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Communication

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A Novel Acylmethylpyridinol Ligand Containing Dinuclear Iron Complex Closely Related to [Fe]-Hydrogenase

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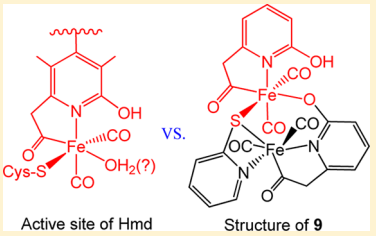
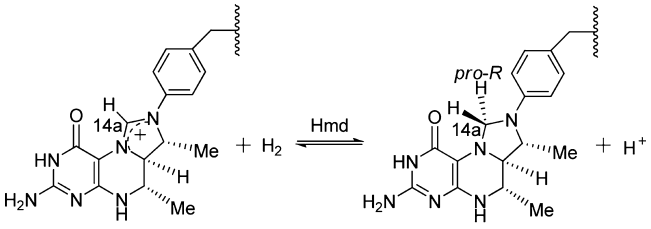
Supporting Information

ABSTRACT: On synthesizing the PMB-protected mononuclear iron complexes [2-$C(O)CH_2$-6-$PMBOC_5H_3N$]$Fe(CO)_3I$ (**6**) and [2-$C(O)CH_2$-6-$PMBOC_5H_3N$]$Fe(CO)_2$(2-SC_5H_4N) (**7**), the novel acylmethylpyridinol ligand containing dinuclear iron complex [2-$C(O)CH_2$-6-HOC_5H_3N]$Fe_2(CO)_4$[2′-$C(O)CH_2$-6′-OC_5H_3N](2-SC_5H_4N) (**9**), which is closely related to the active site of [Fe]-hydrogenase, has been prepared unexpectedly via removal of the PMB protecting group from **7** under the action of excess trifluoroacetic acid. The [Fe]-hydrogenase-related complex **9** and its precursor complexes **6** and **7** have been fully characterized by elemental analysis, spectroscopy, and X-ray crystallography.



In nature, there are three kinds of hydrogenases, namely [FeFe]-, [NiFe]-, and [Fe]-hydrogenases. Although the three enzymes are phylogenetically unrelated, they all can catalyze H_2 metabolism in various microorganisms.[1−4] However, unlike the [FeFe]- and [NiFe]-hydrogenases,[4] [Fe]-hydrogenase (Hmd)[1,2] is not redox-active and catalyzes the reversible reduction of methenyltetrahydromethanopterin (methenyl-H_4MPT^+) with H_2 to methylenetetrahydromethanopterin (methylene-H_4MPT) and H^+ (Scheme 1). This catalytic process is an intermediary step in the reduction of CO_2 to methane using H_2 by methanogens grown under nickel-deficient conditions.[5]

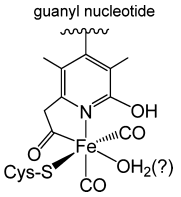
Scheme 1. Catalytic Function of [Fe]-Hydrogenase



Recent X-ray crystallographic[6−8] and spectroscopic[9−12] studies have demonstrated that the active site of [Fe]-hydrogenase contains a unique iron atom ligated by a cysteine S atom, two *cis* carbonyls, a 2-acylmethyl-6-pyridinol, and an as yet unknown ligand, which is presumably a molecule of water (Scheme 2).

So far, a number of biomimetic models for [Fe]-hydrogenase have been synthesized, but none of them contain the natural 2-acylmethyl-6-pyridinol ligand,[13−24] although some model complexes with a similar ligand of acylmethyl(methoxy)-pyridine[20−22] or acylmethyl(hydroxymethyl)pyridine[24] were previously reported. It is worth noting that an [Fe]-hydrogenase model complex with a natural 2-acylmethyl-6-pyridinol ligand is of particular interest, since the hydroxy group that is directly attached to the pyridine ring of the natural ligand in [Fe]-hydrogenase plays an important role in the heterolytic cleavage of dihydrogen.[25] Therefore, in order to further understand the active site structure of [Fe]-hydrogenase and its catalytic mechanism, we initiated a study aimed at synthesizing the 2-acylmethyl-6-pyridinol ligand containing [Fe]-hydrogenase model complex. As a result, in contrast to our original expectation, we did not get such a mononuclear iron model complex; instead, we obtained a novel dinuclear iron complex in which the acylmethylpyridinol ligand is coordinated to one of its two iron atoms and a deprotonated acylmethylpyridinol ligand is coordinated to both of its iron atoms. In this communication, we report the synthesis and structural characterization of this novel dinuclear complex, which is closely related to the active site of [Fe]-hydrogenase.

Scheme 2. Active Site of [Fe]-Hydrogenase



The synthetic route for preparation of such a dinuclear complex, namely **9**, is shown in Schemes 3 and 4. First, as shown in Scheme 3, the methoxycarbonyl-substituted pyridinol 2-MeO_2C-6-HOC_5H_3N (**1**) reacted with 4-$MeOC_6H_4CH_2Cl$ in MeCN in the presence of K_2CO_3/NaI to give the *p*-

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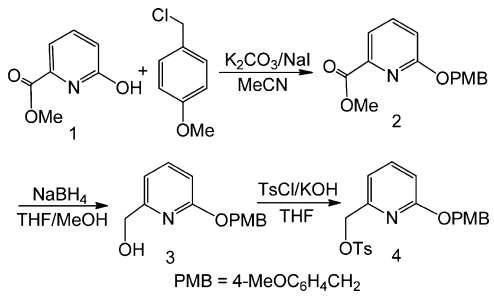
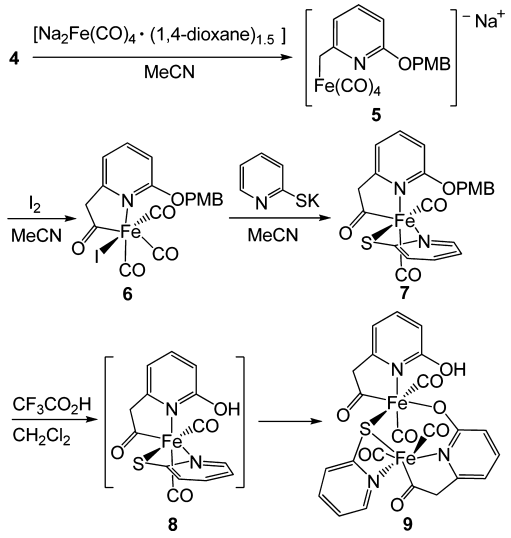
Scheme 3. Synthesis of the PMB-Protected Pyridinol Derivatives 2−4



Scheme 4. Synthesis of the Mono- and Dinuclear Complexes 6, 7, and 9



methoxybenzyl (PMB)-protected pyridinol derivative 2-MeO_2C-6-$PMBOC_5H_3N$ (**2**). Then, the methoxycarbonyl group of **2** was reduced to a hydroxymethyl group by $NaBH_4$ in THF/MeOH to produce 2-$HOCH_2$-6-$PMBOC_5H_3N$ (**3**). Furthermore, **3** reacted in THF with 4-toluenesulfonyl (Ts) chloride in the presence of KOH to afford the corresponding disubstituted pyridine derivative 2-$TsOCH_2$-6-$PMBOC_5H_3N$ (**4**) in a nearly quantitative yield. All three new PMB-protected pyridinol derivatives **2**−**4** were fully characterized by elemental analysis and IR and NMR spectroscopic methods (see the Supporting Information).

Then as shown in Scheme 4, when the PMBO/$TsOCH_2$-disubstituted pyridine **4** reacted with $Na_2Fe(CO)_4$·1.5(1,4-dioxane) in MeCN, similar to the case for its $HOCH_2$/$TsOCH_2$-disubstituted analogue,[24] the intermediate iron(0) complex salt Na(2-CH_2-6-$PMBOC_5H_3N$)$Fe(CO)_4$ (**5**) was first formed and the in situ CO migratory insertion/oxidation reaction of **5** in the presence of iodine[26] afforded the PMB-protected acylmethylpyridinol ligand containing iron(II) iodide complex [2-$C(O)CH_2$-6-$PMBOC_5H_3N$]$Fe(CO)_3I$ (**6**). Further treatment of **6** with potassium 2-mercaptopyridinate, via displacement of iodide by 2-mercaptopyridinate and subsequent coordination of the pyridyl N atom and loss of one CO ligand, yielded the corresponding iron(II) mercaptopyridinate complex [2-$C(O)CH_2$-6-$PMBOC_5H_3N$]$Fe(CO)_2$(2-SC_5H_4N) (**7**). It is particularly worth pointing out that when we attempted to use CF_3CO_2H to remove the protecting group PMB from **7**, the initially expected mononuclear model complex **8** was not obtained; instead, the novel dinuclear iron complex [2-$C(O)CH_2$-6-HOC_5H_3N]$Fe_2(CO)_4$[2′-$C(O)CH_2$-6′-OC_5H_3N](2-SC_5H_4N) (**9**), which contains the natural acylmethylpyridinol ligand, was obtained in 36% yield, unexpectedly. It should be noted that according to the proton acid catalyzed ether cleavage mechanism[27] and the Lewis acid catalyzed PMB-removed mechanism,[28] complex **7** might be first converted to the initially expected **8**, and then **9** was generated via the in situ self-assembly of **8** in the presence of excess CF_3CO_2H (the suggested pathway for formation of the unexpected **9** is shown in Scheme S1 of the Supporting Information).

These three complexes were fully characterized by elemental analysis, spectroscopy, and X-ray crystallography. The solid-state IR spectrum of **6** showed three absorption bands in the range 2085−2005 cm^{-1} for its three terminal CO ligands, whereas **7** and **9** displayed two absorption bands in the regions 2022−1958 and 2031−1977 cm^{-1} for their two and four terminal CO ligands, respectively. The IR spectra of **6**, **7**, and **9** also displayed one strong absorption band in the range 1672−1653 cm^{-1} for their acyl groups, which are very close to those of the previously reported acylmethylpyridinyl ligand containing model complexes.[20,24]

The ^1H NMR spectra of **6**, **7**, and **9** showed two doublets in the range 3.75−5.12 ppm for the two diastereotopic H atoms in their acylmethyl groups, whereas their ^{13}C NMR spectra displayed one or two singlets in the region 258−265 ppm for their acyl C atoms. These NMR data are also very close to those of the previously reported acylmethylpyridinyl ligand containing model complexes.[20,24] It is particularly noteworthy that the IR and ^1H NMR spectra of **9** all showed the presence of the hydroxy group of the acylmethylpyridinol ligand by having a weak band at 3469 cm^{-1} and a singlet at 13.58 ppm, respectively (see the Supporting Information).

The molecular structures of **6**, **7**, and **9** have been unambiguously confirmed by X-ray crystal diffraction analysis. As can be seen in Figures 1 and 2, the Fe1 centers of **6** and **7** are six-coordinate and their acylmethyl/PMBO-disubstituted pyridine ligands each construct a five-membered ferracycle with their Fe1 centers, respectively. The three terminal CO ligands

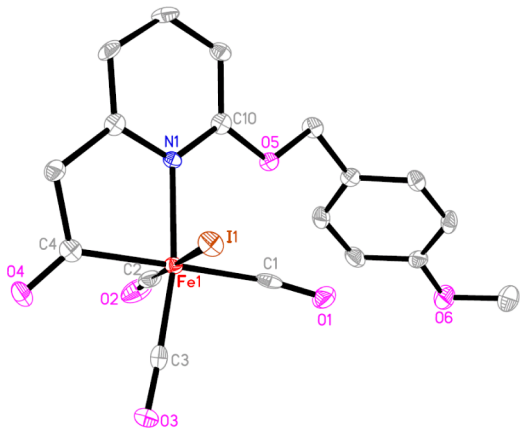


Figure 1. Molecular structure of **6** with 50% probability level ellipsoids. Key bond lengths (Å) and angles (deg): Fe(1)−C(1) = 1.893(5), Fe(1)−C(4) = 1.989(4), Fe(1)−N(1) = 2.035(3), Fe(1)−I(1) = 2.6582(11), O(4)−C(4) = 1.198(4); C(1)−Fe(1)−C(4) = 175.50(16), C(3)−Fe(1)−N(1) = 167.90(17), C(2)−Fe(1)−C(1) = 94.43(19), C(1)−Fe(1)−I(1) = 87.25(13).

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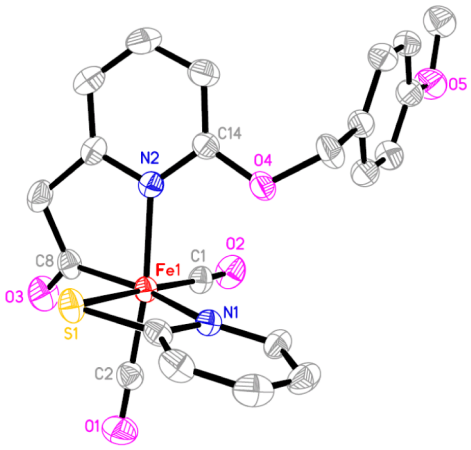

Figure 2. Molecular structure of **7** with 30% probability level ellipsoids. Key bond lengths (Å) and angles (deg): Fe(1)−C(8) = 1.923(3), Fe(1)−N(2) = 2.057(3), Fe(1)−N(1) = 2.060(2), Fe(1)−S(1) = 2.3765(11), O(3)−C(8) = 1.211(4), O(4)−C(14) = 1.348(4); C(2)−Fe(1)−N(2) = 172.13(12), C(1)−Fe(1)−S(1) = 175.56(10), C(1)−Fe(1)−N(2) = 90.19(12), C(2)−Fe(1)−C(1) = 91.67(16).

in **6** occupy the facial positions of the Fe1 octahedral geometry, whereas the two terminal CO ligands of **7** lie in positions *cis* to its acyl ligand. In addition, in **7** there is also a bidentate mercaptopyridinate ligand chelated to its Fe1 center.

It can be seen in Figure 3 that complex **9** is indeed a dinuclear complex, in which the Fe1 center is coordinated by a

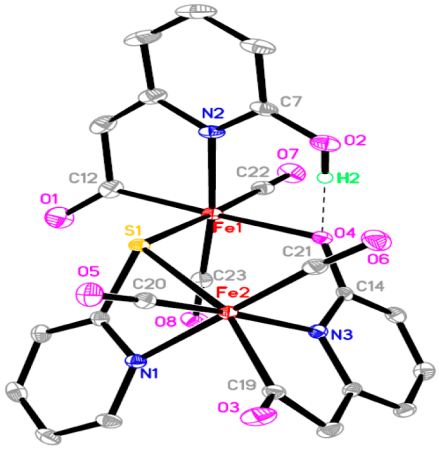

Figure 3. Molecular structure of **9** with 30% probability level ellipsoids. Key bond lengths (Å) and angles (deg): O(2)−C(7) = 1.323(3), O(4)−C(14) = 1.306(2), Fe(1)−C(12) =1.927(2), Fe(1)−N(2) = 2.0484(17), Fe(1)−O(4) = 2.0861(14), Fe(1)−S(1) = 2.3301(6), Fe(2)−C(19) = 1.933(2), Fe(2)−N(3) = 2.0188(17), Fe(2)−N(1) = 2.0221(17), Fe(2)−S(1) = 2.4837(6); C(23)−Fe(1)−C(22) = 89.30(9), C(22)−Fe(1)−S(1) = 176.90(7), C(21)−Fe(2)−N(1) = 178.20(8), C(19)−Fe(2)−S(1) = 159.73(6), C(21)−Fe(2)−C(20) = 91.40(9).

2-acylmethyl-6-pyridinol ligand (C7−O2 = 1.323 Å) via its acyl C12 and pyridyl N2 atoms and the Fe2 center is coordinated by a deprotonated 2-acylmethyl-6-pyridinol ligand via its acyl C19 and pyridyl N3 atoms (this deprotonated pyridinol ligand might be also regarded as a deprotonated pyridone ligand, since the bond lengths of C14−O4 (1.306 Å) and C14−N3 (1.365 Å) are between those of the corresponding single and double bonds).[29,30] In addition, the Fe1 center of **9** is also coordinated by the 2-mercaptopyridinate S1 atom, two *cis* carbonyls, and the deprotonated pyridinol O4 atom, whereas the Fe2 center of **9** is coordinated by the corresponding ligand atoms such as S1, C21/C20, and N1. It follows that (i) the Fe1 center of complex **9** has a complete set of coordinated atoms of the active site of [Fe]-hydrogenase and (ii) the Fe1 and Fe2 centers both have a formal oxidation state of +2 achieved by coordination of the corresponding negative ligands around the Fe1 and Fe2 centers. Although early studies indicate the Fe center in [Fe]-hydrogenase to be either low-spin Fe(0) or low-spin Fe(II),[11] recent studies show that the Fe center of [Fe]-hydrogenase is most likely low-spin Fe(II).[14,31] Therefore, the formal oxidation state assigned to the Fe1 and Fe2 centers of the dinuclear complex **9**, as well as that assigned to the Fe1 centers of mononuclear complexes **6** and **7** as mentioned above, are all consistent with that recent assignment of Fe(II) for the Fe center of [Fe]-hydrogenase.[14,31] Finally, it should be noted that in molecular structure of **9** there exists an intramolecular hydrogen bond between the hydroxy H2 atom of the acylmethylpyridinol ligand and the O4 atom of the deprotonated pyridinol ligand (O2−H2- - -O4 = 2.483 Å, ∠O2−H2- - -O4 = 173.71°). Such a type of hydrogen bond might be helpful in understanding the natural hydrogen bonding present in [Fe]-hydrogenase.[5,8]

In summary, we have prepared the novel dinuclear iron complex **9** via a multistep synthetic route involving starting compound **1**, PMB-protected derivatives **2**−**4**, and PMB-protected complexes **6** and **7**. It is particularly noteworthy that the final step of the multistep synthetic route includes the unexpected reaction of **7** with CF_3CO_2H to give **9**. The most striking feature of **9** is that it has one Fe(II) center with a natural 2-acylmethyl-6-pyridinol ligand and a complete set of coordinated atoms of the active site of [Fe]-hydrogenase. Another feature of **9** is to have a deprotonated pyridinol ligand coordinated to both of its Fe(II) centers. The third feature of **9** is to have an intramolecular hydrogen bond between the pyridyl hydroxy group and the deprotonated pyridinol O atom. It follows that the preparation and structural characterization of **9** makes it possible to further study the chemical reactivities of the pyridyl hydroxy group so as to further understand the catalytic mechanism assisted by such a hydroxy group in [Fe]-hydrogenase.

■ ASSOCIATED CONTENT

Supporting Information

Text and a scheme giving full experimental details for **2**−**4**, **6**, **7**, and **9** and a table and CIF files giving crystallographic data for **6**, **7**, and **9**. 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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