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Artificial Hydrogenases

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Abstract

Decades of biophysical study on the hydrogenase (H₂ase) enzymes have yielded sufficient information to guide the synthesis of analogues of their active sites. Three families of enzymes serve as inspiration for this work: the [FeFe]-, [NiFe]-, and [Fe]-H₂ases, all of which feature iron centers bound to both CO and thiolate. Artificial H₂ases effect the oxidation of H₂ and the reverse reaction, the reduction of protons. These reactions occur via the intermediacy of metal hydrides. The inclusion of amine bases within the catalysts is an important design feature that is emulated in related bioinspired catalysts. Continuing challenges are the low reactivity of H₂ towards biomimetic H₂ases.

Introduction

Hydrogenases (H₂ases) are enzymes that catalyze the interconversion of protons and electrons with H₂. [1] They exist in a variety of bacterial and archaeal organisms where they dispose of reducing equivalents as gaseous H₂ (a waste product!) or oxidize H₂ in processes that are coupled to the reduction of an oxidant such as sulfate. [2] Otherwise, H₂ is inert in most biological contexts. The ability of evolutionarily primitive organisms to efficiently process H₂ reflects the reducing environment assumed for early Earth. [2] The biochemistry underpinning such organisms is potentially relevant to a variety of technologies that use hydrogen, either directly (e.g., hydrogenations of alkenes) or indirectly (e.g., conversion of nitrogen into ammonia using natural gas). New technologies could, in principle, be based on the active sites of the H₂ases, which has encouraged efforts to replicate their behavior in vitro. Furthermore, a mechanistic understanding of these enzymatic processes could underpin therapies for certain bacterial infections. [3]

Hydrogen is a potential energy vector for the future. New production, storage, and utilization technologies are needed to enable this “hydrogen economy.” [4] Study of artificial H₂ases could contribute solutions to all of these activities. Hydrogen is currently produced from hydrocarbons by steam reforming. The process is estimated to be 60–85% energy-efficient and uses Ni catalysts. [5] Carbon-neutral routes to H₂ mainly rely on the decomposition of water. High temperature electrolysis is even more efficient than steam reforming but is not competitive because of the high price of electricity. Ultimately, H₂-producing electrolyzers are likely to be powered by solar energy. [6]

Artificial H₂ases are metal complexes that exhibit at least some of the catalytic properties of the enzymes. Their design is informed by structural biology. Targeted properties for artificial H₂ases include that they be (i) inexpensive, (ii) efficient (i.e., operate at low overpotentials and rates of thousands of moles of H₂ produced per mole of catalyst per second), and (iii) rugged.

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[7] Enthusiasm for catalysts derived from “earth-abundant metals” (e.g., Fe, Ni, possibly Co) is high,[8] but it should be noted that iron- and cobalt-based catalysts have often been displaced in favor of expensive platinum-metal catalysts.[9] Artificial H₂ases derived from nonprecious metals remains the primary focus.[10] In Nature, there are three classes of H₂ase, each designated by the metal content of their active sites: [FeFe], [NiFe], and [Fe].

“H₂ases cleave H₂ *heterolytically*, which means that H₂ is cleaved into H[−] and H⁺; H[−] is bound to the metal, and H⁺ is bound to a base or released to the solvent. In contrast, low-valent platinum metals typically excel at homolytic activation (“oxidative addition”) of H₂, in which H₂ is reduced into two equivalents of metal bound H[−] while the metal is oxidized. (Figure 1). [11] H[−] binds to metals in two main ways: (i) as a “terminal hydride” (i.e. M-H) or (ii) as a “bridging hydride” (i.e. M-H-M). [FeFe]-H₂ases operate via terminal hydrides, and the [NiFe]-H₂ases feature μ -hydrides (“ μ -hydrides”). It is likely that μ -hydrides arise via transient terminal hydrides. Metal hydrides can be oxidized by two electrons, whereupon the H[−] ligand is converted to H⁺. Heterolytic activation is ideal for the hydrogenation of polar substrates[12], as is practiced by the [Fe]-H₂ase, and for the extraction of electrons for chemical work, as is practiced by the other two H₂ases.[10] Heterolytic activation is an essential step in H₂-based fuel cells utilizing first row metals.

Artificial H₂ases based on [FeFe]-H₂ases

The [FeFe] H₂ases utilize two key states in the catalytic cycle, an oxidized state (H_{ox}) that is poised to convert H₂ to protons (as required for an H₂-based fuel cell), and a reduced state (H_{red}) that is poised to convert protons to H₂ (as required for energy storage). Artificial [FeFe]-H₂ases have the formulae Fe₂[(SCH₂)₂X](CO)_{6-x}L_x where L is a Lewis basic ligand, often organophosphines (R₃P); Nature employs CN[−] and an 4Fe-4S cluster for L (Figure 2), but artificial [FeFe]-H₂ases almost always dispense with such complicating ligands.[13] The dithiolate can be varied from [−]SCH₂CH₂S[−] to [−]SCH₂XCH₂S[−], where X = CH₂, O, or the biomimetic[14] NR' (R' = H, alkyl, aryl). For the design of artificial H₂ases, the amine-functionality not only assists with proton shuttling (see below), but provides a convenient site for attachment of other groups such as photosensitizers. The redox potentials of catalysts can be adjusted by variations in the ligands.[15]

It is clear that protonation of many artificial [FeFe]-H₂ases occurs at a single Fe center,[17–19] as foretold by biophysical studies. It is tempting to speculate that catalysis via “terminal protonation” is evolutionarily advantaged. Relative to protonation of the Fe-Fe bond, the reorganizational energy associated with proton transfer at one metal may be smaller and the protonation/deprotonation rates would be correspondingly higher.[20] Additional advantages to terminal hydrides are that they reduce at milder potentials[18] and are adjacent to the dithiolate cofactor (see below). The majority of artificial [FeFe]-H₂ases feature hydrides that *bridge* the two Fe centers, the so-called μ -hydrides. In terms of structure, μ -hydrides appear more relevant to the [NiFe]-H₂ases, not the [FeFe]-H₂ases where the bridging site is occupied by a CO ligand. Despite their abiological stereochemistry, some diiron μ -hydrides are excellent catalysts for H₂ evolution.[21]

Most [FeFe]-inspired artificial H₂ases require additional energy beyond the thermodynamic minimum, thus they operate at large overpotentials (>500 mV). High overpotentials are often manifested by the requirement that H₂ evolution only occurs with strong acids. Protonations can be very slow with weaker acids, e.g. those with pK_a's close to neutral pH, resulting in low catalytic rates.[22,23] Terminal protonation of [FeFe] models requires that the diiron center distort to a ‘rotated’ form that is primed for protonation. Adopting this rotated form has been calculated to require up to 10 kcal/mol, which may also contribute to the overpotential.[24]

Recent work shows that both steric bulk[25] and electronic asymmetry[26] can lower the barriers to rotation.

In artificial H₂ases, the amine has recently been shown to strongly influence the rates of proton transfer to and from the diiron center. Weak acids are slow to protonate typical substituted metal centers, but complexes of the type Fe₂((SCH₂)₂NH)(CO)₂(PR₃)₄ readily catalyze H₂ evolution even from weak acids via intermediacy of Fe(II)Fe(II) hydrides (Figure 3).[27] Similarly, with suitable bases, such amine-complemented-hydrides readily deprotonate. The ease of these acid-base reactions is attributable to the low barriers associated with protonation at amines and the easy proton relay from the amine to the nearby Fe(I). The amine relay strategy promises also to be applicable to catalysts that operate via μ -hydrides.[28]

Models for the H_{ox} state have been prepared simply by oxidizing diiron(I) complexes,[16,29] These mixed valence models fail to react readily with H₂. [30] One clue into their flawed design is that these models bind CO only weakly, whereas the enzyme is strongly inhibited by CO. The H₂-binding site appears to be Fe(I) but models and theory show that H₂ prefers Fe(II) (ferrous).[31] The binding of H₂ could conceivably be coupled to oxidation at Fe (reader does not know what distal/proximal mean in the enzyme) to the Fe(II) via proton-coupled electron transfer (PCET).[32] This analysis suggests more elaborate designs for the next-generation artificial [FeFe]-H₂ases.

With the ultimate goal of obtaining H₂ from water or possibly other renewable materials, much work has focused on photocatalytic ensembles containing mimics of the [FeFe]-H₂ase active site. Relevant parameters include the redox properties and robustness of the diiron center and the sensitizer.[33–35] Hydrogen has recently been obtained with hundreds of turnovers by irradiation (455–850 nm) of solutions containing ascorbate, Ru(bipy)₃²⁺, and the catalyst Fe₂(S₂C₆H₂Cl₂)(CO)₆. [36] H₂ evolution occurs at the diiron center which is reduced by Ru(bipy)₃⁺, which in turn is generated by ascorbate reduction of the photoexcited dication *Ru(bipy)₃²⁺. Thus, while the source of the reducing equivalents differs from the usual electrochemical experiments, the overall chemistry of the diiron hydrides remains the same as in thermal reactions. This area is poised for rapid growth with a focus on robustness, rates, photon energies, and the source of the reducing equivalents.

Artificial [NiFe]-H₂ases

Artificial H₂ases based on the active site of the [NiFe] H₂ases are obvious targets because this enzyme is widespread and has been characterized crystallographically to high precision.[37, 38] As for the [FeFe]-H₂ases, only a few states are catalytically relevant.[1] Advanced structural models feature ferrous cyanide centers bound to nickel(II) dithiolates.[39] The compound [(CO)₃Fe(μ -S₂C₃H₆)(μ -H)Ni(dppe)]BF₄ is a unique hydride-containing model. This salt catalyzes the evolution of H₂ from acetonitrile solutions of trifluoroacetic acid (pK_a = 12.65, E°(H⁺/H₂) = -1.36 vs NHE) at -1.83 V vs NHE.[40] The overpotential of ~450 mV is competitive with most artificial [FeFe]-H₂ases. The mechanism of proton reduction catalysis is partially clarified by the fact that the hydride complex itself is unreactive toward protons; it must first be reduced (Figure 4).

The reverse reaction, hydrogen oxidation by Ni-Fe thiolates, has not yet been achieved. Solutions to this challenge can be expected with the development of unsaturated models with biologically relevant oxidation states, i.e. Ni(II)Fe(II) and Ni(III)Fe(II).

Artificial [Fe]-H₂ases

The third H₂ase is the [Fe]-H₂ase, also called Hmd (H₂-forming methylene-tetrahydromethanopterin dehydrogenase). Because Hmd contains only a single metal and no

redox-cofactors, it is an unusual platform for the activation of H₂. Hmd-inspired artificial H₂ases however pose challenging targets since the carbocationic substrate participates in the H₂ activation process.[41] Artificial H₂ases inspired by Hmd are just appearing.[42,43] As with the other artificial H₂ases, phosphine ligands are useful as illustrated by the most advanced model, which features a phosphine-stabilized Fe-acyl thiolate carbonyl center.[44] Both the structural biology and literature precedents suggest that the pyridone group is mechanistically important (Scheme 1), but such modules have not yet been installed into catalytic systems.

Artificial H₂ases that are “bioinspired” but not biomimetic

Many artificial H₂ases are inspired by biology but bear little structural similarity to the active sites of the enzymes. DuBois *et al.* in particular have pioneered the development of artificial H₂ases using “PNP” ligands wherein ordinary bidentate diphosphine ligands are complemented by non-coordinating amine bases.[45] Catalysis by Ni-PNP complexes is sharply accelerated relative to complexes of ordinary diphosphines. The reactions of [Ni (PNP)₂]²⁺ complexes are facilitated because they require two components (i.e. complex + H⁺ or H₂) vs. three-component processes (i.e. complex + H₂/H⁺ + base). Complexes of diaminodiphosphines (P₂N₂'s, Scheme 2) are even more active, producing H₂ at 350 s⁻¹, about 50% of the enzymatic rate. The high activity of the P₂N₂-Ni systems is attributed to their structure, which position amines near the H₂⁻ binding site on Ni(II). These Ni-PNP systems have now been interfaced with conducting carbon nanotubes to give efficient, low-overpotential catalysts for both the production *and* oxidation of H₂. [46]

The excitement over artificial H₂ases has revived interest in the ability of cobaloximes to catalyze H₂ evolution.[47] Modified cobaloximes are excellent electrocatalysts in terms of high rates and low overpotentials.[48] These catalysts are structurally austere: the metal carries a single hydride with sparse adjacent functionality. They owe their activity to the ability of the imino ligands (RC=NR') to stabilize the metal in several oxidation states, a property reminiscent of the corrinoid ligand in vitamin B₁₂-dependent enzymes. Mechanisms for H₂ evolution remain slightly mysterious since metal hydride intermediates are not observed. Kinetic analyses indicate that this family of artificial H₂ases operate, at least in part, via bimetallic mechanisms, i.e., 2 L_xM-H 2 L_xM + H₂. The dioxime platform is particularly amenable to optimization leading to rugged catalysts with both cobalt and nickel.[49]

Conclusions

Study of artificial H₂ases is motivated by topical interest in energy-related catalysis, but, equally importantly, progress has been underpinned by a multiyear investment in the fundamental coordination chemistry of H₂. [11] Relative to the enzymes, the great advantage offered by artificial H₂ases derives from the fact that their properties (redox potentials, solubility, basicity) can be manipulated with some degree of predictability. Furthermore, such complexes can often be prepared on multigram scale (Figure 5).

Certain trends can be anticipated. Most obviously, the active sites of all H₂ases feature Fe-SR-CO centers.[41] A wide range of Fe-S-CO compounds await analysis. Such approaches will also be relevant to the design of rugged catalyst as required for practical photocatalysis.

Most artificial H₂ases exhibit only weak affinities for H₂, thus limiting prospects for oxidation of hydrogen and related applications. The recently popularized concept of “frustrated Lewis pairs” provides guidance on this issue.[50] Within this paradigm, a Lewis acid (usually a cationic metal center) and Lewis base are constrained within close proximity but are prevented from combining, as illustrated by complexes of the PNP and azadithiolate ligands.[45]

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heterolytic activation:

hydride oxidation:

homolytic activation:

Figure 1.

Simplified stoichiometries for the homolytic and heterolytic activation of H_2 , ligands are omitted. In H_2 ases, the initial heterolytic step is followed by oxidation of the resulting hydride.

Figure 2.

Proposed location of hydride ligands during catalysis by [FeFe]-, [NiFe]-, and [Fe]-H₂ases, oxidation states and charges not shown.[16]

Figure 3.
Pathway for H₂ evolution from an catalysts inspired by the [FeFe]-H₂ase.[16]

Figure 4.

Top: Possible pathway for reduction of protons by an artificial $[\text{NiFe}]\text{H}_2\text{ase}$. Bottom: protonation a $\text{Ni(I)}-\text{Fe(I)}$ complex with $\text{CF}_3\text{CO}_2\text{H}$ to give a H^- -hydride.

Figure 5.
A sample of $\text{Fe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CO})_6$, an artificial hydrogenase.

Scheme 1.
Proposed equilibrium between pyridone-H₂ and hydroxypyridine-hydride complexes.

Scheme 2.

Proposed equilibrium between a nickel(II) aminodiphosphine complex of H_2 and the related diammonium nickel(0) derivative.