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Iron Carbonyl Sulfides, Formaldehyde, and Amines Condense To Give the Proposed Azadithiolate Cofactor of the Fe-Only Hydrogenases

Hongxiang Li and Thomas B. Rauchfuss*

Department of Chemistry, University of Illinois at Urbana−Champaign, 601 South Goodwin Avenue, Urbana, Illinois 61801

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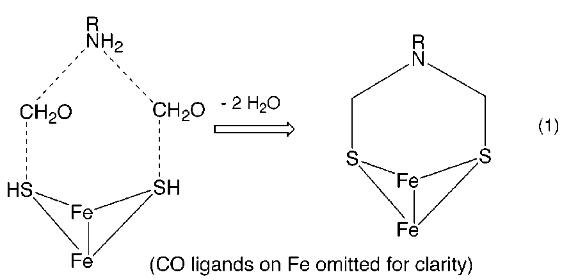
Hydrogenases are highly efficient enzymes that process hydrogen, promoting both the reduction of protons and the oxidation of dihydrogen, depending on the particular enzyme and its location in the cell.[1] The iron-only hydrogenases have attracted considerable attention because of the novel mechanistic features implicit in the unusual structure of its active site, the so-called H-cluster (Scheme 1). Research in this area is also motivated by economic considerations due to the fuel value of dihydrogen and the attractiveness of replacing platinum metal catalysts with base metals.[2]

Modeling studies initially focused on the preparation of $[Fe_2(SR)_2(CN)_2(CO)_4]^{2-}$,[3] but we have turned our attention to the dithiolate cofactor,[4] which recent crystallographic studies suggest is $^{-}SCH_2NHCH_2S^{-}$, or its *N*-protonated derivative.[5] The amine functionality in this dithiolate is geometrically restrained from direct coordination, but it likely complements the catalytic function of the dimetal unit, this view being supported both by crystallographic studies of models[4] and recent theoretical calculations.[6]

Previous syntheses of diiron azadithiolates $Fe_2[(SCH_2)_2NR](CO)_6$ involved the reaction of $(ClCH_2)_2NR$ and $Li_2[Fe_2(S)_2(CO)_6]$.[4,7] Our salt-elimination method could not be applied to the synthesis of the actual cofactor, which is a secondary amine. This problem led us to develop a fundamentally new approach to the azadithiolates, an approach that entails the unprecedented condensation formaldehyde, amines, and a metal sulfide. Recently Sharpless and coworkers have discussed the efficiency, biosynthetic significance, and diversity of Mannich-based (and related) heteroatom-centered condensations[8] ("Click Chemistry"); the present report constitutes an organometallic application of this powerful approach.

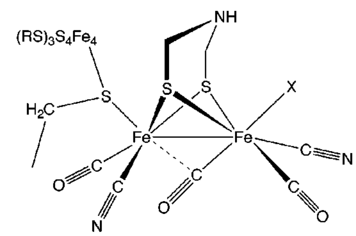
We found that $Fe_2(SH)_2(CO)_6$ (**1**)[9] efficiently condenses with formaldehyde in the presence of primary amines to give the corresponding azadithiolates (eq 1). The conditions simply call for



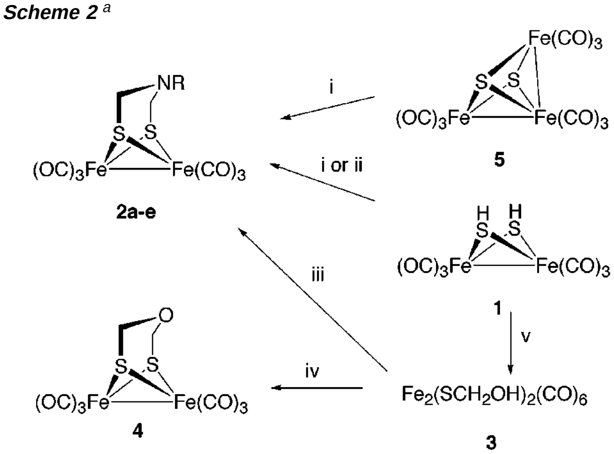
(1)

addition of the diiron complex to a premixed THF solution of paraformaldehyde and the amine at 0 °C followed by warming to room temperature. The efficiency of the process can be tested by thin-layer chromatography on silica gel.[10] From *tert*-butylamine and benzylamine we obtained $Fe_2[(SCH_2)_2N\text{-}t\text{-}Bu](CO)_6$ (**2a**) and $Fe_2[(SCH_2)_2NCH_2Ph](CO)_6$ (**2b**) in 91 and 87% isolated yields, respectively. We realized that the amine and formaldehyde would condense to give imine derivatives, and this idea led to a revised

Scheme 1



Scheme 2 [a]



[a] Reagents: (i) $(CH_2O)_n/RNH_2$; (ii) $(CH_2)_3(NR)_3$ or $(CH_2)_6N_4$ (for **2e**); (iii) RNH_2; (iv) H_2SO_4; (v) CH_2O (aqueous).

synthetic protocol. Treatment of **1** with the trimeric imines 1,3,5-$(CH_2)_3(NMe)_3$ and 1,3,5-$(CH_2)_3(NPh)_3$ afforded $Fe_2[(SCH_2)_2NMe](CO)_6$ (**2c**) and $Fe_2[(SCH_2)_2NPh](CO)_6$ (**2d**) in 85 and 89% yields, respectively. Qualitatively, these reactions are proposed to proceed via protonation of an imine nitrogen by **1** followed by nucleophilic attack of the resulting thiolate anion at the adjacent electrophilically activated methylene. Crystallographic characterization confirms the structure of **2d**.

The synthesis of $Fe_2[(SCH_2)_2NH](CO)_6$ (**2e**), which contains the actual (proposed[5]) cofactor, was enabled by the new methodology. Treatment of **1** with a premixed solution of paraformaldehyde and $(NH_4)_2CO_3$ afforded **2e** in ~40% yield. Compound **2e** also arises via the reaction of **1** and hexamethylenetetramine, $(CH_2)_6N_4$ (the condensation product of ammonia and formaldehyde). The latter method involves the cleavage of several C−N bonds, which may explain the modest (24%) yield. The 75 °C ^{1}H NMR spectrum of **2e** consists of a doublet (CH_2) and broadened quintet (NH). At −40 °C, whereupon the flexing of the $Fe_2S_2C_2N$ bicycle is slowed, the methylene proton signals become nonequivalent, and the NH appears as a triplet due to coupling to only two of the four methylene protons. We converted[3] **2e** into $(Et_4N)_2\{Fe_2[(SCH_2)_2NH](CN)_2(CO)_4\}$ to obtain a crystalline derivative (Figure 1). The

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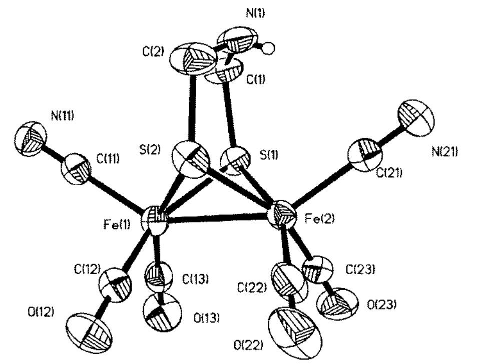

Figure 1. Structure of the anion in $(Et_4N)_2[Fe_2[(SCH_2)_2NH](CN)_2(CO)_4]$ with thermal ellipsoids set at 50% probability. Selected distances (Å): Fe1−Fe2, 2.509(5); Fe1−S1, 2.2877(6); Fe1−S2, 2.2779(7); Fe1−C11, 1.945(3); Fe1−C12, 1.741(3); Fe2−C21, 1.939(2); Fe2−C22, 1.745(3); N1−C1, 1.394(4); S1−C1, 1.858(3); C1−N1−C2, 119.4(3); sum of angles at N1, 330°.

N−H is axial, as anticipated,[6] and the amine is pyramidal. The cyanide ligands are positioned approximately trans to the Fe−Fe bond, although we suspect that the energy differences between various rotamers is low.

Omitting the amine from the recipe, the reaction of **1** and aqueous formaldehyde afforded a species tentatively assigned as $Fe_2(SCH_2OH)_2(CO)_6$ (**3**) on the basis of its polarity (TLC and solubility) and reactivity. Intermediate **3** reacts at room temperature with *t*-$BuNH_2$ to give **2a** and with aqueous $(NH_4)_2CO_3$ to give **2e** (35% yield). Treatment of CH_2Cl_2 solutions of **3** with neat H_2SO_4 gives the oxadithiolate $Fe_2[(SCH_2)_2O](CO)_6$ (**4**).

Previous studies indicated that the amine in **2c** exhibits diminished basicity, which is attributed to an interaction between the nonbonding electron pair on *N*Me and the low-lying C−S σ^* orbitals. For **2c**, the analysis of the amine's basicity was complicated by a significant nonbonding interaction between methyl and an underlying CO ligand, which was manifested by a flattening of the amine.[7] Because of these complications, we were keen to examine the conformation of the actual cofactor which lacks the relatively bulky methyl group. Protonation of the amine in **2e** by HOTf was indicated by $\Delta\nu_{CO(avg)} = 17\ cm^{-1}$. IR studies show that in MeCN solution ammonium ion **2e**H^+ is deprotonated by water ($pK_a = 2.3$). With respect to the mechanism of enzyme action, such an acidic ammonium proton could protonate even a weakly basic iron hydride.

In recent reports iron carbonyls have been discussed for their possible role in "primordial" chemistry.[11,12] Within the context of these speculative ideas, the cluster $Fe_3S_2(CO)_9$ (**5**) must be evaluated as a biosynthetic intermediate because it is very stable and readily forms under diverse conditions.[13] Treatment of **5** with formaldehyde and *t*-$BuNH_2$ indeed afforded **2a** in ~60% isolated yield. The mechanism of this reaction remains under study, but formaldehyde clearly plays a role more significant than simply forming imines. We also prepared **2e** from the reaction of **5**, $(NH_4)_2CO_3$, and paraformaldehyde (28% yield). The conversion of **5** into azadithiolate derivatives constitutes the assembly of a major portion of a precatalyst for hydrogen production, especially in view of the easy conversion of **2e** into the dicyanide.

In summary, azadithiolato diiron species can be prepared under mild conditions via the condensation of metal sulfides, formaldehyde, and amines. The results may be biosynthetically relevant, especially in view of the facility of the reactions, their tolerance of aqueous conditions, and the simplicity of the reagents. Further studies on the reactivity of M(SH) complexes[14] toward aldehydes and imines is indicated.

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Supporting Information Available: Crystallographic details for **2d** and $(Et_4N)_2[Fe_2[(SCH_2)_2NH](CN)_2(CO)_4]$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **2a**: A solution of 0.6 g (0.02 mol) of paraformaldehyde and 0.7 g (0.0096 mol) of *t*-$BuNH_2$ in 20 mL of THF was stirred for 4 h and then treated with a solution of 0.17 g (0.49 mmol) of **1** in 20 mL of THF. The product was purified by silica gel chromatography eluting with hexane. Identified by comparison with authentic samples[7] by ^1H NMR, IR, CHN analysis. **2b**: ^1H NMR (CD_3CN) δ 7.20−7.32 (m, 5H, C_6H_5), 3.76 (s, 2H, $PhCH_2N$), 3.42(s, 4H, NCH_2S). IR (hexane) 2076, 2038, 2004, 1998, 1983 cm^{-1}. %CHN. **2c**: A solution of 0.14 g (0.40 mmol) of **1** in 20 mL of THF was treated with 0.45 g (3.5 mmol) of $(CH_2)_3(NMe)_3$ at −78 °C. After warming to room temperature, the reaction solution was stirred for 5 h. The product crystallized from a concentrated hexane solution at −33 °C and identified by comparison with authentic samples (ref 4) by ^1H NMR, IR, and TLC. For **2d**: ^1H NMR (C_6D_6) δ 6.20−7.20 (m, 5H, C_6H_5), 3.57 (s, 4H, SCH_2N). IR (hexane) 2077, 2039, 2007, 2002, 1983 cm^{-1}. HR-MS (FAB^+). Calcd for $C_{14}H_9Fe_2NO_6S_2$ 462.857009 (M), found 462.856800. **2e**: A mixture of 0.6 g (0.02 mol) of paraformaldehyde, 0.57 g (0.0059 mol) of $(NH_4)_2CO_3$ and 20 mL of THF was stirred for 4 h then treated with a solution of 0.17 g (0.49 mmol) of **1** in 20 mL of THF. After 10 h, THF was removed under vacuum, a hexane extract was chromatographed on silica gel eluting with 1:8 CH_2Cl_2:hexane, giving **2e** as a red solid. ^1H NMR (CD_3CN, 75 °C) δ 3.71 (d, 4H, NCH_2S), 2.22 (bm, 1H, N*H*). ^1H NMR (CD_3CN, − 40 °C) δ 3.89 (m, 2H, NC*H*HS), 3.45 (t, 2H, NCH*H*S), 2.24 (t, 1H, N*H*). IR (hexane) 2076, 2036, 2008, 1989, 1979 cm^{-1}. HR-MS (FAB^+) calcd for $Fe_2S_2C_8H_5NO_6$ 386.825700. Found 386.825709. **4**: A solution of 0.18 g (0.5 mmol) of **1** in 20 mL of THF was treated with 1 mL of 37% $HCHO/H_2O$ for 5 h. THF and unreacted HCHO were removed under vacuum, and the residue was washed with 40 mL of hexane. A 20 mL CH_2Cl_2 extract of the product was stirred over 1 mL of H_2SO_4 for 10 h followed by chromatography on silica gel, eluting with hexane. Yield: 0.035 g (32%). ^1H NMR (CD_3CN) 4.29 (s, 4H, $(SCH_2)_2O$). IR (hexane) 2079, 2043, 2007, 2004, 1987 cm^{-1}. HRMS (EI). Calcd for $Fe_2S_2C_8H_4O_7$ 387.810027, found 387.809725. The dicyanide of **2e** was prepared and crystallized as described previously.[4] **2a from $Fe_3S_2(CO)_9$**: A mixture of 0.6 g (0.02 mol) of paraformaldehyde, 0.7 g (0.0096 mol) of *t*-$BuNH_2$, was slurried in 20 mL of THF for 4 h, then treated with 0.19 g (0.44 mmol) of **5** in 20 mL of THF. Chromatographic on silica gel gave 0.12 g of **2a**. Crystal data for **2d** $C_{14}H_9Fe_2NO_6S_2$: $M = 463.0$; triclinic; $P\bar{1}$; $a = 7.7279(17)$ Å, $b = 10.967(2)$ Å, $c = 11.194(2)$ Å, $\alpha = 73.729(4)°$, $\beta = 85.332(4)°$, $\gamma = 69.856(4)°$, $V = 854.9(3)$ Å^3; 193(2) K; $Z = 2$; max. min. transmission 0.7082, 0.9788; $D_c = 1.799$ g cm^{-3}; 7914 reflections collected, 4011 unique; $R_{int} = 0.0177$, $R_1 = 0.0239$, $WR_2 = 0.0665$ [$I > 2\sigma(I)$]. Crystal data for **2e**: $C_{24}H_{45}Fe_2N_5O_4S_2$: $M = 643.5$; orthorhombic, $P2_12_12_1$; $a = 11.9966(6)$ Å, $b = 14.2977(6)$ Å, $c = 18.1645(8)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 3115.6(2)$ Å^3; 293(2) K; $Z = 4$; max. min. transmission 0.5878, 0.7022; $D_c = 1.372$ g cm^{-3}; 29223 reflections collected, 7554 unique; $R_{int} = 0.0447$, $R_1 = 0.0296$, $WR_2 = 0.0622$ [$I > 2\sigma(I)$].

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