Inorg. Chem. **2008**, *47*, 395–397

Coordination Chemistry of a Model for the GP Cofactor in the Hmd Hydrogenase: Hydrogen-Bonding and Hydrogen-Transfer Catalysis

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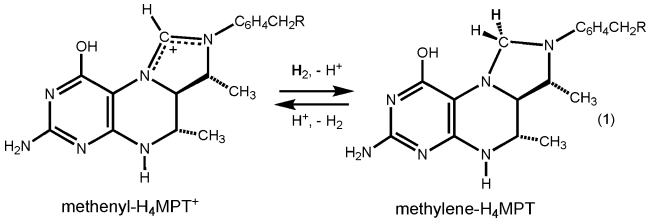
Received September 20, 2007

Cp^*M^{2+} complexes (M = Rh, Ir; Cp* = C_5Me_5) are described for 6-(carboxymethyl)-4-methyl-2-hydroxypyridine ($cmhpH_2$), an analogue of the guanylylpyridone cofactor in the hydrogenase Hmd. Three findings indicate that $Cp^*M(Hcmhp)^+$ stabilizes the binding of hydrogen-bond acceptors to the sixth coordination site: (i) water binds in preference to Cl^-, (ii) the adduct Cp*Rh(cmhp)(2-hydroxypyridine) exhibits a very short intramolecular hydrogen bond (r_{O-O} = 2.38 Å; ^1H NMR δ_H 17.2), and (iii) Cp*Ir(cmhpH)Cl efficiently catalyzes the dehydrogenation of PhCH(OH)Me to PhC(O)Me.

The enzyme H_2-forming methylenetetrahydromethanopterin dehydrogenase, abbreviated Hmd, is associated with a central step in the methanogenesis pathway by archaea grown in nickel-limited media. Hmd catalyzes the reversible reduction of methenyltetrahydromethanopterin (methenyl-H_4MPT$^+$) with H_2 to methylenetetrahydromethanopterin (methylene-H_4MPT) (eq 1).[1]



In the presence of the substrates methylene-H_4MPT or methenyl-H_4MPT$^+$, Hmd also catalyzes the exchange of D_2 with H_2O. Thus, Hmd can be viewed as a "third" hydrogenase, supplementing the well-known [NiFe] and [FeFe] hydrogenases.[2] In recent work, Thauer et al. have demonstrated that Hmd consists of a 38 000 Da homodimeric protein containing one organometallic cofactor per subunit.[3]

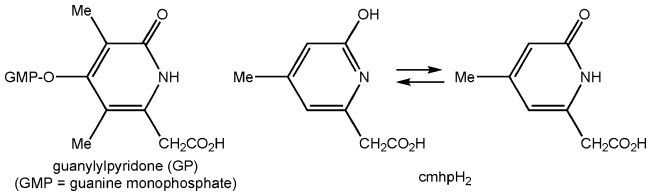


Figure 1. Structure of the organic component, GP, of an organometallic cofactor (left) and 2-hydroxypyridine/2-pyridone tautomers of the simplified analogue $cmhpH_2$ (right).

This cofactor features an $Fe(CO)_2$ subunit (ν_{CO} = 2011 and 1944 cm^{-1})[4] bound to an organic component, guanylylpyridone (GP), which has been spectroscopically characterized (Figure 1).[5] GP features a 3,5-dimethylpyrid-2-one-4-ol-6-acetic acid group conjugated to a guanidine nucleotide. The exact coordination of GP to Fe is unknown.

The heterocycle 6-(carboxymethyl)-4-methyl-2-hydroxypyridine ($cmhpH_2$) is known[6] and represents a simplified analogue of GP, bearing both the 2-hydroxyl and 6-carboxymethyl functionalities, but lacking the attached guanylyl group (Figure 1). In this report, we describe an initial evaluation of the coordinating properties of this model cofactor using the simplified octahedral metal platforms provided by Cp^*M^{2+} (M = Rh, Ir; Cp* = C_5Me_5).[7] The resulting adducts should approximate the environment provided by low-spin ferrous iron, as is likely to exist in the enzyme.[8] The coordination chemistry of 2-pyridones is well-developed, but coordination of 2-pyridones bearing functionality is generally limited.[9] Intriguingly, Cp^*Ir^{III} complexes of 2-pyridones have recently been shown to catalyze

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10.1021/ic7018692 CCC: $40.75
Published on Web 12/15/2007

hydrogen transfer,[10] which is relevant to the methanogenesis pathway (eq 1).

We found that treatment of $[Cp^*MCl_2]_2$ with $cmhpH_2$ and a base afforded excellent yields of the air-stable solids Cp*M(cmhpH)Cl for M = Ir (**1**) and Rh (**2**). The NMR spectra for the new complexes exhibited diastereotopic signals for the methylene group, consistent with complexation of both the heterocycle and the acetate arm. As verified crystallographically, Cp*Rh(cmhpH)Cl adopts a chiral "piano-stool" structure with a chelating $cmhpH^-$. The presence of the intact 2-hydroxy group on the pyridine was confirmed crystallographically, indicating that the heterocycle is bound as the 2-hydroxypyridine tautomer (Figure 2). The O(1)−C(11) and N(1)−C(11) bond distances and the O(1)−C(11)−N(1) and O(1)−C(11)−C(12) angles of the cmhpH ligand also confirm the pyridine form.[9,11] In the crystal, this hydroxy group forms an intermolecular hydrogen bond to the carbonyl on the carboxylate of a neighboring complexes with a O−O distance of 2.582(2) Å.

Complexes **1** and **2** exhibit good solubility in water and alcohols. This hydrophilicity is proposed to arise from both the solvation 2-hydroxyl group and its ability to stabilize the replacement of chloride by hydrogen-bond acceptors such as water.[12] In aqueous solutions of **1** or **2**, chloride is fully ionized, as indicated by the finding that the ^{1}H NMR spectrum was unaffected by the addition of $AgPF_6$; i.e., chloride is ionized prior to the addition of a Ag^+ source. In contrast, NMR studies indicate that Cp*Ir(paa)Cl (**3**; paaH = 2-pyridylacetic acid) and Cp*Ir(pa)Cl (**4**; paH = picolinic acid, C_5H_4N-2-CO_2H) require the addition of $AgPF_6$ for complete conversion to the aqua complexes (eq 2, K's evaluated at room temperature).

$$Cp^*Ir(N\text{-}O)Cl + H_2O \underset{}{\overset{K}{\rightleftharpoons}} [Cp^*Ir(N\text{-}O)(H_2O)]^+ + Cl^- \quad (2)$$

N-O	K
2-picolinate	1.4
pyridine-2-acetate	0.53
$cmhpH^-$	>30

We investigated the affinity of **2** for ligands that could serve as hydrogen-bond acceptors. Treatment of **2** with 2-pyridone (hpH) in the presence of Et_3N afforded the neutral complex Cp*Rh(cmhpH)(hp) (**5**). The ^{1}H NMR spectra for **5** indicated the formation of a single species. Crystallographic analysis of the orange crystals revealed four molecules in the asymmetric unit, each of which was very similar, exhibiting *intra*molecular hydrogen bonding between the two pyridone-derived ligands (Figure 3). The O−O separations in **5** range from 2.327(18) to 2.480(17) Å, and this is virtually the only difference between the four molecules (Table 1). The short O−O distances are indicative of a strong hydrogen bond (a "low-barrier hydrogen bond" or LBHB)[13,14] and are among the shortest O−O separations reported, especially for a coordination complex.[15] Previous studies have shown that intramolecular LBHBs are favored when ΔpK_a, the difference in the acidities of the hydrogen-bond donor and acceptor, is ~0. This aspect indicates, not surprisingly, that the 4-methyl and 6-carboxymethyl substituents in H_2cmhp have little effect on the pK_a of the hydroxyl group relative to the parent 2-hydroxypyridine. The C−O, N−C, and Rh−N distances, as well as the O−C−N and N−C−C angles for the 2hp and cmhpH ligands, are averaged between the pyridone and pyridine binding modes.[9,11]

The clearest characterization technique for a LBHB in solution is ^{1}H NMR spectroscopy.[14] In compounds containing LBHBs, the chemical shifts of the participating proton range from δ 16 to 20. The ^{1}H NMR spectrum of **5** exhibits a

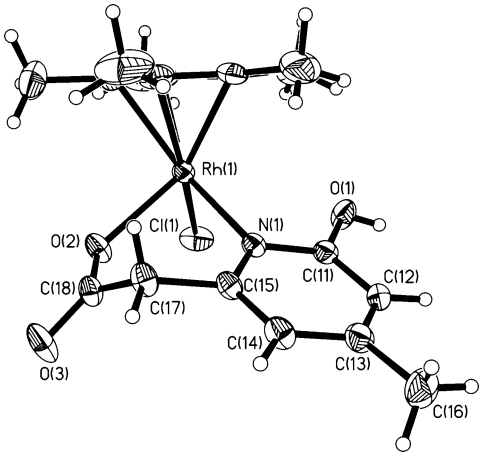

Figure 2. Structure of **2** with thermal ellipsoids drawn at the 50% probability level. Selected bond distances and angles: Rh(1)−N(1) 2.1383(16), Rh(1)−O(2) 2.1223(14), Rh(1)−Cl(1) 2.4042(5), Rh(1)−Cp*(centroid) 1.771(2), O(1)−C(11) 1.326(2), N(1)−C(11) 1.349(3); O(1)−C(11)−N(1) 116.02(17), O(1)−C(11)−C(12) 121.39(18).

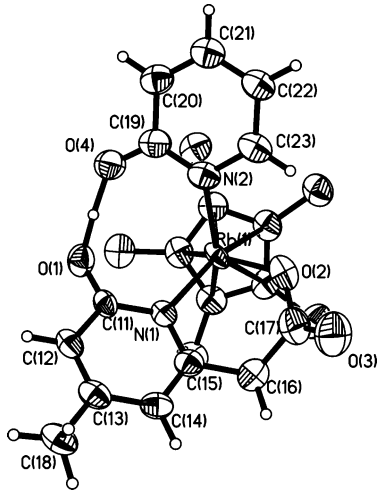

Figure 3. Structure of one of four similar molecules in the asymmetric unit of **5** with Cp* protons removed for clarity and 50% probability ellipsoids. Selected bond distances (Å) and angles (deg): Rh(1)−N(1) 2.165(6), Rh(1)−N(2) 2.178(6), O(1)−C(11) 1.286(9), O(4)−C(19) 1.282(10), N(1)−C(11) 1.357(9), N(2)−C(19) 1.347(10); O(1)−C(11)−N(1) 120.5(8), O(4)−C(19)−N(2) 121.4(9), N(1)−C(11)−C(12) 120.5(8), N(2)−C(19)−C(20) 119.0(9). O−O distances [O−H−O angles]: 2.327(18) [171(4)], 2.348(17) [159(8)], 2.384(17) [173(9)], and 2.480(17) [173(9)].

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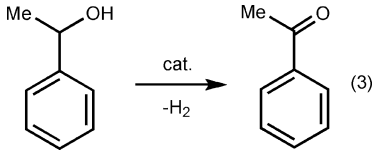
singlet at δ 17.1 (CD_2Cl_2 solution) vs δ 9.83 in **2**, which lacks a LBHB. Pyrazolate (pyz^-) also replaced the chloride in **2** to give Cp*Rh(Hcmhp)(pyz) with a similarly strong hydrogen bond (δ 16.3).

In view of the ability of the 2-hydroxy group to encourage the binding of hydrogen-bond acceptors and in view of the biological function of Hmd as a hydrogen-transfer catalyst, we examined these Hcmhp-derived complexes to promote hydrogen transfer. Iridium complexes are well-known to promote hydrogen-transfer reactions.[10,16] Although the rhodium complex **2** is not sufficiently robust thermally, **1** is an excellent catalyst for the dehydrogenation of PhCH(OH)Me to acetophenone (eq 3).



(3)

In terms of turnover number (TON) and catalyst longevity, **1** is superior to structurally related complexes lacking the 2-OH group (Table 1).

Table 1. TONs and Turnover Frequencies (TOFs) for Catalytic Dehydrogenation of PhCH(OH)Me to PhC(O)Me (Neat, 130 °C) Using 0.10 mol % of Ir as Catalyst Precursor

catalyst precursor	TON (24 h)	TOF (2 h)	TOF (24 h)
Cp*Ir(Hcmhp)Cl	169	21	8
Cp*Ir(C_5H_4N-2-CH_2CO_2)Cl	64	10	2.7
Cp*Ir(C_5H_4N-2-CO_2)Cl	8	trace	0.33
$[Cp^*IrCl_2]_2$	24	2.7	1
Cp*Ir(Hcmhp)Cl[a]	339	40	14

[a] 1 mL of 1-phenylethanol, 1 mL of toluene, and 0.10 mol % of iridium catalyst under reflux conditions.

Our findings indicate that the 2-hydroxy substituent in $cmhpH^-$ can significantly influence the reactivity of the sixth coordination site in octahedral complexes. In $cmhpH^-$, the chelating nature of the ligand constrains the orientation of this hydroxy substituent to be adjacent to the open coordination site.[17] It is intriguing that $cmhpH^-$, like the cofactor GP, confers high activity for hydrogen transfer to the metal.

Acknowledgment. This research was supported by the Department of Energy and NIH. We thank Professors Chris Pickett (East Anglia) and Peter Beak (UIUC) for advice and assistance.

Supporting Information Available: Experimental methods and CIF files for crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

IC7018692

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