systems most relevant to organometallic H_2ase-inspired chemistry will be highlighted below. Coupling model catalysts with photochemical water splitting is being investigated by several groups, and impressive breakthroughs have recently been reported in *Science* and other prestigious journals in the past year and will be the major focus. It should be kept in mind that water splitting involves both oxygen- and hydrogen-evolving processes (Scheme 11).

Water would be oxidized in the module shown on the right side in a molecular system mimicking biological photosystem II and electrons transferred to a hydrogen-evolving module mimicking hydrogenase. The fundamental feature of H_2 production via bioinspired water splitting and other related processes is the stepwise combination of protons and electrons on a metal center to form a labile H_2 ligand (the "hydrogen-evolving module" e.g. as in Scheme 12), often assisted by proton relays such as in the [FeFe]-H_2ases. This is essentially the microscopic reverse of intramolecular heterolytic splitting of H_2 (Scheme 6). Electrocatalysis is an essential ingredient in the overarching methodology for hydrogen-based energy. Proton-exchange membrane (PEM) electrolyzers and fuel cells (discussed below) are key components in systems for powering homes and vehicles. Although bimetallic systems have been the focus of the most straightforward efforts to model H_2ase function, monometallic complexes also activate H_2 and can act as electrocatalysts for H_2 splitting/production, as shown for example in the extensive work by DuBois and co-workers on Fe and Ni systems analogous to that in Scheme 8.[6c,g,7b,30,113,114] A Ni system inspired by the latter has been covalently attached onto multiwalled carbon nanotubes in a high-surface-area cathode material by Le Goff et al. (Figure 7)[149]

Scheme 12



□ = coordinatively unsaturated site or weakly bound ligand

The pendant nitrogen again acts as the proton relay here. Unlike previous work with related catalysts that relied on organic solvents and exogenous acid or base, surface immobilization of the catalyst allows operation under the *aqueous* conditions crucial for using such catalysts in PEM electrolyzers and fuel cells. The catalyst operated under conditions comparable to those encountered in PEM devices and demonstrated sustained performance for both the production (>100 000 turnovers, or cycles of the reaction) and oxidation (>35 000 turnovers) of H_2. Challenges remain, as this catalyst has turnover rates only one-tenth as high as those of DuBois' complexes,[6g] possibly because of the bulky functional groups used for immobilization. The current densities are $\sim 10^2$ lower than those achieved on commercial Pt electrodes, but further optimization could result in a viable, non-noble metal electrocatalyst.

Photochemical Water Splitting and Fuel Cell Electrocatalysts. Hydrogen directly and efficiently derived from the splitting of water by *solar energy* is clearly an attractive route that would be an enormous scientific achievement. There have been many attempts to construct molecular and biomolecular devices for photohydrogen production. This was publicized as one of the "Holy Grails of Chemistry" 15 years ago, but use of organometallic chemistry was hardly even on the periphery back then.[150] Now there are dozens of schemes to produce H_2 using molecular photocatalysis involving inorganic compounds, which have been well reviewed,[8d] and thus only some recent results will be highlighted here. Utilization of tris(bipyridine)ruthenium, zinc porphyrin, or related inorganic compounds as photosensitizers in conjunction with a tethered or free electrocatalyst (or enzymic system as will be discussed below) and a sacrificial electron donor is one popular trend.[6m,151,152] For example, electrons could be supplied to a [FeFe]-H_2ase model complex by a photochemical module: e.g., the well-known $Ru(bipy)_3$ type systems, as studied by the groups of Sun, Ott, and Artero.[6m,151] Eisenberg and also Alberto have developed systems employing as photocatalysts Co−dimethylglyoxime complexes previously used for electrocatalytic H_2 production by Fontecave.[153,154] Simple

(149) Le Goff, A.; Artero, V.; Jousselme, B.; Dinh Tran, P.; Guillet, N.; Métayé, R.; Fihri, A; Palacin, S.; Fontecave, M. *Science* **2009**, *326*, 1384. See also the Perspective: Hambourger, M.; Moore, T. A. *Science* **2009**, *326*, 1355.

(150) Bard, A. J.; Fox, M. A. *Acc. Chem. Res.* **1995**, *28*, 141.

(151) (a) Fihri, A.; Artero, V.; Razavet, M.; Baffert, C.; Leibl, W.; Fontecave, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 564. (b) Na, Y.; Wang, M.; Pan, J.; Zhang, P.; Åkermark, B.; Sun, L. *Inorg. Chem.* **2008**, *47*, 2805. (c) Striech, D.; Astuti, Y.; Orlandi, M.; Schwarz, L.; Lomoth, R.; Hammerstrom, L.; Ott, S. *Chem. Eur. J.* **2010**, *16*, 60.

(152) (a) Reisner, E.; Fontecilla-Camps, J. C.; Armstrong, F. A. *Chem. Commun.* **2009**, 550. (b) Reisner, E.; Powell, D. J.; Cavazza, C.; Fontecilla-Camps, J. C.; Armstrong, F. A. *J. Am. Chem. Soc.* **2009**, *131*, 18457.

(153) Razavet, M.; Artero, V.; Fontecave, M. *Inorg. Chem.* **2005**, *46*, 1817.

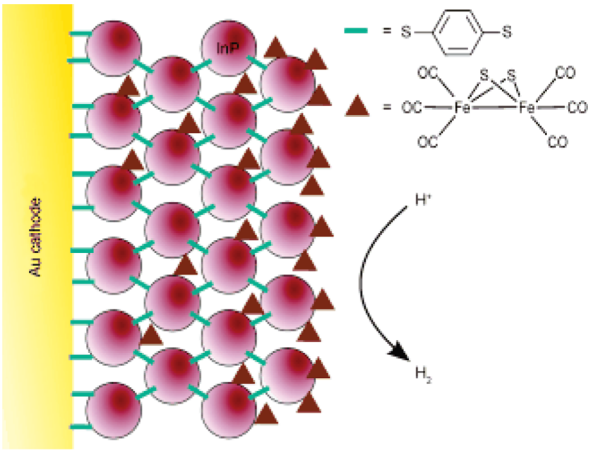


Figure 8. Cross-section of a InP nanocrystal modified gold electrode with adsorbed/intercalated $Fe_2(S_2)(CO)_6$ subsite analogue. Reproduced with permission from ref 156; copyright Wiley-VCH Verlag GmbH & Co. KGaA.

organometallic complexes such as $Fe_3(CO)_{12}$ have even been found to be catalysts, using EtN_3 as sacrificial electron donor and $[Ir(bpy)(ppy)_2]PF_6$ as photosensitizer, giving catalyst turnover numbers of 400.[155] A [NiFeSe]-H_2ase attached to dye-sensitized TiO_2 nanoparticles produced H_2 at a turnover frequency of ~50 at pH 7 under solar radiation, even after prolonged exposure to air.[152b]

Most of the above systems had functional problems, however, e.g. limited lifetimes, but Pickett and co-workers recently made significant strides in showing that an *inexpensive and environmentally benign* inorganic light harvesting nanoarray can be combined with a low-cost electrocatalyst that contains abundant elements.[156] Their assembly (Figure 8) produced H_2 photoelectrochemically by first building up a cross-linked indium phosphide (InP) nanocrystal array layer by layer and then incorporating an iron−sulfur electrocatalyst, namely the versatile organometallic complex $Fe_2(\mu\text{-}S_2)(CO)_6$, highlighted in the Introduction. Fe−S−CO assemblies related to the subsite of [FeFe]-H_2ases have been shown to electrocatalyze the reduction of protons to H_2 at potentials between −0.7 and −1.4 V versus SCE in nonaqueous electrolytes.[6a,b] Pickett chose $Fe_2(\mu\text{-}S_2)(CO)_6$ because the sulfurs in its disulfide bridge were presumed to bind to indium in a solid-state assembly. In this context, disulfide ligands bridging organometallic cuboidal Fe centers were found by Vergamini and Kubas to chemically bind to other metal centers: e.g., reaction of $Cp_4Fe_4(\mu\text{-}S)_2(\mu\text{-}S_2)_2$ with $3AgSbF_6$ led to oxidation and formation of the tricationic complex $[\{Cp_4Fe_4S_6\}_2Ag][SbF_6]_3 + 2Ag$ (Figure 9).[86a]

Also, photochemical reaction of $Cp_4Fe_4S_6$ with $Mo(CO)_6$ gave the charge-neutral $[Cp_4Fe_4S_6][Mo(CO)_4]$, containing analogous sulfide linkages from one cubane to a $Mo(CO)_4$ unit, further demonstrating that disulfide ligands are "sticky" and can be fastened onto other substrates.[86b]

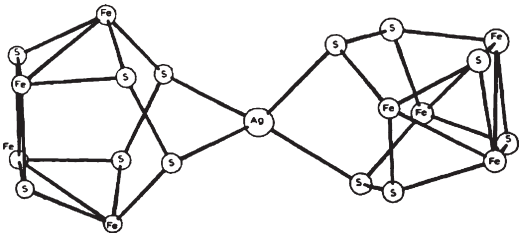


Figure 9. Crystal structure of $[\{Cp_4Fe_4S_6\}_2Ag]^{3+}$. Cp ligands not shown.

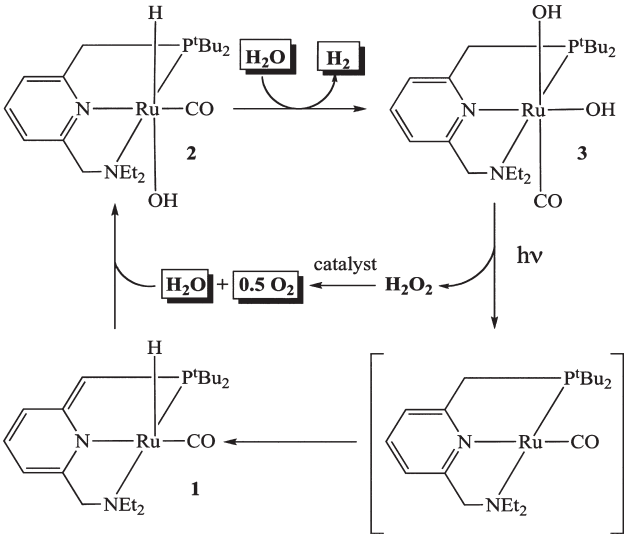


Figure 10. H_2 and light-induced O_2 evolution from water promoted by an organometallic ruthenium "pincer" hydride complex.

Whether or not these types of interactions are present in Pickett's assembly, the presence of the $Fe_2(S_2)(CO)_6$ subsite absorbed within it was confirmed by diffuse reflectance FTIR spectroscopy. The assembly photochemically reduced protons to H_2 at a modest potential of −0.90 V versus SCE at a photoelectrochemical efficiency of >60%, a major breakthrough. A photocurrent could be sustained for at least 1 h without degradation at a bias potential of −400 mV, demonstrating the robustness of the system. The mechanism of the H_2 photoproduction was proposed to involve absorption of incident light by the InP nanocrystals, excitation of an electron into the nanoparticle conducting band, and electron transfer into the LUMO of the catalytic subsite at circa −0.90 V vs Ag/AgCl, giving proton reduction. Of interest here, the mechanism may involve Fe−H and/or S−H intermediates, but evidence was unachievable.

The other half of the cycle for water splitting, i.e. water oxidation to form oxygen, is actually more of a challenge. A recent report by Milstein and co-workers describes consecutive thermal H_2 and light-induced O_2 evolution from water promoted by an organometallic ruthenium "pincer" hydride complex that establishes a novel multistep process for both H_2 and O_2 generation in a single homogeneous system (Figure 10).[157] Although not catalytic, the fact that a

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simple molecular system can accomplish water splitting is thought-provoking and holds hope for future development of organometallic systems for energy production.

The need for H_2 production from water is obvious, but so is the need for efficient "burning" of hydrogen fuel: i.e., the development of efficient, inexpensive fuel cells. A fuel cell, much like a battery, obtains electrical energy directly from a chemical reaction, but unlike a battery, electrical power is furnished as long as the reacting chemicals are supplied to each electrode, with the cathode receiving oxidant and the anode receiving reductant or "fuel".[158] The environmental advantages over combustion is clear, since fuel cells avoid the high temperatures that cause nitrogen oxide production, and they operate at a higher efficiency (ca. 50−60%) than internal combustion engines (20−25%). A fuel cell's power output can be limited by the electrochemical reactions occurring at either of the two electrodes, the anode for oxidizing fuel, and the cathode for reducing oxidant. Thus, the electrodes are usually coated with electrocatalysts, which are often transition metal based. Current polymer electrolyte membrane (PEM) fuel cells use Pt as the catalyst for both half-reactions: oxidation of H_2 and reduction of O_2. Of particular interest is the development of new electrocatalysts that are *not based on Pt or other precious metals*: e.g., Fe or Ni as utilized in H_2ases. A recent tactic is use of an *enzyme fuel cell, which* uses a H_2ase as the electrocatalyst, either at both the cathode and anode or at just one of the electrodes.[152,158] The catalytic properties of redox enzymes offer advantages in fuel cell applications, although examples of devices exploiting enzyme electrocatalysis are almost exclusively at a proof-of-concept stage. Not only are enzymes capable of very high activity (on a per mole basis) but they are also usually highly selective for their substrates. This simplifies fuel cell design because fuel and oxidant need not be separated (e.g., by an ionically conducting membrane) and can be introduced as a mixture: that is, mixed reactant fuel cells are possible. The main disadvantage of enzymes is their large size; hence, multilayers of enzyme are likely to be needed to provide sufficient current. Also, although enzymes are often unstable outside ambient temperature and pH and long-term durability is difficult to achieve, research on these systems will provide inspiration for development of better synthetic catalysts.

VIII. Conclusions and Outlook

The revelation that nature employed organometallic chemistry billions of years ago in the hydrogenases and kept it hidden from inorganic chemists until just over a decade ago was both stunning and inspiring. On the other hand, it may also be considered surprising that transition-metal hydride and subsequent dihydrogen coordination chemistry were established only within the past half-century or so. The similarities of the organometallic principles obeyed in the biological and synthetic systems are fascinating and serve as a primer for development of technology for sustainable, renewable, non-carbon-based energy. The advantages of CO and CN ligands, low-spin configurations, and dinuclear active sites for H_2ases can be rationalized by these basic principles that revolve around H_2 activation. Innumerable models of these sites have been designed, many based on advances by Dietmar Seyferth in the chemistry of the simple organometallic complex precursor $Fe_2S_2(CO)_6$. Heterolytic activation of H_2 is key to designing new systems for H_2 production, particularly critical water-splitting pathways based on solar and other alternate energies. Also vital to the function and understanding of H_2ases are the notions that H_2 coordination is reversible and H_2 splitting and formation are mechanistically reversible and applicable in synthetic systems. The growth of new systems for heterolytic H_2 activation has seemingly been exponential and has even now been extended to main-group compounds (e.g., "frustrated Lewis pairs").[123] The "simple" hydrogen atom, whether neutral, protonic, or hydridic, is remarkably complex in its bonding, chemistry, and extraordinary dynamics, and there would seem to be no limit to potential schemes leading to H_2 production. As in nature, the best way to store energy is in chemical bonds, particularly the very strong H−H bond that can provide 143 MJ/kg, as emphasized by Nocera.[8] Splitting only the amount of water in an average-size swimming pool (per second) would provide enough H_2-based energy to power the entire planet. However, major modeling and design challenges remain, and a complete embodiment of both the structure and function of the hydrogenases is still absent. Important questions still exist: is molecular H_2 ligated to Fe at any stage during turnover and do bridging hydride intermediates have a role? Is there a bridging NH dithiolate and would it function in the heterolytic formation/splitting of H_2? To put everything in final perspective, these questions involve only the biomimetic modeling aspect of the less demanding H_2-producing half-reaction of water splitting, whereas the associated oxygen cycle may prove to be even more challenging.

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