Reducing CO_2 to HCO_2^- at Mild Potentials: Lessons from Formate Dehydrogenase

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ABSTRACT: The catalytic reduction of CO_2 to HCO_2^- requires a formal transfer of a hydride (two electrons, one proton). Synthetic approaches for inorganic molecular catalysts have exclusively relied on classic metal hydrides, where the proton and electrons originate from the metal (via heterolytic cleavage of an M-H bond). An analysis of the scaling relationships that exist in classic metal hydrides reveal that hydride donors sufficiently hydridic to perform CO_2 reduction are only accessible at very reducing electrochemical potentials, which is consistent with known synthetic electrocatalysts. By comparison, the formate dehydrogenase enzymes operate at relatively mild potentials. In contrast to reported synthetic catalysts, none of the major mechanistic proposals for hydride transfer in formate dehydrogenase proceed through a classic metal hydride. Instead, they invoke formal hydride transfer from an orthogonal or bi-directional mechanism, where the proton and electron are not co-located. We discuss the thermodynamic advantages of this approach for favoring CO_2 reduction at mild potentials, along with guidelines for replicating this strategy in synthetic systems.

Electricity is the most common type of energy produced from renewable sources (e.g. solar, wind, hydroelectric). However, our current energy infrastructure relies on the use of easily stored and transportable chemical fuels. The gap between renewable electricity and our chemical fuel infrastructure can be bridged through electrocatalytic reduction of substrates such as CO_2 to more energy dense chemical fuels.[1]

One chemical fuel of interest is formate or formic acid, which can be generated by 2 e^- reduction of CO_2 and C-H bond formation. Both formate and formic acid can be used directly in a fuel cell, and the latter is also a convenient liquid carrier of hydrogen.[2, 3] As CO_2 conversion to formate involves a formal hydride transfer, metal hydrides are a commonly proposed intermediate in successful inorganic heterogeneous and homogeneous electrocatalysts.

An analysis of our work[4] and others[5, 6] suggests that homogeneous metal hydrides sufficiently hydridic to reduce CO_2 are only accessible at potentials more negative than -1.6 V vs. SHE. In contrast, the natural enzyme formate dehydrogenase (FDH) catalyzes the reversible conversion of CO_2 to HCO_2^- near the thermodynamic potential of -0.4 V vs SHE at pH 6.5.[7]

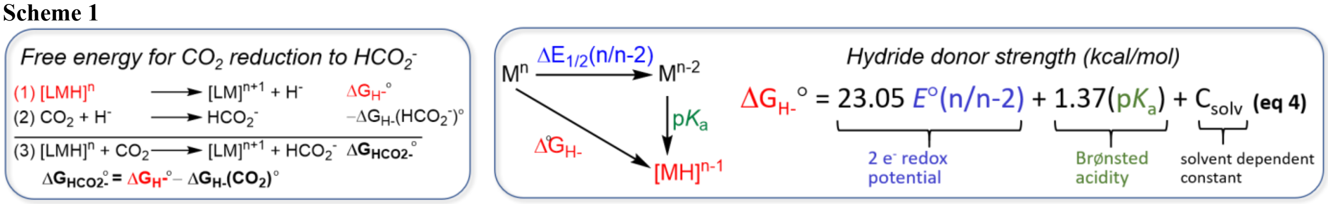
In this study, we discuss how *intrinsic* properties of metal hydrides result in inherent challenges to generating strong metal hydride donors for CO_2 reduction at mild potentials. These limitations are discussed in the context of proposed mechanisms of FDH enzymes. We describe an enzyme-inspired strategy to access strong hydride donors at mild potentials in synthetic inorganic systems.

Hydride transfer is also an essential component of many other reactions aside from CO_2 reduction to HCO_2^-, including reduction of aldehydes, ketones, alkenes, imines, and alkyl halides.[8-15] A bio-inspired strategy of generating strong hydride donors at mild potentials would be broadly useful for minimizing the overpotential for electrocatalysts for many other applications.

Thermodynamic Considerations. The free energy of hydride transfer from a donor is represented by its hydricity, ΔG_{H^-} (Scheme 1, eq 1) From the thermodynamic scheme shown in Scheme 1 (eq 1-3), the free energy of CO_2 reduction to HCO_2^- is dependent on the hydricity of HCO_2^- and the donor.[4-6, 16, 17] The reaction is exergonic if the donor strength is greater (smaller ΔG_{H^-}) than that of HCO_2^-(eq 3).[18] The relationship between thermodynamic hydricity and CO_2 reduction to HCO_2^- was first described by Dubois *et al.* in 2000[18] and has been discussed in detail in multiple reviews and perspectives for transition metal[5, 6, 19] and organic hydride donors.[20] In this analysis we focus on transition metal hydrides as they represent all of the current homogeneous electrocatalysts for CO_2 reduction to formate.

The thermodynamic relationship for hydride donor strength is derived from a Bordwell-type square scheme as

Scheme 1



shown in eq 4 in Scheme 1.[21-25] From eq 4, two metal hydride-dependent properties impact hydricity: the two-electron redox potential (blue) and the pK_a (green). The third quantity (C_{solv}) is a solvent-dependent constant based on the H^+/H^- redox potential.[26]

Efforts to increase hydride donor strength (lower ΔG_{H^-}) for transition metal hydrides have broadly focused on utilizing inductive ligand effects, such as electron-donating ligands,[27-30] or adjusting the ligand geometry through changes in bite angle.[31-33] These modifications adjust the redox potential to more negative values, which in turn increases the hydricity. A consequence of this approach is that strong hydride donors are only accessible at fairly negative potentials. We illustrate our argument using data that has been collected for metal hydrides in CH_3CN, the solvent in which the most measurements have been made.[5, 34, 35] Figure 1 (top) depicts the relationship between measured hydricity values and an average of their respective two-electron reduction potential (also found in Table S1). As would be expected given the relationship described by eq 4 in Scheme 1, there is a strong correlation with more negative redox potentials and increased hydride donor strength. The pink portion of the graph represents hydride donors that are insufficiently hydridic to make a C-H bond with CO_2 ($\Delta G° > 0$) for eq 3 in Scheme 1. The purple portions of the graph delineate hydricity values that can reduce CO_2 to formate. As shown, these are only accessible at an average two-electron potentials that is more negative than ~ −1.5 V vs $Fe(C_5H_5)^{+/0}$. Berben *et al*. has reported the most positive potential for an electrocatalyst for CO_2 reduction to HCO_2^- (-1.6 V vs $Fe(C_5H_5)^{+/0}$ in CH_3CN by $[Fe_4N(CO)_{12}]^-$).[19]

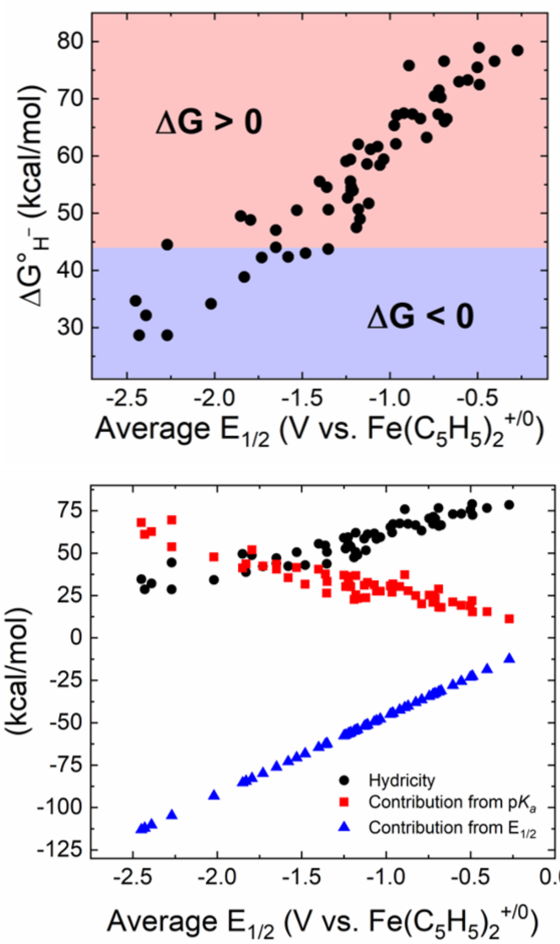
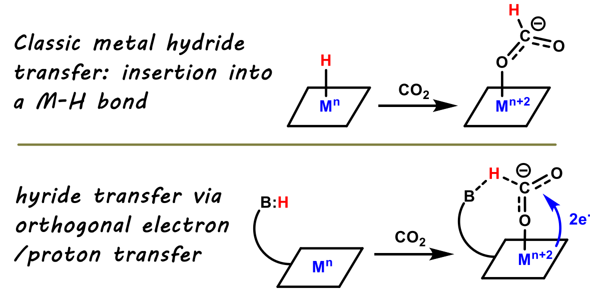


Figure 1. (Top) Average redox potential of metal hydrides versus their hydricity value (ΔG_{H^-}) in CH_3CN. The ΔG_{H^-} of HCO_2^- in CH_3CN is 44; metal hydrides with $\Delta G_{H^-} < 44$ kcal/mol will reduce CO_2 to HCO_2^- (purple region) and metal hydrides with $\Delta G_{H^-} > 44$ will not (pink region) according to eq 4 in Scheme 1. (Bottom) Contribution to ΔG_{H^-} (black circles) of metal hydrides from their 2e$^-$ redox potential (blue triangles) and pK_a (red squares) plotted by their average redox potentials. All data is in CH_3CN. Data compiled from ref. 5, 34, and 35.

Scheme 2 Two pathways for net H^- transfer.



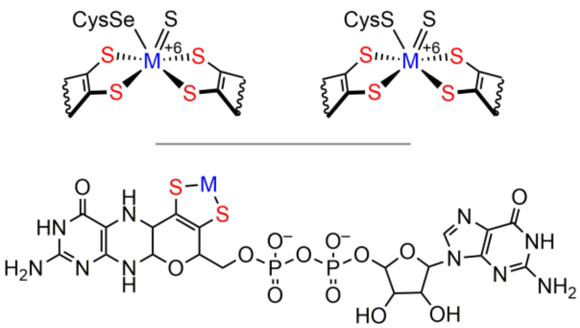
The hydricity values in Figure 1 and the proposed intermediates in known catalysts are all classic metal hydrides – *where both the proton and electrons come from the metal* (Scheme 2, top). The black circles in Figure 1 (top and bottom) display the same data, illustrating metal hydrides become more hydridic with decreasing redox potential. However, hydricity is the sum of both the two-electron redox potential *and* the pK_a of the donor complex.

The redox potential and pK_a are *anti-correlated* in their contribution to hydricity (the pK_a of the metal hydride increases with redox potential, Figure S1).[36] The respective contributions of the redox potential and pK_a to hydricity is illustrated in Figure 1 (bottom). The blue triangles represent the contribution to the hydricity from the redox potential. The red squares represent the contribution of the metal hydride pK_a to the hydride donor strength. The black circles represent the net hydricity, which combines both the redox and pK_a contribution, along with the constant C_{solv} of 79.6 kcal/mol in CH_3CN according to eq 4 in Scheme 1. Ultimately the redox potential is the dominant contributor to hydricity. However, metal hydrides require increasingly negative redox potentials to counteract the effect of increasing pK_a, which impacts the hydricity in the reverse direction.[37] Since a scaling relationships exists for pK_a and the redox potential of the metal (Figure S1), it is not possible to adjust one without impacting the other. Although the data presented in Figure 1 is for CH_3CN, limited aqueous data has also been published. The property trends exhibited by metal hydrides in water are similar, but over a smaller pK_a range (Figure S2-S4, Table S1). Thus, electrocatalytic generation of strong classic metal hydride donors *requires* very negative potentials, of which the anti-correlation between redox potential and pK_a is a significant contributor.

Proposed Mechanisms in Formate Dehydrogenase.

In nature, formate dehydrogenase (FDH) enzymes primarily function to oxidize formate to CO_2.[38, 39] However, the Mo and W containing enzymes also exhibit reversible elec-

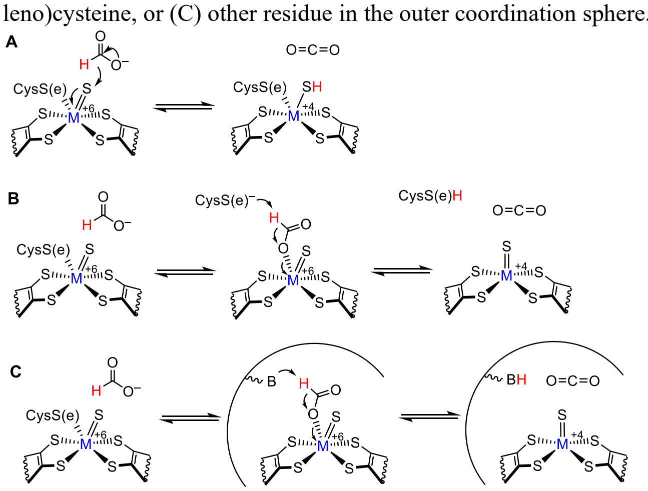
Scheme 3. M = Mo or W. (Top) Active site of formate dehydrogenase in the resting (oxidized) state with abbreviated molybdopterin ligands, which is fully depicted (bottom).



trocatalytic activity between CO_2 to HCO_2^- near the thermodynamic potential with quantitative selectivity (Faradaic efficiency).[38-41] For example, FDH1 from the anaerobic bacterium *Syntrophobacter fumaroxidans* electrocatalyzes the reduction of CO_2 to formate at rates of 10^2 s^{-1} with negligible overpotential.[7] The active site of the molybdenum (Mo-FDHs) and tungsten-dependent enzymes (W-FDHs) is depicted in Scheme 3. In each case, the Mo or W atom is coordinated by two molybdopterin ligands, which resemble dithiolene ligands, and a terminal sulfido. The primary coordination sphere is completed with a sulfur or selenium atom from a cysteine or selenocysteine residue, respectively to form a distorted trigonal prismatic geometry. [38, 39]

While the mechanism of CO_2 and HCO_2^- conversion in tungsten and molybdenum-based formate dehydrogenase enzymes is still under debate, multiple mechanisms have been proposed.[38, 42-44] Of these, only one proposed mechanism invokes a classic metal hydride,[45] which is based on a computational study and is not consistent with the known chemistry of Mo/W enzymes.[38] Instead of a classic metal hydride intermediate, the major mechanistic proposals state that the electrons and protons are not co-located on the metal. In these mechanisms, the Mo or W center cycles between a +4 and +6 oxidation state. The proton required to complete the hydride comes from a ligand or the secondary

Scheme 4. A representation of proposed mechanisms for reversible formate oxidation by formate dehydrogenase enzymes. In each case, oxidation of formate results in two electron transfer to the metal and proton transfer to (A) a terminal sulfido, (B) de-coordinated (seleno)cysteine, or (C) other residue in the outer coordination sphere.



coordination sphere (Scheme 4). A recent mechanism by Moura *et al.*[38] suggests the proton inventory is maintained at a terminal sulfido (Scheme 4a). Another mechanism suggest the (seleno)cysteine dissociates from the metal in order to accept the proton (Scheme 4b).[46] In other mechanistic proposals, the proton resides on an outer-sphere, histidine residue,[47, 48] arginine residue,[49] or cysteine residue (Scheme 4c).[41, 50] In contrast to classic metal hydrides, we classify this type of net hydride transfer from different electron and proton donors as orthogonal hydride transfer (Scheme 2). In these cases, the net hydricity is dependent on the two-electron redox potential of the metal and the pK_a of the proton donor. Hydricity (ΔG_{H-}) is a state function, so the thermodynamic driving force is not dependent on the pathway of the individual components (i.e. protons, electrons), provided there is net hydride transfer.

FDH also exhibits negligible parasitic H_2 evolution during CO_2 reduction in an otherwise reducing environment.[7, 49, 51] We speculate that orthogonal proton-electron transfer of a net hydride contributes to the high selectivity by spatially separating the electron and proton source. A proton source positioned an appropriate distance from the electron source (metal) could transfer both proton and electrons to a larger CO_2 substrate that can 'bridge the gap' between them. Conversely, the smaller size of a proton would prevent it from accepting the necessary electrons/protons for H_2 evolution.

Orthogonal Hydride Transfer. As evidenced by the broad use of classic metal hydrides for H^- transfer for reduction in synthetic chemistry, orthogonal hydride transfer is a non-canonical approach (with exceptions discussed below). However, spatial separation of the redox site and acid/base site is commonly cited in hydrogen atom transfer reactions (often described as orthogonal, bidirectional, or multisite).[52-64]

Separation of the proton and electron source permits independent tuning of the redox potential and pK_a to satisfy the thermodynamic requirements for making or breaking X-H bonds (where X = C, N, O) at mild potentials. For example, challenging C-H bonds (with high bond dissociation free energies) are cleaved at relatively mild potentials at the active

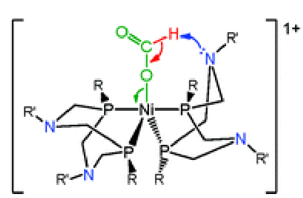


Figure 2. Proposed intermediate/mechanism for the highest performing abundant-metal formate oxidation electrocatalyst. From ref 79.

site of cytochrome P450s. Thermodynamic studies indicate hydrogen atom transfer at less oxidizing potentials are enabled by utilizing a highly basic metal oxo as the proton acceptor.[65-67] There are also recent examples in synthetic catalysts where the pK_a and redox potential were tuned independently in orthogonal proton and electron transfer to cleave a suite of challenging bonds, including O-H, N-H, and C-H bonds.[68-77]

From our analysis of scaling relationships in classic metal hydrides, it is clear that orthogonal hydride transfer can offer clear advantages for generating hydride donors at milder potentials.

Synthetic Examples. Although orthogonal hydride transfer has been minimally pursued in synthetic systems, a few examples support the feasibility of this approach. A proposed mechanism for one of the most active molecular electrocatalysts (Figure 2) for the reverse reaction, formate oxidation, invokes orthogonal hydride transfer.[78, 79] The electrocatalytic activity of a series of nickel bis(diphosphine) complexes with a distal pendant amine for formate oxidation were characterized. The reaction involves a net hydride transfer; however, the rate of catalysis for this series of complexes displayed an *inverse free energy relationship* with the thermodynamic driving force (or hydricity of the nickel complexes). Instead, the rate of catalysis exhibited a positive correlation with the BrØnsted basicity of the pendant base, indicating that while the 2 e^- redox event is mediated through the metal, the H^+ is accepted by the pendant base as shown in the proposed mechanism in Figure 2. The analogous complexes that lack pendant bases are no longer active, underscoring the importance of a distal proton relay in mediating orthogonal movement of the proton and electrons.

A few examples of "orthogonal hydrides" in transition metal complexes have been reported. Dimolybdenum complexes store multiple hydride equivalents through metal reduction and accumulation of protons onto bridging sulfur ligands.[80] Attempts at isolating the metal hydride $[Rh(Cp^*)(bpy)H]^+$, the putative intermediate in transfer hydrogenation[81] and artificial 1,4-NADH regeneration cycles,[82-84] unexpectedly resulted in $[Rh(Cp^*H)(bpy)]^+$, where the proton resides on the Cp* ring.[85, 86] Combined experimental and computational studies by Nocera and Hammes-Schiffer indicate H_2 evolution in several redox active transition metal complexes with pendant acid functionalities likely proceed via metal-ligand cooperation instead of a metal hydride intermediate.[87, 88] Oxidation of organic substrates by some high-valent metal oxo or bimetallic μ-oxo complexes are also believed to involve protonation of the oxo ligand and formal reduction at the metal.[89-95] Additionally, many redox-active ligand frameworks contain proton reservoirs that participate in hydrogen atom or hydride transfer chemistry.[96-105]

To maintain the same hydride donor strength, shifting the redox potential positive requires lowering the pK_a of the proton donor. According to the relationship in eq 4 in Scheme 1, a 100 mV reduction of the average redox potential requires reducing the pK_a of the proton donor by 3.36 units to maintain the same hydride donor strength. Thus, a strong hydride donor accessible at mild potentials would require the pK_a of the proton donor to be low (more acidic). A few practical considerations include the limited accessibility of some pK_a values, depending on the solvent. Additionally, the location of the donor is also important for concerted proton electron transfer to a substrate.

The examples of orthogonal hydride transfer in synthetic systems provide models for designing new catalysts. In some cases, a ligand bound directly to the metal such as terminal or bridging O/S groups[80, 89-95] or Cp ring[85, 86] can serve as a proton reservoir. In this motif, it is more difficult to independently tune the pK_a with the redox properties, as the former would be expected to have some correlation with the latter. However, examples using pendant bases[78, 79] or protonation on ligands further from the metal[87, 88] indicate that spatial separation is possible, which would allow more control over the two components that contribute to the net hydride donor strength.

Outlook

We analyzed the thermodynamics of classic metal hydrides and the two properties that contribute to their hydride donor strength, their redox potential and pK_a. Scaling relationships between the two properties indicate that hydride donor strength increases with more negative potentials, leading to intrinsic challenges for strong hydride donor generation at mild potentials.

It is natural that in our quest to discover synthetic catalysts for efficient conversion of feedstock to fuels under mild conditions we look to biological systems. After all, enzymes have evolved to catalyze many of our targeted reactions with our desired metrics. Over the last two decades, hydrogenase enzymes have inspired synthetic reversible hydrogen evolution catalysts that rival their activity at low overpotentials.[16, 106] In a similar fashion, we can learn from the formate dehydrogenase enzymes to design improved catalysts for CO_2 reduction to formate. Currently accepted mechanisms all propose orthogonal hydride transfer, where the proton and electrons are not co-located. By separating the proton and electron source, the scaling relationships that govern hydricity in classic metal hydrides can be broken. Thus, a bio-inspired approach to hydride transfer may be the route to achieving catalysis at mild potentials.

ASSOCIATED CONTENT

Supporting Information. Data collected from the literature on metal hydricity values, redox potentials, and pK_a and graphic representations can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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