

## Small Molecule Analogues of the Fe-only Hydrogenase Active Site

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The iron-only hydrogenase (Fe H<sub>2</sub>-ase) enzymes are responsible for hydrogen oxidation and proton reduction in microorganisms.<sup>1</sup> The active site (H-cluster) contains a ferredoxin-like [Fe<sub>4</sub>S<sub>4</sub>] cluster bound to a unique two-iron sub-cluster with dithiolate, carbonyl, and cyanide ligands (Figure 1).<sup>2</sup> The two-iron unit is thought to be site of dihydrogen and proton binding. The dithiolate ligand probably contains a central atom capable of hydrogen bonding;<sup>2</sup> DFT calculations favor assignment of NH for X.<sup>3</sup>

Synthesis of binuclear iron-carbonyl compounds containing N-Me analogues of the proposed azadithiolate cofactor was undertaken in an attempt to answer three questions: (i) is the azadithiolate cofactor sufficiently stable that it could exist in the H-cluster, (ii), what are its structural properties, and (iii) what insights into H<sub>2</sub> production/oxidation by the enzyme can be obtained from the characteristics of the synthetic cofactors? Treatment of Li<sub>2</sub>[Fe<sub>2</sub>S<sub>2</sub>(CO)<sub>6</sub>]<sup>4-</sup> with MeN(CH<sub>2</sub>Cl)<sub>2</sub> afforded the desired Fe<sub>2</sub>[(SCH<sub>2</sub>)<sub>2</sub>NMe](CO)<sub>6</sub> (Figure 2). The pK<sub>a</sub> of the protonated N-methyl azadithiolate is between 10.6 and 7.6; HNEt<sub>3</sub><sup>+</sup> has a significantly lower pK<sub>a</sub> value, ca. 18.<sup>5</sup> Treatment of Fe<sub>2</sub>[(SCH<sub>2</sub>)<sub>2</sub>NMe](CO)<sub>6</sub> with Et<sub>4</sub>NCN, following the protocol developed independently in this laboratory,<sup>6</sup> and others,<sup>7, 8</sup> afforded the dicyano derivative, (NEt<sub>2</sub>)<sub>2</sub>{Fe<sub>2</sub>[(SCH<sub>2</sub>)<sub>2</sub>NMe](CN)<sub>2</sub>(CO)<sub>4</sub>}.

Functional models of the proton reduction activity of the H-cluster were also obtained. Early models for the H-cluster of the Fe H<sub>2</sub>-ase enzymes, [Fe<sub>2</sub>(SR)<sub>2</sub>(CN)<sub>2</sub>(CO)<sub>4</sub>]<sup>2-</sup> compounds, were unstable in the presence of acid, and therefore could not be functional for proton reduction.<sup>6</sup> The corresponding bis(phosphine) derivatives, Fe<sub>2</sub>(SR)<sub>2</sub>(CO)<sub>4</sub>(PR'<sub>3</sub>)<sub>2</sub>,<sup>9</sup> are protonated at the Fe-Fe bond to give stable compounds.<sup>10, 11</sup> Treatment of Fe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CO)<sub>6</sub> with Et<sub>4</sub>NCN in the presence of excess PMe<sub>3</sub> gave (Et<sub>4</sub>N)[Fe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>(PMe<sub>3</sub>)]. The mixed cyano-phosphine compound is stable in the presence of excess acid. Electrolysis of a solution of (Et<sub>4</sub>N)[Fe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>(PMe<sub>3</sub>)] and sulfuric acids in MeCN produced H<sub>2</sub> in ca. 100% Faradaic yield, corresponding to six turnovers for the bulk solution. The activity of this compound was comparable to other proton reduction catalysts<sup>12, 13</sup> and it exhibited a significantly lower overpotential than many of such systems.<sup>14</sup> The anion [Fe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>(PMe<sub>3</sub>)]<sup>-</sup> is protonated by strong acids to give HFe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>(PMe<sub>3</sub>) (Figure 3). The hydrido compound HFe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>(PMe<sub>3</sub>) can be further protonated at nitrogen to give [HFe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CNH)(CO)<sub>4</sub>(PMe<sub>3</sub>)]<sup>+</sup>. Electrochemical and analytical data show that reduction of [HFe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CNH)(CO)<sub>4</sub>(PMe<sub>3</sub>)]<sup>+</sup> gives [Fe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>(PMe<sub>3</sub>)]<sup>-</sup> and H<sub>2</sub>. Subtle electronic effects control the initial site of protonation,<sup>15, 16</sup> (e.g., treatment of {Fe<sub>2</sub>(S<sub>2</sub>C<sub>3</sub>H<sub>6</sub>)(CN)(CO)<sub>4</sub>[P(OMe)<sub>3</sub>]}<sup>-</sup> with p-toluenesulfonic acid gives protonation at the cyano ligand as opposed to the Fe-Fe bond).

While  $[\text{HFe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CNH})(\text{CO})_4(\text{PMe}_3)]^+$  is an active catalyst for proton reduction, it is not sufficiently stable in its oxidized form to bind  $\text{H}_2$ . Therefore, new structural models for the  $\text{H}_2$ -oxidizing state of the H-cluster were synthesized. Few ferrous-thiolate compounds exhibit the bridging CO ligand observed in the H-cluster, and these compounds are predominantly unstable.<sup>17</sup> Electron-rich polyisocyano compounds  $\text{Fe}_2(\text{S}_2\text{C}_n\text{H}_{2n})(\text{CO})_2(\text{CNMe})_4$  undergo oxidatively induced reaction with additional CNMe to give  $[\text{Fe}_2(\text{S}_2\text{C}_n\text{H}_{2n})(\text{CNMe})_7](\text{PF}_6)_2$ , the first members of a new class of iron thiolates (Figure 4). Crystallographic characterization established that the  $34 e^-$  dinuclear core resembles the  $[\text{Fe}_2]_{\text{H}}$  portion of the H-cluster, key features being the face-sharing bioctahedral geometry, the bridging  $2e^-$  donor ligand (CNMe in place of CO), and an Fe-Fe separation of 2.6 Å. Treatment of  $[\text{Fe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CNMe})_7](\text{PF}_6)_2$  with excess CNMe leads to  $[\text{Fe}_2(\text{S}_2\text{C}_3\text{H}_6)(\text{CNMe})_{10}](\text{PF}_6)_2$ ; the rate of addition of isocyanide to the binuclear compound is increased by more than three orders of magnitude under photolytic conditions. Analogously, oxidation of the phenylthiolate  $\text{Fe}_2(\text{SPh})_2(\text{CO})_2(\text{CNMe})_4$  led to mononuclear  $[\text{Fe}(\text{SPh})(\text{CNMe})_5](\text{PF}_6)$ .

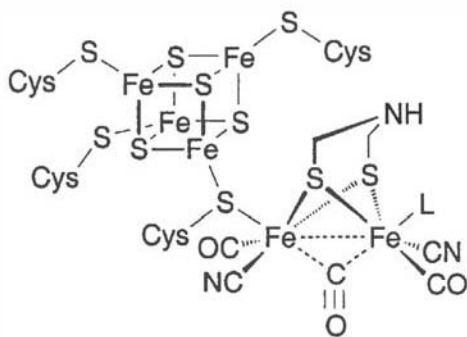


Figure 1

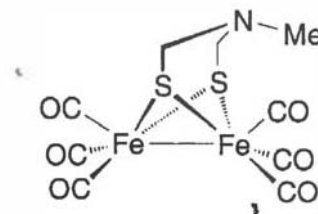


Figure 2

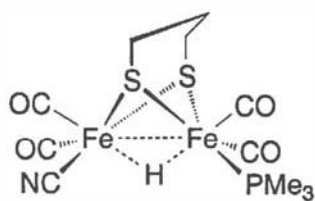


Figure 3

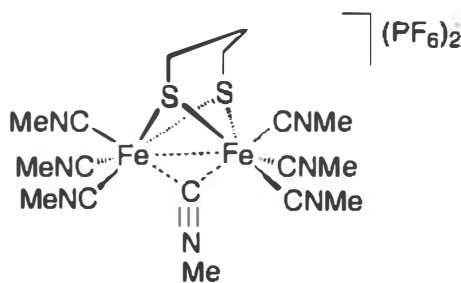


Figure 4

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