3618 *Organometallics* **2009,** *28,* 3618–3620
DOI: 10.1021/om9004059

ORGANOMETALLICS
Communication

Oxidative Addition of Thioesters to Iron(0): Active-Site Models for Hmd, Nature's Third Hydrogenase

Aaron M. Royer, Thomas B. Rauchfuss,* and Danielle L. Gray

Department of Chemistry, University of Illinois at Urbana—Champaign, Urbana, Illinois 61801

Received May 17, 2009

Summary: The thioester $Ph_2PC_6H_4$-2-C(O)SPh reacts with $Fe_2(CO)_9$ to give $[Ph_2PC_6H_4C(O)]Fe(SPh)(CO)_3$, a model for the CO-inhibited active site of the enzyme Hmd. This species, which reversibly decarbonylates to give a diiron derivative, reacts with cyanide to give $[[Ph_2PC_6H_4C(O)]Fe(SPh)(CN)(CO)_2]^-$.

One of the great surprises in bioinorganic chemistry was the discovery of the iron carbonyl sites in the [NiFe]- and the [FeFe]-hydrogenases.[1] A third hydrogenase, Hmd (methylenetetrahydromethanopterin dehydrogenase), formerly thought to be "metal-free," was recently shown to also contain an iron carbonyl center.[2] Because it features only a single Fe center at its active site, this enzyme is also called the [Fe]-hydrogenase. Hmd represents possibly the last hydrogenase to be discovered: it is strongly expressed only under special conditions (Ni deficiency) and only by methanogenic archaea. The fact that three genetically independent hydrogenases evolved similar catalytic motifs underscores the versatility of the Fe−S−CO compounds for reactions involving hydrogen.

Synthetic modeling of the active sites of the hydrogenases, in parallel with biophysical studies, provides mechanistic insights. Good progress is being made in the biomimicry of the active sites of the [NiFe]- and [FeFe]-hydrogenases.[3,4] The active site of Hmd consists of a $Fe(CO)_2$ center bound to a thiolate and the pyridine-like nitrogen of the guanylylpyridinol (GP) cofactor. This ensemble, the Fe-GP cofactor, is extractable from the protein via transthiolation using mercaptoethanol. Because it is bound to the protein via this single exchangeable residue, this active site is particularly ripe for modeling, and indeed models have already been described.[5] Recently, however, the structural assignment of the active site has been significantly revised.[6] The new analysis indicates that Fe is bound also to an *acyl* ligand, provided by the GP cofactor (Figure 1). Acyl ligands are rarely encountered in bioinorganic chemistry,[7] and their coexistence with thiolato ligands defines a novel platform from the perspective of homogeneous catalysis. The new structural information—i.e. Fe(SR)(N-donor)$(CO)_2$(acyl)—provides sufficient information to enable the design of a first-generation model for this active site, which is described below.

In terms of retrosynthetic analysis, the structure of the Fe center at the active site suggests that thioesters would oxidatively add to Fe(0) reagents. The interaction of thioesters with metal complexes has been intermittently investigated,[8] including studies suggesting that this interaction is of prebiotic significance.[9] The oxidative addition of a thioester has been established for rhodium(I) complexes.[10] Our approach focused on the use of a donor-functionalized thioester, which upon oxidative addition would simultaneously deliver the Lewis base, thiolate, and acyl groups. To simplify the analysis of the synthetic studies, we chose to use a phosphine in place of the nitrogen heterocycle, since ^{31}P NMR analysis provides a convenient means to monitor reactive intermediates. The probe thioester, $Ph_2PC_6H_4C(O)SPh$, was efficiently generated by condensation of 2-diphenylphosphinobenzoic acid[11] and benzenethiol. Related phosphine thioesters are known[12] but have been only lightly studied.

*To whom correspondence should be addressed. E-mail: rauchfuz@illinois.edu.

(1) Nicolet, Y.; Lemon, B. J.; Fontecilla-Camps, J. C.; Peters, J. W. *Trends Biochem. Sci.* **2000**, *25*, 138–143.
(2) Shima, S.; Pilak, O.; Vogt, S.; Schick, M.; Stagni, M. S.; Meyer-Klaucke, W.; Warkentin, E.; Thauer, R. K.; Ermler, U. *Science* **2008**, *321*, 572–575.
(3) Ohki, Y.; Yasumura, K.; Kuge, K.; Tanino, S.; Ando, M.; Li, Z.; Tatsumi, K. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 7652–7657. Chiou, T.-W.; Liaw, W.-F. *C. R. Chim.* **2008**, *11*, 818–833. Barton, B. E.; Whaley, C. M.; Rauchfuss, T. B.; Gray, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 6942–6943.
(4) Gloaguen, F.; Rauchfuss, T. B. *Chem. Soc. Rev.* **2009**, *38*, 100–108. Singleton, M. L.; Bhuvanesh, N.; Reibenspies, J. H.; Darensbourg, M. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 9492–9495. Felton, G. A. N.; Vannucci, A. K.; Chen, J.; Lockett, L. T.; Okumura, N.; Petro, B. J.; Zakai, U. I.; Evans, D. H.; Glass, R. S.; Lichtenberger, D. L. *J. Am. Chem. Soc.* **2007**, *129*, 12521–12530. Tard, C.; Liu, X.; Ibrahim, S. K.; Bruschi, M.; De Gioia, L.; Davies, S. C.; Yang, X.; Wang, L.-S.; Sawers, G.; Pickett, C. J. *Nature* **2005**, *433*, 610–614. Ezzaher, S.; Capon, J.-F.; Gloaguen, F.; Petillon, F. Y.; Schollhammer, P.; Talarmin, J.; Kervarec, N. *Inorg. Chem.* **2009**, *48*, 2–4.
(5) Obrist, B. V.; Chen, D.; Ahrens, A.; Schünemann, V.; Scopelliti, R.; Hu, X. *Inorg. Chem.* **2009**, *48*, 3514–3516. Wang, X.; Li, Z.; Zeng, X.; Luo, Q.; Evans, D. J.; Pickett, C. J.; Liu, X. *Chem. Commun.* **2008**, 3555–3557. Yang, X.; Hall, M. B. *J. Am. Chem. Soc.* **2008**, *130*, 14036–14037.
(6) Hiromoto, T.; Ataka, K.; Pilak, O.; Vogt, S.; Stagni, M. S.; Meyer-Klaucke, W.; Warkentin, E.; Thauer, R. K.; Shima, S.; Ermler, U. *FEBS Lett.* **2009**, *583*, 585–590.
(7) Dougherty, W. G.; Rangan, K.; O'Hagan, M. J.; Yap, G. P. A.; Riordan, C. G. *J. Am. Chem. Soc.* **2008**, *130*, 13510–13511. Ragsdale, S. W. *J. Inorg. Biochem.* **2007**, *101*, 1657–1666. Lindahl, P. A.; Graham, D. E. *Met. Ions Life Sci.* **2007**, *2*, 357–415.
(8) Li, C.-F.; Xiao, W.-J.; Alper, H. *J. Org. Chem.* **2009**, *74*, 888–890. Arisawa, M.; Kubota, T.; Yamaguchi, M. *Tetrahedron Lett.* **2008**, *49*, 1975–1978. Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261. Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734–15735. Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132–1140. Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051. Wenkert, E.; Chianelli, D. *J. Chem. Soc., Chem. Commun.* **1991**, 627–628.
(9) Huber, C.; Wächtershäuser, G. *Science* **1998**, *281*, 670–672.
(10) Shaver, A.; Uhm, H. L.; Singleton, E.; Liles, D. C. *Inorg. Chem.* **1989**, *28*, 847–851.
(11) Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 175.
(12) Burger, S.; Therrien, B.; Süss-Fink, G. *Inorg. Chim. Acta* **2004**, *357*, 1213–1218.

 Published on Web 05/28/2009

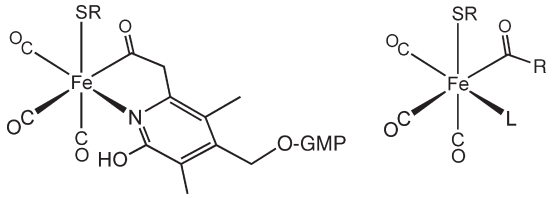


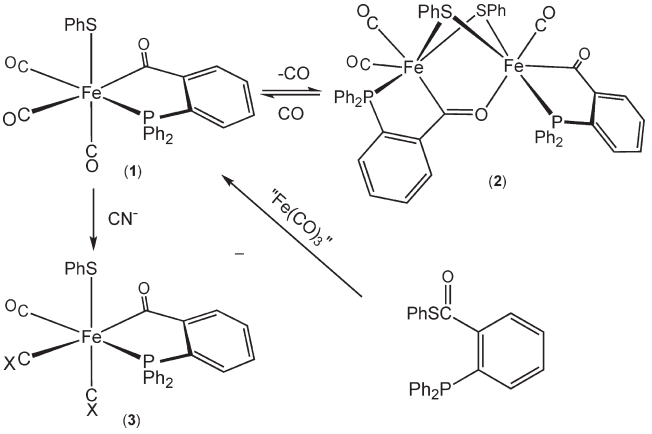
Figure 1. Structure of the CO-inhibited active site of Hmd (left) and a general motif of proposed models (right).

Table 1. Comparison of ν_{CO} and ν_{CN} Bands for Hmd Derivatives and Models

sample[a]	ν_{CO} (cm^{-1})
Hmd^{CO}	2074, 2025, 2001
$[Ph_2PC_6H_4C(O)]Fe(SPh)(CO)_3$ (**1**)	2075, 2020, 1981
Hmd^{CN}	2090 (ν_{CN}), 2020, 1956
$[Fe(SPh)(Ph_2PC_6H_4C(O)]_2(CN)(CO)_2]^-$ (**3**)	2094 (ν_{CN}), 2013, 1954
$Hmd^{13}CN$	2047 (ν_{CN}), 2017, 1956
$[Fe(SPh)(Ph_2PC_6H_4C(O)]_2(^{13}CN)(CO)_2]^-$ (**3**^{13}CN)	2050 (ν_{CN}), 2012, 1954

[a] Enzyme data from ref 18.

Scheme 1. Oxidative Addition of Thioester−Phosphines to Fe(0) and Reactions of the Ferrous Acylthiolate



We found that $Fe_2(CO)_9$, a source of the reactive $Fe(CO)_4$ entity, reacted readily with the phosphine thioester to give a new derivative **1** (^{31}P NMR: δ 72.5). Compound **1** is assumed to be the targeted acyliron(II) thiolate $[Ph_2PC_6H_4C(O)]Fe(SPh)(CO)_3$ (eq 1).

$$Fe_2(CO)_9 + Ph_2PC_6H_4C(O)SPh \rightarrow [Ph_2PC_6H_4C(O)]Fe(SPh)(CO)_3 + Fe(CO)_5 + CO \quad (1)$$

Compound **1** proved to be labile: it partially decarbonylates upon standing. It is known that Hmd also binds a third CO ligand only weakly.[13] When solutions of **1** were allowed to decarbonylate under an inert gas, we obtained black, air-stable crystals of derivative **2**. Fresh solutions obtained from these crystals gave a simple ^{31}P NMR spectrum consistent with a pair of uncoupled, nonequivalent phosphine ligands. As indicated crystallographically, **2** has the formula $Fe_2(SPh)_2[Ph_2PC_6H_4C(O)]_2(CO)_3$. Although it features ferrous centers, **2** is related to the well-studied diiron(I) dithiolates $(Fe_2(SR)_2(CO)_6)$[14]

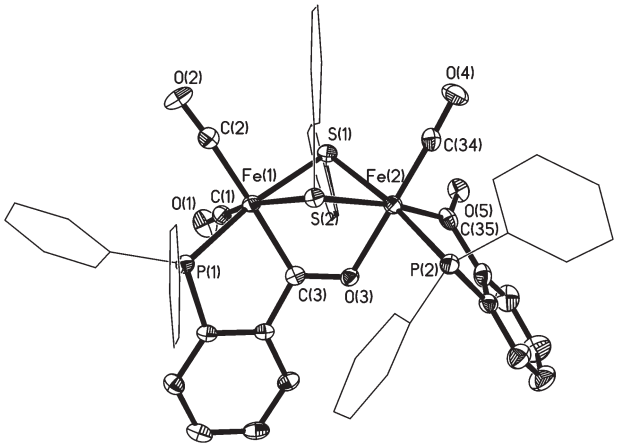
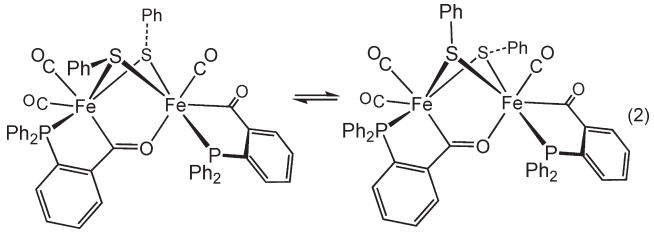


Figure 2. Structure of $Fe_2(SPh)_2[Ph_2PC_6H_4C(O)]_2(CO)_3$ (**2**). Selected distances (Å): Fe1−C1, 1.760(3); Fe1−C2, 1.828(3); Fe1−C3, 1.963(3); Fe1−P1, 2.2115(8); Fe1−S2, 2.3258(8); Fe1−S1, 2.3581(8); Fe2−C34, 1.748(3); Fe2−C35, 1.937(3); Fe2−O3, 2.0104(18); Fe2−P2, 2.2094(8); Fe2−S1, 2.3102(8); Fe2−S2, 2.3972(8).

and thiolato acyls $(Fe_2(SR)(C(O)R')(CO)_6)$.[15] Two acyl−phosphine ligands are chelating, one on each Fe. One acyl group is bridging, indicative of the basicity inherent in acyl oxygen.[15,16] In solution, **2** was found to isomerize over the course of several hours, as indicated by the appearance of new pairs of singlets in the ^{31}P NMR spectrum. The isomerization is attributed to the reorientation of the μ-SPh groups, a well-known phenomenon (eq 2).[14,17]



Treatment of solutions of **2** with 1600 psi of CO (24 h, 25 °C) resulted in its conversion back to **1**. The carbonylation of **2** provided us with highly pure samples of **1**, allowing its more definitive characterization. The IR spectrum of **1** resembles that for Hmd^{CO}, the CO-inhibited state of the active site (Table 1).[18]

The presence of three ν_{CO} bands in the IR spectrum established the facial geometry for **1**, analogous to the case for CO-inhibited Hmd.[18] Exposure of a solution of **1** to an atmosphere of ^{13}CO resulted in rapid exchange of all sites to give $Fe(SPh)[Ph_2PC_6H_4C(O)](^{13}CO)_3$. The ^{31}P NMR spectrum of this species confirmed the arrangement of the CO ligands, since three separate $^{13}C-^{31}P$ couplings are observed, (J = 58, 21, and 16 Hz). Treatment of Hmd with ^{13}CO results in stereoselective substitution,[19] in contrast to our model. The differing CO exchange pathways for the protein vs the

(13) Shima, S.; Thauer, R. K. *Chem. Record* **2007**, *7*, 37–46.
(14) Maresca, L.; Greggio, F.; Sbrignadello, G.; Bor, G. *Inorg. Chim. Acta* **1971**, *5*, 667–674.
(15) Seyferth, D.; Womack, G. B.; Archer, C. M.; Dewan, J. C. *Organometallics* **1989**, *8*, 430–432.
(16) Ciganda, R.; Garralda, M. A.; Ibarlucea, L.; Pinilla, E.; Torres, M. R. *Dalton Trans.* **2009**, 4227–4235.
(17) King, R. B. *J. Am. Chem. Soc.* **1962**, *84*, 2460.
(18) Lyon, E. J.; Shima, S.; Boecher, R.; Thauer, R. K.; Grevels, F.-W.; Bill, E.; Roseboom, W.; Albracht, S. P. J. *J. Am. Chem. Soc.* **2004**, *126*, 14239–14248.
(19) Shima, S.; Lyon, E. J.; Thauer, R. K.; Mienert, B.; Bill, E. *J. Am. Chem. Soc.* **2005**, *127*, 10430–10435.

model may be due to the phosphine vs pyridine or may arise from the role of the oxygen functionality on the 2-position of the pyridine ring in the GP cofactor (see Figure 1).

Analogous to the behavior of the enzyme,[18] cyanide forms a stable adduct from **1**, giving $[Fe(SPh)(Ph_2PC_6H_4C(O)]_2(CN)(CO)_2]^-$ (**3**) (Scheme 1 and Figure 2). This yellowish species, which is highly sensitive to air, was initially characterized by ESI-MS. The ^{31}P NMR spectrum indicated a single isomer. The IR data for the cyanide again match well with the data for the cofactor. Using $^{13}CN^-$, we generated the corresponding labeled derivative. The close match of the IR data for **3** and Hmd^{CN} is consistent with a low-spin iron(II) center in Hmd (Table 1). From the ^{31}P NMR spectrum of ^{13}CN-labeled **3**, we obtained $J(^{31}P,^{13}C)$ of 24 Hz, indicating that CN is cis to the phosphine.[20] Unlike **1**, **3** is stable with respect to loss of CO.

In summary, we have shown that donor-functionalized thioesters oxidatively add to Fe(0) to afford acyl ferrous thiolates, which provide models for the inhibited active site of Hmd. In view of the assembly strategy described here, functional modeling of this active site appears highly feasible. More broadly, the work shows that thioesters are precursors to versatile organometallic platforms.[8−10,21]

Acknowledgment. This research was supported by the DoE and PRF. We thank Drs. S. Shima and R. K. Thauer for advice.

Supporting Information Available: Text, figures, and a CIF file giving preparative, spectroscopic, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Rocchini, E.; Rigo, P.; Mezzetti, A.; Stephan, T.; Morris, R. H.; Lough, A. J.; Forde, C. E.; Fong, T. P.; Drouin, S. D. *Dalton Trans.* **2000**, 3591–3602.

(21) Zhang, J.; Wang, H.; Xian, M. *J. Am. Chem. Soc.* **2009**, *131*, 3854–3855.