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Modulation of H+/H- Exchange of Iridium-hydride 2-Hydroxypyridine Complexes by Remote Lewis Acids†

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A series of iridium hydride complexes featuring dihydrogen bonding are presented and shown to undergo rapid H+/H- exchange (1240 s^{-1} at 25 °C). We demonstrate that the H+/H- exchange rate can be modified by post-synthetic modification at a remote site using BH$_3$, Zn(C$_6$F$_5$)$_2$, and Me$_3$O[BF$_4$]. This route provides a complementary strategy to traditional methods that rely on pre-metalation modifications to a metal's primary sphere.

The heterolytic activation of dihydrogen is central to both biological and abiological energy conversion/storage schemes.[1] Hydrogenase enzymes exploit extremely rapid and reversible proton/hydride interconversions for energy storage and release.[2] [Fe]-hydrogenase contains a biologically unusual 2-hydroxypyridine motif and this bifunctional ligand has been proposed to serve a unique role; facilitating reversible H$_2$ heterolysis into hydride and proton equivalents (Figure 1A).[3] Our group[4] and others[5] have shown that synthetic complexes featuring 2-hydroxypyridine derived ligands can mediate H+/H- exchange[4c] and promote reversible hydrogenation/dehydrogenation reactions.[5a, 6] Computational studies of [Fe]-hydrogenase have shown that the rate of H$_2$ activation is tunable, and intimately tied to the electronic environment at the iron center, as modulated by subtle perturbations to both the primary and secondary coordination environment.[7]

Assessing the interplay between primary-sphere modifications and secondary-sphere effects that control the reactivity of [Fe]-hydrogenase (and inspired synthetic systems) can provide new design principles to improve activity for

hydrogenative or dehydrogenative reactivity.[8] In analogy to [Fe]-hydrogenase, iridium (III) hydride complexes have low spin d^6 electronic configurations and increased stability.[9] Thus, iridium complexes can be used to assess the extent to which a given H$_2$ transformation may be regulated by subtle changes to the metal electronic environment and/or appended acidic groups.[10]
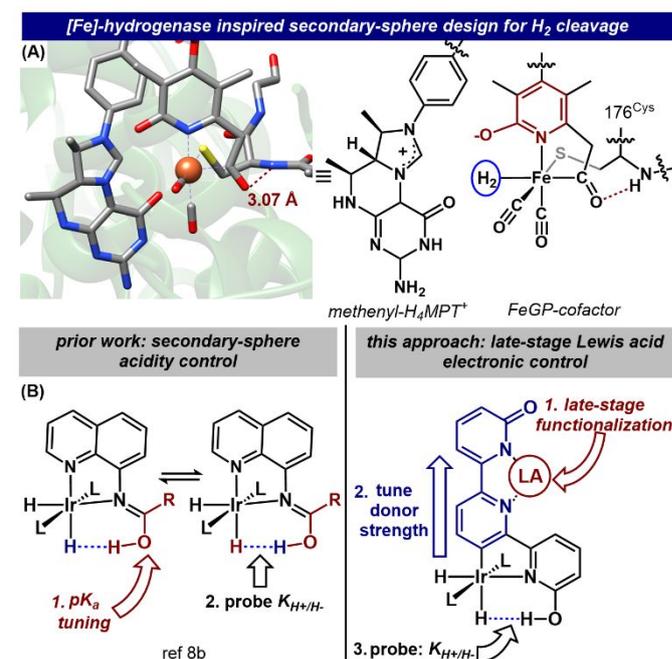

Figure 1. Dihydrogen bond motifs in (A) [Fe]-hydrogenase (Protein Databank: 6hae) and (B) synthetic complexes with pK_a (left) and remote modification control (right).

Transition-metal hydrides engaged in dihydrogen-bonding have been proposed to be key intermediates in heterolytic H$_2$ activation (Figure 1B). Their key reactions, which include H+/H- exchange and (de)hydrogenation catalysis, are sensitive to the supporting ligands (electronic donation[10a] steric hindrance,[10b] and metal cation induced hemilability).[7, 11,12] Most prior examples to tune the H$_2$ heterolysis rate have been through

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modifications to the metal's primary coordination sphere.[8c] As an alternative to inner-sphere electronic modifications, strategies
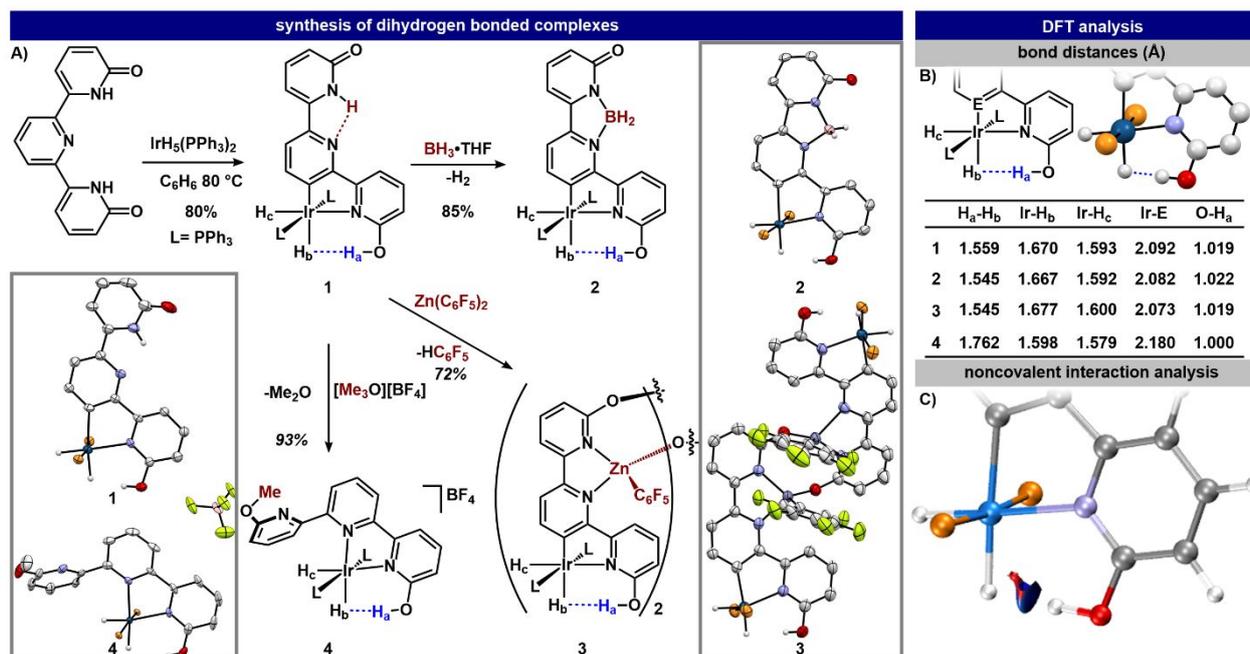

Figure 2. (A) Synthesis and crystal structure of **1**, **2**, **3**, and **4**. Ellipsoids are shown at the 50% probability level and hydrogen atoms bound to carbon, phenyl rings and the BF_4^- anion of **4** are removed for clarity . (B) Calculated primary and secondary-sphere bond distances with representative structure of **1**. (C) Representative dihydrogen bond critical point of **1**.

that functionalize ligands at remote sites have been shown to regulate metal centered electronic properties, and impart large changes to reaction rates[13] and selectivity.[14] To extend this concept, we demonstrate how H^+/H^- exchange rates of dihydrogen bonded iridium hydrides vary as a function of remote functionalization.

To interrogate the extent to which an H_2 heterolysis rate can be tuned by modifications at a remote ligand site, we prepared a series of dihydrogen bonded iridium hydrides. The metalation of 6,6'-dihydroxyterpyridine (dhtp) with $Ir(H)_5(PPh_3)_2$ afforded the rollover C-H activated terpyridine complex $Ir(H)_2(dhtp')(PPh_3)_2$ (**1**) (Figure 2A). Crystallographic analysis indicated that one of the two 2-hydroxypyridine units was not coordinated to iridium and remained in the 2-pyridone tautomeric form. Although the X-ray structure indicated two Ir-H environments, the ^{1}H NMR spectrum at ambient temperature exhibited only one triplet resonance at high field (-17.59 ppm; $^2J_{HP}$ = 16.5 Hz) as well as one low field −*NH* resonance at 10.55 ppm. Upon cooling, two additional broad peaks were resolved: a resonance at 9.94 ppm and a second low field resonance (-11.45 ppm) assigned as H_a and H_b respectively (Figure 2). Analysis of the spin-lattice relaxation times, T_1, of H_a and H_b revealed short (0.18(1) s; 248 to 258 K, 500 MHz), and equivalent values at all measured temperatures, consistent with a dynamic exchange process.

To evaluate how the dihydrogen bonding interaction from the 2-hydroxypyridine group influences the structural dynamics and reactivity of the iridium hydrides, we investigated the H^+/H^- exchange behavior of **1**. Upon addition of 1000 equivalents

CD_3OD to **1**, the NH, H_a, and H_b ^{1}H NMR resonances diminished within 5 minutes. The results are consistent with H/D exchange with the NH and H_a followed by a subsequent D^+/H^- exchange between H_a and H_b. In contrast, no deuterium incorporation at the H_c position was observed after 2 days; inconsistent with dynamic exchange of H_c.[15]

We hypothesized that the interaction between H_a and H_b could be perturbed by altering the electronics at Ir. In addition to a κ-C,N dhtp' primary coordination environment, **1** also features a remote bipyridine-like site (Figure 1B). To modulate H^+/H^- exchange rates, we targeted remote functionalization of the bipyridine-like fragment. We envisioned that induction through the pyridone *para* to the Ir-C bond would strongly perturb donor properties, and thus, the basicity of the iridium hydride, H_b. Two Lewis acids were incorporated into the bipyridine-like site. The reaction of **1** with either $NaBH_4$ or $THF•BH_3$ afforded $Ir(H)_2(dhtp-BH_2)(PPh_3)_2$ (**2**) (Figure 2A), which was characterized by X-ray crystallography. Addition of $Zn(C_6F_5)_2$ to **1** afforded the dimeric compound $[Ir(H)_2(dhtp-Zn(C_6F_5))(PPh_3)_2]_2$ (**3**) (Figure 2) with loss of C_6F_5H (Figure S35). Analysis of the $^{31}P\{^1H\}$ spectrum of **3** revealed two signals, consistent with a dimeric structure in solution.[16] To maximize the electron withdrawing ability of the remote functionalization partner, we targeted an alkylation (CH_3^+) strategy to impart a coulombic charge difference on the ligand. Selective methylation of **1** was achieved using $[Me_3O]BF_4$ to generate $Ir(H)_2(tpy^{OHOMe}- \kappa^2-N,N)(PPh_3)_2BF_4$ (**4**) in good yield (93 %; Figure 2). Importantly, alkylation of the dhtp ligand afforded a primary sphere rearrangement from κ^2-C,N to κ^2-N,N coordination.

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The late-stage functionalized complexes were characterized by NMR spectroscopy to assess dynamic H^+/H^- exchange processes. Both **2** and **3** exhibited similar ^{1}H NMR spectra to **1** at high field: one triplet was observed at room temperature and a second broad singlet appeared upon cooling. For both **2** and **3**, a single low field resonance appeared upon cooling (10.41 ppm and 9.80 ppm respectively), consistent with only small changes to the pendent hydroxyl group acidity, compared to **1.** In contrast to **1-3**, the cationic complex **4** exhibited two triplet of doublet high field resonances (-17.66 ppm and -20.27 ppm) at room temperature, each coupling to both each other $^2J(H_b$-$H_c)$ 8 Hz, and to the PPh$_3$ ligands. The high field resonance at -20.16 ppm was identified as H_b by a 1D NOESY detected close contact to H_a; representing an 8.7 ppm shift from **1** upon changing the *trans*-donor ligand.

Since crystallographic determination of H_a-H_b distances are often imprecise, we calculated the H-H distance using the dipolar relaxation contribution to the T_1(min) value.[17] For complexes **1-3**, the T_1 (min) for the H_a and H_b were equivalent and span 0.172 (2) s at 238 K (**2**) to 0.247 (11) at 268 K (**3**) (Figure S4). In contrast, the T_1 values for H_a and H_b of **4** were *inequivalent* (T_1 (min) H_a = 0.369(10) s at 253 K; H_b = 0.200(13) s at 273 K). The corresponding H_a-H_b distances of **1**, **2**, and **4** were calculated[17] to be between 1.8-2.0 Å (Table S8), indicating similar local primary (Ir-(H)$_2$) and secondary sphere 2-hydroxypyridine geometries (See SI for full discussion). We attribute the similar distances for the series to the rigid coordination geometry at Ir imposed by the dhtp ligand scaffold.[18]

Compounds **1**-**3** feature distinct electronic environments at Ir, via remote modification, and thus provide a unique opportunity to examine differences in dihydrogen bonding interactions and H^+/H^- exchange. The short H-H contacts are consistent with a dihydrogen bond interaction and were further supported by detection of through-space ^1J coupling through the dihydrogen bond at low temperatures (Figure S2). The low field resonances of **1**, **2**, and **3** featured $^1J_{HH}$ coupling with values of 6.9 Hz, 8.7 Hz and 6.5 Hz at 238 K respectively. The smaller $^1J_{HH}$ for **2** and **3** and absence of observable coupling for **4** are consistent with weaker dihydrogen bonding interactions than in **1**, imparted by perturbing the *trans*–C ligand donor, and thus Ir-H strength. Combined, the ^{1}H NMR analyses (*vide infra*) provide multiple sets of data that enable the dihydrogen bond interaction to be scrutinized. Data for compounds **1**, **2**, and **3** are consistent with rapid exchange between the H_a and H_b positions. However, the spectral data for **4** (inequivalent T_1 values and no $^1J(H_a$-$H_b)$ coupling) are consistent with a static structure at room and low temperature, despite the close contact analogous to **1-3**.[19] To evaluate the perturbations of H^+/H^- exchange upon remote functionalization, we determined the exchange rates and associated thermodynamic parameters for compounds **1-3**. The rate of H_a/H_b exchange was determined by a variable temperature ^{1}H NMR spin-saturation transfer, where irradiation of H_b caused a loss of signal intensity of H_a.[20] The extrapolated room temperature $\Delta G^\ddagger$ and exchange rates (rate$_{298K}$) were determined through an Eyring analysis (Table 1). For –H, –BH$_2$, –ZnL$_2$, the rate$_{298K}$ are 1240 s^{-1}, 350 s^{-1}, and 390 s$^-$

[1], respectively. A maximum limit for the exchange rate of **4** at 298 K was calculated to be 0.42 s^{-1}.[21] In contrast, complexes **1-3** exhibit the fastest exchange rate among reported Ir-dihydrogen bonds; outcompeting the rate$_{298K}$ = 62.8 s^{-1} for the most acidic iminol quinoline complex.[8b22]

Table 1. Experimental $\Delta G^\ddagger_{298K}$, extrapolated rate of H^+/H^- exchange, H-bond strength (E_{HB}) and NBO charge at Ir of **1-4**.

	$\Delta G^\ddagger_{298K}$ (kcal/mol)	Rate$_{298K}$ (s^{-1})	E_{HB} (kcal/mol)	Ir NBO Charge
1	13.2 (2)	1240 ± 430	-7.2	-1.22
2	14.0(2)	350 ± 120	-7.8	-1.21
3	13.9(2)	390 ± 134	-7.5	-1.23
4	-	< 0.42	-5.1	-1.01

The likely mechanism for H^+/H^- exchange proceeds via deprotonation of the pendent hydroxyl group to afford an intermediate η^2-H_2 complex, which upon rotation is subsequently deprotonated by the pendent 2-pyridone base.[2324] The barrier for the rotation of η^2-H_2 in metal-dihydrogen complexes is generally small (< 3 kcal/mol), relative to proton transfer.[25] Since exchange facilitated by a rigid bidentate ligand requires minimal reorganization energy, the rate of exchange is proposed to be limited by pK_a matching of the η^2-H_2 intermediate and the pendent hydroxyl group. The late-stage functionalization imparts increasing hydricity of H_b across the series - κ^2-*N,N* (CH$_3^+$) < –BH$_2^+$≈ –ZnL$_2$ < –H$^+$ and thus, increasing basicity, favoring deprotonation of the pendent hydroxyl group. For **4**, we propose that the lack of H^+/H^- exchange is due to both the decreased hydricity of H_b (containing a weaker *trans-N* donor), and the cationic charge of the complex. Alternatively, ion pairing effects with the BF$_4^-$ anion in **4** could inhibit intramolecular exchange.[10b2616,36]

To interrogate the impact that ligand functionalization imparts on the electronic structure of **1-4**, we used computational methods. Structure optimization, charge, and bonding analysis were calculated using methods that are highly reliable for both iridium transformations,[27] and H-bonding.[28, 29] To assess the electronic effects from remote functionalization, we evaluated the NBO charges, and found that the perturbations at Ir and H_b track with the exchange behavior of **1-4** (Table 1). Structural analysis of the primary sphere (Figure 2B, Tables S7 and S9) feature Ir-H_b distances that report on the electronic differences of the *trans-* donor ligand: - κ^2-*N,N* (CH$_3^+$) << –BH$_2^+$ ≈ –ZnL$_2$ < –H$^+$, and identical to the observed exchange rates. A *trans-* donor controlled rather than secondary-sphere pK_a controlled exchange is further supported by minimal changes to the calculated H-bond donor proton (H_a) charge for **1-4**. The computational analyses demonstrate that ligand tuning effects of Lewis acids can serve as an important role to effect secondary-sphere facilitated reactions.

To assess how the ligand perturbations influence the H-bond interaction, we analyzed bond critical points[30] along the dihydrogen bond H_a-H_b coordinate (Figure 2C). From the calculated potential energy density at the critical point ($V(r_{BCP})$), we found that the H-bond energies (E_{HB})[31] spanned -7.8 to -5.1 kcal/mol (**2** and **4** respectively). Although the energies for **1-3** (< 1 kcal/mol) did not track with the observed exchange rates, the differences were small and we attribute these to a combination

of the small geometric differences of the Ir-E distances, as well as small electronic changes of the optimized complexes. For instance, compound **2** was optimized to have a slightly shorter Ir–C contact (ΔIr–C = 0.009 Å) than **1**, which repositions the chelating 2-hydroxypyridine ligand fragment for a closer H-bond contact (ΔH_a–H_b = 0.003 Å) and a stronger H-bond interaction. These subtle changes in H-bond energies for **1**-**3** emphasize that discrete remote functionalization from electronic effects can be minor[32] and, in this case, competitive with small geometric changes to the molecules.

In summary, we showed that late stage functionalization of **1** can impart: (1) control of H^+/H^- exchange rate by 1000 s^{-1} and (2) influence the ΔG of proton transfer. The 2-hydroxypyridine ligand exerts an unusually strong dihydrogen bond with the iridium hydrides that influence H_2 heterolysis. Rapid equilibria established for the iridium systems **1-3** are analogous to the low spin d^6 metal center in [Fe]-hydrogenase. The remote electronic perturbation at the metal center further highlights the sensitivity of H_2 heterolysis mechanisms to the ancillary ligands. This approach could provide future applications for late stage modification of (de)hydrogenation catalysts where hydricity fine-tuning could be used to influence proton reduction vs hydrogen oxidation pathways.[33]

Conflicts of interest

There are no conflicts to declare.

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