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Biomimetic Models for the Active Site of [Fe]Hydrogenase Featuring an Acylmethyl(hydroxymethyl)pyridine Ligand

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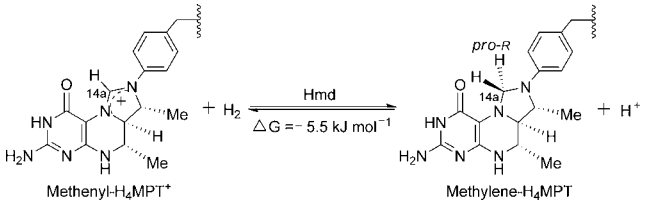
Supporting Information

ABSTRACT: The first acylmethyl(hydroxymethyl)-pyridine ligand-containing [Fe]hydrogenase model complexes **2**−**4** have been synthesized starting from the nucleophilic substitution reaction of 2-(4-$MeC_6H_4SO_3CH_2$)-6-$HOCH_2C_5H_3N$ with $Na_2Fe(CO)_4$. While the reaction course for producing complex **3** via the highly unstable intermediate complex **1** is monitored by in situ IR spectroscopy, the isolated model complexes **2**−**4** are fully characterized.

[Fe]Hydrogenase is also named as dihydrogen-forming methylenetetrahydromethanopterin dehydrogenase (Hmd), which contains only one Fe atom at its active site and no iron−sulfur cluster.[1−3] Unlike the [NiFe]- and [FeFe]-hydrogenases,[4,5] [Fe]hydrogenase is not redox-active and catalyzes the reversible stereospecific hydride transfer from H_2 to C_{14a} of methenyltetrahydromethanopterin (methenyl-H_4MPT^+) to form methylenetetrahydromethanopterin (methylene-H_4MPT) and H^+ (Scheme 1). This reaction is an intermediate step in the reduction of CO_2 to methane under the action of methanogens grown under nickel-deficient conditions.[6]

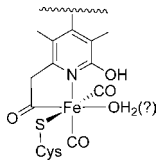
Scheme 1. Reaction Catalyzed by [Fe]Hydrogenase



The X-ray crystallographic[7,8] and spectroscopic[9−11] studies revealed that the active site of [Fe]hydrogenase consists of an Fe atom ligated by a cysteine S atom, two cis-carbonyl ligands, a 6-hydroxypyridylacyl ligand, and a yet unknown ligand, which is presumably a disordered solvent molecule (Scheme 2).

Although various synthetic models for [Fe]hydrogenase have been reported so far,[12−20] none of them contains a 6-hydroxymethylpyridylacyl ligand, the structurally closest ligand to the natural 6-hydroxypyridylacyl ligand present in [Fe]-hydrogenase. It should be noted that the [Fe]hydrogenase model complex with a 6-hydroxymethylpyridylacyl ligand is of particular interest because the hydroxy group attached to the 6 position of the acylmethylpyridine ring in [Fe]hydrogenase

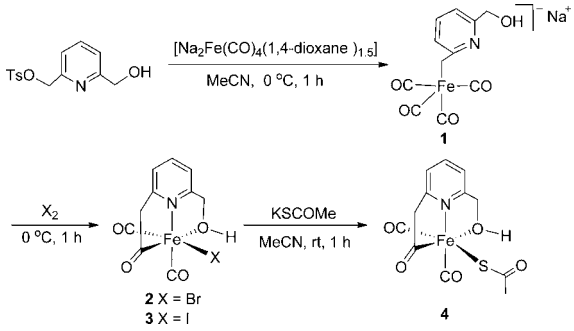
Scheme 2. Basic Structure of the [Fe]Hydrogenase Active Site



plays an important role in the heterolytic cleavage of dihydrogen.[21] Herein we report the synthesis and structural characterization of the first [Fe]hydrogenase model complexes with a novel acylmethyl(hydroxymethyl)pyridine ligand.

The synthetic route to such a new type of model complexes **2**−**4** is shown in Scheme 3. First, the nucleophilic substitution

Scheme 3. Synthesis of Model Complexes 2−4 via Intermediate Complex 1



reaction of the disubstituted pyridine derivative 2-(4-$MeC_6H_4SO_3CH_2$)-6-$HOCH_2C_5H_3N$ with $Na_2Fe(CO)_4(1,4\text{-dioxane})_{1.5}$ in MeCN gave the iron(0) complex salt [Na(2-CH_2-6-$HOCH_2C_5H_3N$)$Fe(CO)_4$] (**1**). Then, the in situ CO migratory insertion reaction[22] of this complex salt followed by coordination of its hydroxyl group and oxidation by Br_2 or I_2 afforded the acylmethyl(hydroxymethyl)pyridine ligand-containing iron(II) model complexes [(2-$COCH_2$-6-$HOCH_2C_5H_3N$)$Fe(CO)_2X$] (**2**, X = Br; **3**, X = I). It is worth noting that our method to construct the acylmethylpyridinyl unit present in the natural enzyme is different from Hu's method involving the in situ reaction of the methylpyridine anion with $Fe(CO)_5$.[19] Finally, in order to obtain a more natural model with the whole ligand set of the active site of

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[Fe]hydrogenase, **2** and **3** were further treated with KSCOMe in MeCN to give the final model complex [(2-$COCH_2$-6-$HOCH_2C_5H_3N$)Fe$(CO)_2$(SCOMe)] (**4**) via replacement of bromide or iodide in **2** and **3** by $MeCOS^-$ (see the Supporting Information).

Interestingly, we have successfully employed in situ IR spectroscopy[23] to monitor the reaction course for the formation of complex **3** by observing changes of the ν_{CO} absorption bands for the starting material $Na_2Fe(CO)_4$, intermediate complex **1** (which was too unstable to be isolated), and product **3**. As shown in Figure 1, when 2-(4-$MeC_6H_4SO_3CH_2$)-6-$HOCH_2C_5H_3N$ was added to a MeCN solution of $Na_2Fe(CO)_4$, the original ν_{CO} absorption bands of $Na_2Fe(CO)_4$ at 1760 (vs), 1866 (w), 1886 (m), and 1915 (w) cm^{-1} gradually diminished, and after 10 min, they were completely replaced by a very strong band at 1885 cm^{-1} and a middle band at 2001 cm^{-1}. This implies that $Na_2Fe(CO)_4$ was completely consumed and intermediate complex **1** formed. The in situ IR spectroscopy further indicated that, after the addition of I_2 (ca. 15 min), the aforementioned two ν_{CO} absorption bands disappeared, and instead a strong band at 2030 cm^{-1}, a middle band at 1967 cm^{-1}, and a weak band at 1671 cm^{-1} appeared. The three new bands can be assigned to the two cis-orientated terminal carbonyl ligands and one acyl ligand for the newly formed product **3**, respectively.

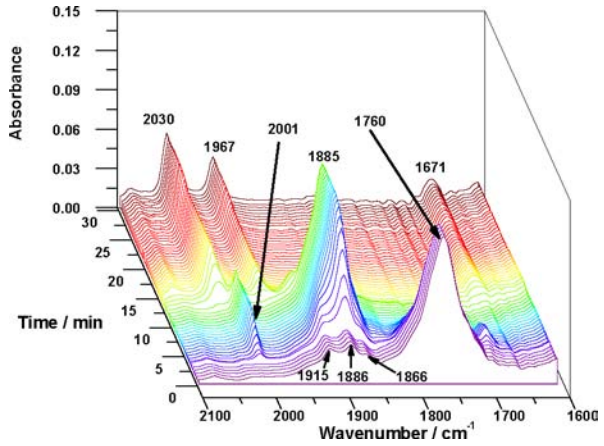

Figure 1. In situ IR spectra for the formation of **3** starting from $Na_2Fe(CO)_4$ via intermediate complex **1** in MeCN at 0 °C.

Model complexes **2**–**4** are air-stable solids, which were fully characterized by elemental analysis, spectroscopy, and X-ray crystallography. The IR spectra of **2**–**4** in the solid state displayed two very strong absorption bands in the range 2035–1963 cm^{-1} for their two cis-orientated terminal carbonyls, one band in the region 1668–1665 cm^{-1} for the acyl groups attached to their Fe centers, and one band in the range 3464–3448 cm^{-1} for their hydroxy groups, respectively. The ^1H NMR spectra of **2**–**4** showed two doublets or a singlet at 4.26–4.52 ppm for their CH_2CO groups and a singlet or two doublets at 5.15–5.33 ppm for their CH_2O groups, depending upon whether the two H atoms in each of the CH_2CO and CH_2O groups are diastereotopic or not under the determined conditions. Compounds **2** and **3** displayed a singlet at 6.45 and 6.50 ppm for their hydroxy groups, while **4** exhibited a singlet at 10.52 ppm for its hydroxy group. The ^{13}C NMR spectra of **2**–**4** exhibited a signal at 254–256 ppm characteristic of their acyl C atoms.[19]

The molecular structures of **2**–**4** were unequivocally confirmed by X-ray crystallography. As can be seen intuitively in Figures 2–4, the Fe^{II} centers of **2**–**4** are six-coordinate and

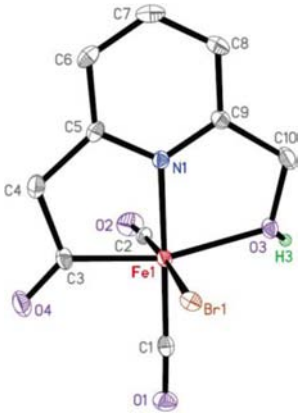

Figure 2. Molecular structure of **2**. The thermal ellipsoids are displayed at 30% probability. Selected bond lengths [Å] and bond angles [deg]: Fe1–C3 1.921(3), Fe1–N1 1.948(2), Fe1–O3 2.116(2); C3–Fe1–Br1 90.51(9), N1–Fe1–O3 78.47(9).

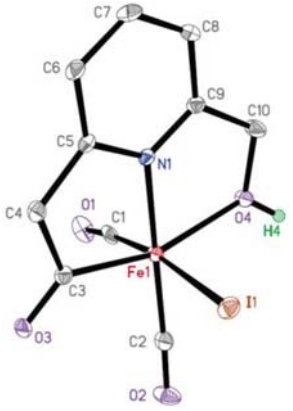

Figure 3. Molecular structure of **3**. The thermal ellipsoids are displayed at 30% probability. Selected bond lengths [Å] and bond angles [deg]: Fe1–C3 1.921(3), Fe1–N1 1.965(3), Fe1–O4 2.153(3); C3–Fe1–I1 88.67(10), N1–Fe1–O4 76.45(11).

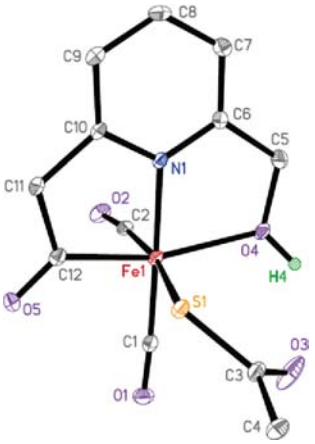

Figure 4. Molecular structure of **4**. The thermal ellipsoids are displayed at 30% probability. Selected bond lengths [Å] and bond angles [deg]: Fe1–C12 1.924(3), Fe1–N1 1.947(3), Fe1–O4 2.128(3); C12–Fe1–S1 84.02(11), N1–Fe1–O4 78.13(11).

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their acylmethylpyridyl or hydroxymethylpyridyl moiety forms a five-membered ferracycle with their Fe^{II} centers, respectively. The two terminal CO ligands of **2**–**4** occupy the positions cis to their acyl ligands, whereas the Br atom in **2**, I atom in **3**, and S atom in **4** are located in the positions trans to one of their two CO ligands. Particularly noteworthy is that in models **2**–**4** their acyl ligands are trans to a weakly coordinated hydroxy group, which is exactly the same as the geometric arrangement between acyl ligand and the weakly coordinated H_2O molecule in [Fe]hydrogenase.[7,8] In addition, when the geometric parameters for **4** are compared with those of [Fe]hydrogenase (see the Supporting Information), **4** is indeed a good and more natural model for the active site of [Fe]hydrogenase.

In summary, we have synthesized the first acylmethyl(hydroxymethyl)pyridine ligand-containing [Fe]hydrogenase model complexes **2**–**4**, starting from the nucleophilic substitution reaction of 2-(4-$MeC_6H_4SO_3CH_2$)-6-$HOCH_2C_5H_3N$ with $Na_2Fe(CO)_4$. While the reaction course for producing complex **3** via the highly unstable intermediate complex **1** is monitored by in situ IR spectroscopy, the isolated model complexes **2**–**4** are fully characterized by elemental analysis, spectroscopy, and X-ray crystallography. The most prominent feature of model complexes **2**–**4** is for each to have an acylmethyl(hydroxymethyl)pyridine ligand that is coordinated to the Fe^{II} center via their acyl C atom, pyridyl N atom, and hydroxy O atom. Another prominent feature of **2**–**4** is for each to have a hydroxy group weakly coordinated trans to their acyl ligands. Therefore, models **2**–**4** are the first models with a coordinated hydroxy group, which is not only structurally mimicking the hydroxy group in the active site of [Fe]-hydrogenase but also mimicking the coordinated H_2O in the 6 position of the [Fe]hydrogenase active site. Apparently, the ready availability of models **2**–**4** makes it possible to study the chemical reactivities of their coordinated hydroxy groups so as to further understand the catalytic mechanism assisted by the hydroxy group present in the natural enzyme.[21]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and crystallographic information files for **2**–**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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