Synthesis of an Amino-Functionalized Model of the Fe-Only Hydrogenase Active Site

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Abstract: A dinuclear 2Fe2S mimic **6** of the active site of the Fe-only hydrogenases has been synthesized. Complex **6** contains a free amino group which enables linkage to a protein backbone or to a redox active species for the study of electron transfer processes in proteins or in supramolecular systems. The structures of the complex **6** and its Boc-protected precursor **5** could be verified by X-ray crystallography.

Keywords: bioinorganic chemistry · biomimetic synthesis · iron carbonyl sulfides · iron-only hydrogenase

Introduction

The iron-only hydrogenases form a wide-spread class of enzymes in microorganisms, which mediate both the metabolism of hydrogen and the reverse reaction, formation of molecular hydrogen from protons.[1–7]

The X-ray crystal structures of two types of Fe-only hydrogenases, CpI (*Clostridium pasteurianum*)[8] and DdH (*Desulfovibrio desulfuricans*)[9] were reported recently. The active sites in both systems contain an uncommon six-Fe cluster(H-cluster), which consists of a 4Fe-4S cubane structure, bridged by cysteine-S to a novel 2Fe2S subunit. The 4Fe-4S unit probably mediates electron transfer while the 2Fe-2S subunit is responsible for the formation and activation of hydrogen. In this subunit, the two Fe ions are linked by two non-cysteine thiolate groups and have CO and CN^- diatomic terminal ligands.[10] Very recent crystallographic studies suggest that the bridging dithiolate ligand has the structure of $^-SCH_2NHCH_2S^-$, or the N-protonated equivalent.[11]

Since the elucidation of the X-ray crystal structures of Fe-only hydrogenases, some synthetic 2Fe-2S complexes have been prepared as structural mimics of the active site.[12–15] Rauchfuss et al. have reported a model complex with the structure of $\{Fe_2[\mu\text{-}S_2(CH_2)_3](CN)(CO)_4(PMe_3)\}^-$.[16] Using electrochemistry, they could demonstrate catalytical hydrogen production with this complex in homogeneous solution in the presence of strong acid.

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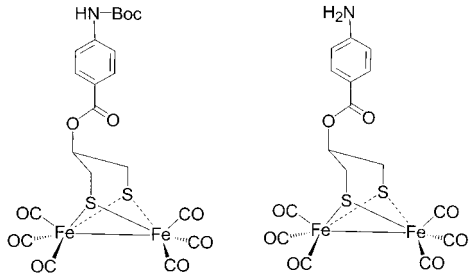
Because of our interest in photochemical hydrogen production,[17] and a general interest in attaching a 2Fe2S unit to a protein structure, we decided to try to develop synthetic procedures for preparing such units which contain a suitable functional group. The protected and unprotected amine substituted Fe dimer carbonyl sulfide complexes **5** and **6** have therefore been synthesized and characterized.



5 **6**

Results and Discussion

In the 1980s, Winter, Zsolnai, and Huttner[18] prepared $Fe_2(SR)_2(CO)_6$ derivatives through the reaction of propane-1,3-dithiol and $[Fe_3(CO)_{12}]$. However, very few diiron hexacarbonyl complexes, functionalized at 2-position in the dithiolate ring, have been described, probably because of the limited availability of functionalized 1,3-dithiols. We would therefore like to present a general synthetic route for such 1,3-dithiols, whereby sulfur bridged diiron complexes can be synthesized in a relatively simple procedure (Scheme 1).

The synthesis of the 2-functionalized 1,3-dithiolpropane subunit **4** from 1,3-dibromopropan-2-ol turned out to be a challenging problem, because the dibromo functionality is both heat and base sensitive. The acid-catalyzed esterification

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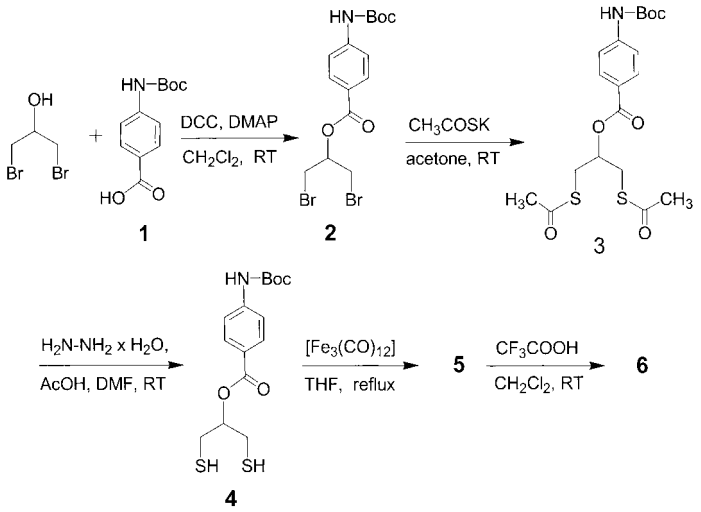

Scheme 1. The synthetic procedure of complexes **5** and **6**.

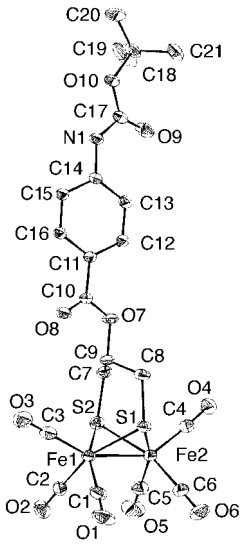

Figure 1. ORTEP (ellipsoids at 30% probability level) view of $C_{21}H_{22}Fe_2NO_{10}S_2$ (**5**).

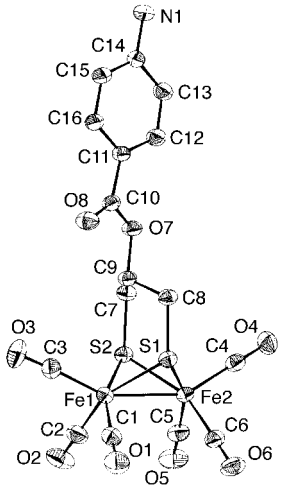

Figure 2. ORTEP (ellipsoids at 30% probability level) view of $C_{16}H_{11}Fe_2NO_8S_2$ (**6**).

of 1,3-dibromopropanol[19] gave only low yields (<5%). More recently, Boyes and Hewson have reported[20] the esterification of similar compounds by using *N*,*N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). After several trials, we managed to find reaction conditions, which gave an ester derivative **2** of 1,3-dibromopropan-2-ol in reasonable yields.

The most critical step in our synthesis seemed to be the replacement of the bromides by thiol groups. The direct preparation of thiols from alkyl halides and metal sulfides should be facile, but in our hands direct methods gave only a moderate yield of di-thiol.[21] Indirect methods involving thiourea[22] and xanthate derivatives[23] are commonly utilised for the synthesis of thiols, but these intermediates have to be transformed to thiols by hydrolysis with base or by reduction with lithium aluminium hydride, which will react also with the ester group in compound **2**.[24] However, treatment of thioacetates with amines under mild conditions has recently been shown to give thiols in good yields.[25, 26] In accordance, we were able to prepare the dithioacetate **3** by treatment of **2** with potassium thioacetate.[27] Unfortunately, the reaction of **3** with amines failed, but we were able to obtain the ester-dithiol **4** in excellent yields by treating **3** with hydrazine hydrate in acetic acid solution.[28]

Reaction of the dithiol ligand **4** with $[Fe_3(CO)_{12}]$ in THF gave the product **5** in a rather good yield (87%) after purification by column chromatography on silica gel. Treatment of **5** with trifluoroacetic acid (TFA) in dichloromethane at room temperature[29] gave complex **6** which has a free amino functional group. The synthetic steps for preparing complexes **5** and **6** could be repeated; furthermore it was no problem to scale-up the synthesis. It is worth to mention that the Fe dimer core structures in **5** and **6** were stable even in fairly strongly acidic conditions such as in the presence of TFA. These complexes were also stable during purification by column chromatography on silica gel.

All new compounds synthesized herein were characterized by ^{1}H NMR spectroscopy and elemental analysis.

Single crystal X-ray diffraction shows that the two $Fe_2(\mu\text{-}S)_2(CO)_6$ units of **5** (Figure 1) and **6** (Figure 2) are very similar and to a large extent analogous to those found in other $Fe_2(\mu\text{-}SR)_2(CO)_6$ structures.[13, 30] In the central $Fe_2(\mu\text{-}SR)_2(CO)_6$ unit the two Fe atoms and the two S atoms form a butterfly conformation in which the metal atoms are connected to each other through a Fe–Fe single bond with 2.509(1) and 2.499(1) Å for **5** and **6**, respectively. The first S_2C_3 coordination shell surrounding each Fe atom is best described as a square-pyramidal coordination geometry with one of the carbonyl C atoms in the apical position. The Fe atom is displaced from the basal plane in the direction to the apical C atom. Intermolecular N-H···O hydrogen bonds are present in both **5**, N1···O8 2.988(2) Å, and **6**, N1···O8 3.212(8) Å. A potentially important structural feature of these complexes is that the amino group is well separated from the dimeric Fe core. (Fe1···N1 11.163(2), Fe2···N1 11.351(2) Å in **5** and Fe1···N1 11.186(7), Fe2···N1 11.240(6) Å in **6**). Selected bond lengths of compounds **5** and **6** are listed in Table 1.

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Table 1. Selected bond lengths [Å] for **5** and **6**.

	5	6
Fe1–S1	2.2699(7)	2.278(2)
Fe1–S2	2.2603(7)	2.257(2)
Fe1–Fe2	2.5093(5)	2.499(1)
Fe2–S1	2.2528(7)	2.256(2)
Fe2–S2	2.2466(7)	2.261(2)
Fe1–C1	1.797(3)	1.794(7)
Fe1–C2	1.798(3)	1.787(7)
Fe1–C3	1.807(3)	1.808(7)
Fe2–C4	1.807(3)	1.804(7)
Fe2–C5	1.797(3)	1.789(7)
Fe2–C6	1.799(3)	1.815(7)
S1–C8	1.833(2)	1.824(6)
S2–C7	1.824(2)	1.827(6)

Conclusion

An amino-functionalized model **6** for the active site of the Fe-only hydrogenases has been prepared by covalently linking 4-aminobenzoic acid to a 2Fe2S structure. The Fe dimers of **6** and its precursor **5** are fully stable during the reaction conditions invetsigated. The crystal structures of **5** and **6** show that the functional group and the Fe dimer are separated from each other by about 11 Å. This suggests that these complexes will be useful for protein modification and the build up of supramolecular systems, where a 2Fe2S unit is linked to one or more redox components for the study of electron transfer processes.

Experimental Section

All reagents and solvents were purchased from Aldrich and used as received. ^{1}H NMR spectra were recorded on a Varian 400 spectrometer. Elemental analysis was performed in Analytische Laboratorien, Lindlar (Germany).

4-Butoxycarbonylaminobenzoic acid (1): 4-Aminobenzoic acid (2.74 g, 20 mmol) was suspended in water (40 mL) and then *tert*-butanol (30 mL) was added. To this solution di-*tert*-butyl-dicarbonate (8.73 g, 40 mmol) and solid NaOH (0.88 g, 22 mmol) were added and the temperature was increased to 60 °C. After completion of reaction the mixture it was diluted with water (100 mL), washed with CH_2Cl_2 (2 × 50 mL) and the water phase was cooled to 0–5 °C. Ethyl acetate was added (50 mL), and under intensive stirring the pH was lowered to 2 by the addition of 2 M HCl. The organic phase was separated and the extraction was repeated with ethyl acetate (2 × 50 mL). Combined extracts were dried over Na_2SO_4, and evaporated in vacuo giving 4-butoxycarbonylaminobenzoic acid (**1**; 4.62 g, 97.5 %). The solid off-white powder was directly used for the next step. ^{1}H NMR ([D$_6$]DMSO): $\delta = 1.48$ (s, 9H), 7.54–7.56 (m, 2H), 7,82–7.84 (m, 2H), 9.72 (s, 1H), 12.59 (s, 1H).

1,3-Dibromo-2-(4-butoxycarbonylaminobenzoyl)propanol (2): DMAP (0.128 g, 1.05 mmol) and 1,3-dibromopropan-2-ol (0.26 mL, 2.54 mmol) were added to a suspension of compound **1** (0.6 g, 2.53 mmol) in dry CH_2Cl_2 (50 mL). The resulting suspension was stirred at room temperature for 15 min, and then a CH_2Cl_2 (15 mL) solution of DCC (0.87 g, 4.21 mmol) was added dropwise (~15 min) under N_2 atm at ambient temperature. The reaction was followed by TLC, and when the starting material disappeared (~4 h) the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica with toluene/EtOAc (6:1) as eluent. After evaporation of the solvent **2** was obtained as a white powder (0.905 g, 86 %). ^{1}H NMR ($CDCl_3$): $\delta = 1.53$ (s, 9H), 3.72 (dd, $J = 11.0$, 5.4 Hz, 1H), 3.77 (dd, $J = 11.0$, 4.9 Hz, 1H), 5.35 (app. pent., $J = 5.4$ Hz, 1H), 6.67 (s, 1H), 7.44–7.47 (m, 2H), 7.98–8.01 (m, 2H); elemental analysis calcd (%) for $C_{15}H_{19}Br_2NO_4$: C 41.21, H 4.38, Br 36.56, N 3.20; found: C 41.71, H 4.58, Br 35.67, N 3.21.

1,3-Dithioacetyl-2-(4-butoxycarbonylaminobenzoyl)propanol (3): The dibromo derivative **2** (0.219 g, 0.5 mmol) was dissolved in acetone (15 mL), and then potassium thioacetate (4.5 equiv; 0.257 g, 2.25 mmol) was added. The reaction was stirred under N_2 at ambient temperature and followed by TLC. When starting material disappeared (ca. 4 h) the precipitated KBr was filtered off, and the filtrate was evaporated in vacuo. The residue was purified by flash column chromatography with toluene/EtOAc (6:1) as eluent, giving **3** (177 mg, 82.5 %) as an oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.52$ (s, 9H), 2.32 (s, 6H), 3.26 (dd, $J = 10.5$, 4.8 Hz, 1H), 3.29 (dd, $J = 10.5$, 3.9 Hz, 1H), 5.22–5.28 (m, 1H), 6.71 (s, 1H), 7.42–7.44 (m, 2H), 7.91–7.93 (m, 2H); elemental analysis calcd (%) for $C_{19}H_{25}Br_2NO_6S_2$: C 53.38, H 5.89, N 3.28, S 15.00; found: C 53.20, H 5.97, N 3.17, S 15.14.

1,3-Dithiolo-2-(4-butoxycarbonylaminobenzoyl)propanol (4): The thioacetate derivative **3** (124 mg, 0.29 mmol) was dissolved in DMF (5 mL). To solution hydrazine hydrate (3.5 equiv; 50 µL, 1.027 mmol) was added dropwise under N_2 at ambient temperature, and then the solution was stirred for 10 min. Afterwards, acetic acid (3.5 equiv; 60 µL, 1.027 mmol) was added dropwise under N_2 at ambient temperature. The reaction was followed by TLC, and when the starting material disappeared (ca. 30 min) the mixture was diluted with water (10 mL) and ethyl acetate (10 mL). After phase separation the organic layer was washed with 2 × 10 mL of water, and then the water phase was extracted with ethyl acetate. The combined organic phase was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography with toluene/EtOAc (6:1) as eluent, giving **4** (94.5 mg, 95.5 %) as a thick oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.46$ (t, $J = 8.8$Hz, 2H), 1.53 (s, 9H), 2.97 (dd, $J = 5.7$ Hz,1 Hz, 1H), 3.00 (dd, $J = 5.7$ Hz, 1.5 Hz, 1H), 5.16 (app. pent., $J = 5.7$ Hz, 1H), 6.66 (s, 1H), 7.43–7.46 (m, 2H), 7.96–7.99 (m, 2H); elemental analysis calcd (%) for $C_{19}H_{25}Br_2NO_6S_2$: C 52.45, H 6.16, N 4.08, S 18.67; found: C 52.45, H 6.21, N 4.03, S 18.58.

Synthesis of [µ-(SCH$_2$)$_2$CHCO$_2$C$_6$H$_4$NHCO$_2$C(CH$_3$)$_3$]Fe$_2$(CO)$_6$ (5): The dithiol derivative **4** (90 mg, 0.207 mmol) was dissolved in dry THF (20 mL), and then triiron dodecacarbonyl (105 mg, 0.208 mmol) was added. The resulting solution was warmed up to 65–67 °C, stirred for 0.5 h under N_2, and then concentrated by evaporating the solvent in vacuo. The crude product was purified by flash column chromatography on silica gel with toluene/pentane (1:1) as eluent followed by pure toluene. The crystalline product **5** was obtained by cooling the concentrated toluene solution at ca −20 °C overnight (141.5 mg, 87 %). ^{1}H NMR ($CDCl_3$): $\delta = 1.52$ (s, 9H), 1.69 (dd, $J = 12.9$, 12.0 Hz, 1H), 2.91 (dd, $J = 13.5$, 4.5 Hz, 1H), 4.42–4.49 (m, 1H), 6.65 (s, 1H), 7.39–7.42 (m, 2H), 7.86–7.88 (m, 2H); elemental analysis calcd (%) for $C_{21}H_{19}Fe_2NO_{10}S_2$: C 40.6, H 3.08, N 2.25, S 10.32; found: C 43.76, H 3.46, N 2.11, S 9.37. The deviation is due to the presence of ca 20 % toluene solvent in the crystal structure.

Crystal data for 5: $C_{21}H_{19}Fe_2NO_{10}S_2$: $M = 621.20$, monoclinic space group, $P2_1/c$ (No. 14), $a = 11.1598(10)$, $b = 11.9372(12)$, $c = 22.735(3)$ Å, $\beta = 92.002(12)°$, $V = 3026.8(6)$ Å^3, $Z = 4$, $T = 170$ K, $\rho_{calcd} = 1.466$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 1.15$ mm^{-1}, $F(000) = 1356$, 22301 reflections measured, 5651 unique ($R_{int} = 0.048$), 4956 observed ($I > 2\sigma(I)$), 365 parameters refined, absorption correction (numerical): $T_{min}/T_{max} = 0.788/0.916$. $R1 = 0.0335$, ($I > 2\sigma(I)$), $wR(F^2) = 0.1050$, $S = 1.11$ (all data). Max./min. residual electron density: 0.52/−0.46. Data collection: STOE-IPDS image plate diffractometer with a rotating-anode using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The intensities of the reflections were integrated with the STOE software, and the numerical absorption correction was performed with the programs X-RED and X-SHAPE.[31] The structure was solved by direct methods[32] and refined by full matrix least-squares on F^2.[33]

Synthesis of [µ-(SCH$_2$)$_2$CHCO$_2$C$_6$H$_4$NH$_2$]Fe$_2$(CO)$_6$ (6): Trifluoroacetic acid (0.51 mL, 3 mmol) was added to a solution of the diiron complex **5** (90 mg, 0.14 mmol) in dry dichloromethane (10 mL), and then stirred at ambient temperature. The reaction was followed by TLC, and when the starting material disappeared (3–4 h) the solvent and unreacted TFA were evaporated in vacuo. The residue was purified by flash chromatography with toluene/EtOAc (6:1) as eluent to give **6** (67 mg, 89 %). A single crystalline product was obtained by cooling the concentrated toluene/pentane (1:1) solution of **6** at about −20 °C overnight. ^{1}H NMR ($CDCl_3$): $\delta = 1.67$ (dd, $J = 13.0$, 11.5 Hz, 1H), 2.90 (dd, $J = 13.0$, 4.1 Hz, 1H), 4.09 (s,

2H), 4.39 – 4.44 (m, 1H), 6.59 – 6.62 (m, 2H), 7.73 – 7.76 (m,2H); elemental analysis calcd (%) for $C_{16}H_{11}Fe_2NO_8S_2$: C 36.88, H 2.13, N 2.69, S 12.30; found: C 37.04, H 2.31, N 2.63, S 12.19.

Crystal data for 6: $C_{16}H_{11}Fe_2NO_8S_2$: $M = 521.08$, triclinic space group, $P\bar{1}$ (No. 2), $a = 8.4739(14)$, $b = 9.9920(16)$, $c = 13.296(2)$ Å, $\alpha = 69.81(2)^\circ$, $\beta = 71.99(2)^\circ$, $\gamma = 85.96(2)^\circ$, $V = 1004.0(3)$ Å^3, $Z = 2$, $T = 293$ K, $\rho_{calcd} = 1.724(1)$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 1.70$ mm^{-1}, $F(000) = 524$, 7898 reflections measured, 3641 unique ($R_{int} = 0.032$), 2991 observed ($I > 2\sigma(I)$), 266 parameters refined, absorption correction (numerical): $T_{min}/T_{max} = 0.723/0.822$. $R1 = 0.0483$ ($I > 2\sigma(I)$), $wR2 = 0.1743$, $S = 1.19$ (all data). Max./min. residual electron density: 0.558/ − 0.767. Data collection: STOE-IPDS image plate diffractometer with a rotating-anode using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The intensities of the reflections were integrated with the STOE software, and the numerical absorption correction was performed with the programs X-RED and X-SHAPE.[31] The structure was solved by direct methods[32] and refined by full matrix least-squares on F^2.[33]

CCDC-192065 (**5**) and CCDC-192066 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

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