

Beyond Fe-only hydrogenases: *N*-functionalized 2-aza-1,3-dithiolates $\text{Fe}_2[(\text{SCH}_2)_2\text{NR}](\text{CO})_x$ ($x = 5, 6$)

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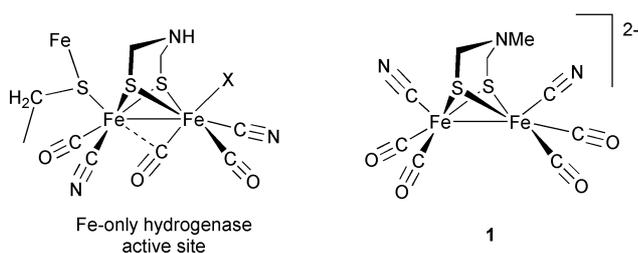
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Primary amines undergo chloromethylation with $\text{CH}_2\text{O}/\text{SOCl}_2$ to give $\text{RN}(\text{CH}_2\text{Cl})_2$, which in turn react with $\text{Li}_2[\text{Fe}_2\text{S}_2(\text{CO})_6]$ to give $\text{Fe}_2[(\text{SCH}_2)_2\text{NR}](\text{CO})_6$; in the case of $\text{R} = \text{CH}_2\text{CH}=\text{CH}_2$ and $\text{CH}_2\text{CH}_2\text{SMe}$, Me_3NO -induced decarbonylation afforded pentacarbonyl derivatives wherein the pendant functionality is coordinated to Fe.

The Fe-only hydrogenases are a topical class of proteins with organometallic reaction centers of the formula $[\text{Fe}_2(\text{S}-\text{R})_2(\text{CN})_2(\text{CO})_3\{\text{Fe}_4\text{S}_4(\mu-\text{SR})(\text{SR})_3\}(\text{X})]$ ($\text{X} = \text{H}_2\text{O}, \text{CO}, \text{H}^-/\text{H}_2$).^{1,2} Significant progress has been achieved in characterizing the first coordination shell of the diiron core,^{3–5} including high quality crystal structures of the dicyanides $[\text{Fe}_2(\text{S}-\text{R})_2(\text{CN})_2(\text{CO})_4]^{2-}$.^{1,3} It has recently been proposed that the dithiolate ligand is an azadithiolate $\text{SCH}_2\text{NH}_x\text{CH}_2\text{S}$,⁶ and we have used $(\text{ClCH}_2)_2\text{NMe}$ to introduce this novel functionality (Scheme 1).⁷

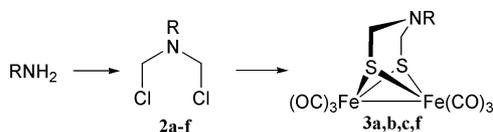


Scheme 1

Because the azadithiolate cofactor defines an unprecedented coordination motif, we sought to explore its scope. The only known bis(chloromethyl)amine, $(\text{ClCH}_2)_2\text{NMe}$, is however prepared *via* an uninviting degradation of triazine $[\text{CH}_2\text{NMe}]_3$ using PCl_5 .⁸

We have found that many primary amines undergo efficient chloromethylation upon treatment with a solution of paraformaldehyde followed by $2\times$ excess of SOCl_2 (Scheme 2). The reactions occur under mild conditions, and the chloromethylated amines are isolated as the free bases. In some cases the amines were further purified by vacuum distillation, but usually evaporation of ether extracts provided the targeted species. These compounds were identified by ^1H NMR spectroscopy (characteristic NCH_2Cl singlet at δ 5.5–5.2) as well as elemental analysis or high resolution mass spectrometry. The following derivatives were prepared: allyl (2a), *tert*-butyl (2b), methylcarboxylethyl (2c), benzyl (2d), 4-nitroaniline (2e), and 2-(methylthio)ethyl (2f).[†] Compounds 2a–f are stable under anhydrous conditions at 0°C .

Iron thiolate carbonyl dimers were prepared from bis(chloromethyl)amines 2a, 2b, 2c, 2f by treatment with $\text{Li}_2[\text{Fe}_2-$



Scheme 2

$(\text{S})_2(\text{CO})_6]$ (Scheme 2), as for the synthesis of **1**.⁷ Recrystallization from hexanes gave analytically pure samples with isolated yields of *ca.* 50% for $\text{Fe}_2[(\text{SCH}_2)_2\text{NR}](\text{CO})_6$, **3a**, **3b**, **3c**, (**3f** was generated *in situ* and used immediately, see below).[‡] We found that these alkylations proceeded more efficiently when the crude product mixture is treated with Et_3N at -78°C to complex the BEt_3 coproduct.⁹

Suitable substituents on the amine nitrogen should be capable of coordinating to one of the two Fe centers. Decarbonylation of **3a** with Me_3NO afforded a single new derivative. Recrystallization afforded *ca.* 50% yield of the deep red pentacarbonyl $\text{Fe}_2[(\text{SCH}_2)_2\text{N}-\eta^2-\text{CH}_2\text{CH}=\text{CH}_2](\text{CO})_5$ **4a**.[§] ^1H NMR measurements indicate that the alkene is coordinated, *e.g.*, the $\text{CH}_2\text{CH}=\text{CH}_2$ signals show greatly increased coupling and chemical shift range (2.5 ppm) relative to the hexacarbonyl **3a**. Furthermore the 2-D ^1H NMR spectrum demonstrated that all methylene hydrogen atoms are diastereotopic indicative of lowered symmetry. The IR spectrum for **4a** was characteristic of a $\text{Fe}_2(\text{SR})_2(\text{CO})_5\text{L}$ species.¹⁰

Crystallographic characterization[¶] shows that **4a** adopts a cage-like structure with one Fe center bound to a pair of S atoms and the alkene (Fig. 1). The alkene is approximately *trans* to the Fe–Fe bond. The remaining Fe–Fe and Fe–C and Fe–S distances are normal, indicating that the chelation does not impose strain on the Fe_2S_2 core. Alkene adducts of iron thiolates are not widely known, the closest examples being (1) $\text{Fe}_2(\text{S}-\text{Me})_2(\text{CO})_6\text{C}_2\text{F}_4$, which results from the oxidative addition of tetrafluoroethene across the Fe–Fe bond,¹¹ and (2) $\text{Fe}_2(\text{S}-\text{Ph})(\text{CH}_2=\text{CHCHCHCH}_2)(\text{CO})_5$, which contains both alkene and allyl ligands.¹²

Analogously to the preparation of **4a**, MeCN solutions of **3c** and **3f** were subjected to Me_3NO -induced decarbonylation. We were unable to effect coordination of the ester group in **3c**, but the thioether did cyclise to give $\text{Fe}_2[(\text{SCH}_2)_2\text{NCH}_2\text{CH}_2\text{SMe}](\text{CO})_5$ **4f** (Scheme 3). Crystallographic

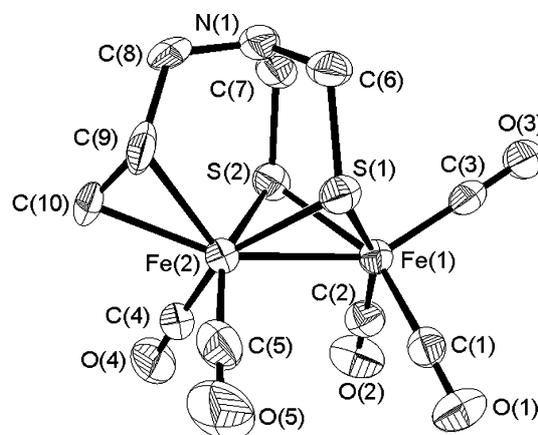
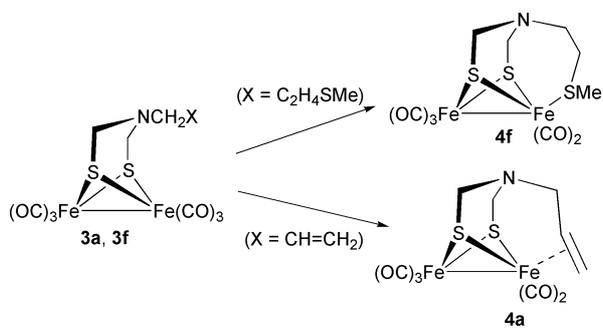


Fig. 1 Structure of $\text{Fe}_2[(\text{SCH}_2)_2\text{NCH}_2\text{CH}=\text{CH}_2](\text{CO})_5$ **4a** with thermal ellipsoids set at the 50% probability level. Selected distances (\AA) and angles ($^\circ$): Fe(1)–Fe(2), 2.5132(6); Fe(2)–C(9), 2.185(10); Fe(2)–C(10), 2.149(8); C(9)–C(10), 1.401(11); S(1)–C(6), 1.851(3); S(2)–C(7), 1.858(3); C(6)–N1–C(7), 113.6(3); C(7)–N(1)–C(8), 123.1(7); C(6)–N(1)–C(8), 107.0(7).



Scheme 3

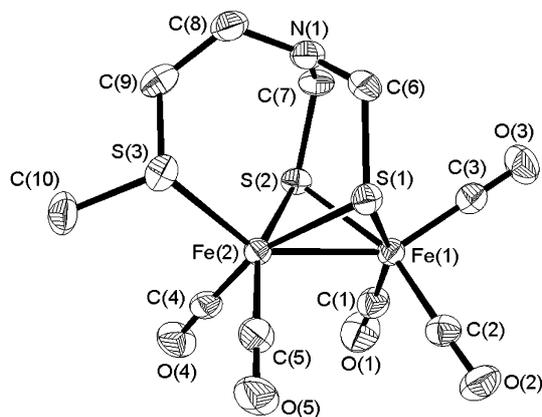


Fig. 2 Structure of $\text{Fe}_2[(\text{SCH}_2)_2\text{NCH}_2\text{CH}_2\text{SMe}](\text{CO})_5$ **4f** with thermal ellipsoids set at the 50% probability level. Selected distances (\AA) and angles ($^\circ$): Fe(1)–Fe(2), 2.5144(14); Fe(2)–S(3), 2.2703(15); S(1)–C(6), 1.870(3); S(2)–C(7), 1.865(3); C(6)–N(1)–C(7), 115.4(3); C(7)–N(1)–C(8), 121.3(3); C(6)–N(1)–C(8), 118.3(3).

characterization showed that the thioether is coordinated in **4f** (Fig. 2). Pickett and coworkers have recently reported a similar complex $\text{Fe}_2[(\text{SCH}_2)_2\text{CHCH}_2\text{SMe}](\text{CO})_5$.¹³ For **4a**, and to an even greater extent, **4f**, C–S distances are lengthened and C–N–C angles are increased due to the anomeric effect.⁷

In summary, a new route to bis(chloromethyl)amines allows general access to a broad class of *N*-functionalized azadithiolato complexes. Independent of any biological relevance, azadithiolates could be applied more generally, especially as bridging ligands with functionality.¹⁴

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Notes and references

† *Representative procedure*: a mixture of 1.8 g (0.025 mol) Bu^tNH_2 , 1.95 g (0.065 mol) paraformaldehyde, and 30 mL CH_2Cl_2 was stirred for ca. 3 h; the resulting suspension was treated dropwise with 11.9 g (0.1 mol) of SOCl_2 . After gas evolution had ceased, solvent and unreacted SOCl_2 were removed under vacuum and the products were purified by extraction into Et_2O . **CAUTION**: chloromethylamines resemble mustards and should be handled cautiously. **2a**: Colorless oil; bp 40 $^\circ\text{C}$ (0.6 mm Hg); yield: 70%. Anal. Calc. for $\text{C}_5\text{H}_9\text{Cl}_2\text{N}$: C, 38.99; H, 5.89; N, 9.09. Found: C, 38.98; H, 6.27; N, 9.16%. $^1\text{H NMR}$ (CDCl_3): δ 5.75 (1H, m, $\text{CH}_2=\text{CH}$), 5.30–5.32 (2H, m, $\text{CH}_2=\text{CH}$), 5.18 (4H, s, NCH_2Cl), 3.48 (2H, m, CHCH_2N). MS (EI): 153 (M). **2b**: Colorless oil; bp 50 $^\circ\text{C}$ (0.8 mm Hg); yield: 60%. Anal. Calc. for $\text{C}_6\text{H}_{13}\text{Cl}_2\text{N}$: C, 42.37; H, 7.70; N, 8.24; Cl, 41.69. Found: C, 42.22; H, 7.85; N, 8.01; Cl, 41.62%. $^1\text{H NMR}$ (CDCl_3): δ 5.42 (4H, s, NCH_2Cl), 1.34 (9H, s, $(\text{CH}_3)_3\text{C}$). MS (EI): 169 (M^+). **2c**: Colorless solid; mp 51 $^\circ\text{C}$; yield: 33%. Anal. Calc. for $\text{C}_5\text{H}_9\text{Cl}_2\text{NO}_2$: C, 32.28; H, 4.88; N, 7.53. Found: C, 32.62; H, 5.36; N, 7.67%. $^1\text{H NMR}$ (CDCl_3): δ 5.20 (4H, s, NCH_2Cl), 3.76 (2H, s, NCH_2CO_2), 3.75 (3H, s, CO_2CH_3). **2d**: Colorless oil; bp 80 $^\circ\text{C}$ (0.05 mm Hg); yield: 50%. $^1\text{H NMR}$ (CDCl_3): δ 7.40 (5H, m, C_6H_5), 5.22 (4H, s,

NCH_2Cl), 4.15 (2H, s, $\text{C}_6\text{H}_5\text{CH}_2\text{N}$). HR-EIMS: Calc. for $\text{C}_9\text{H}_{11}\text{Cl}_2\text{N}$, m/z 202.018731 ($\text{M} - 1$). Found: 202.019030 ($\text{M} - 1$). **2e**: pale yellow solid; mp 99 $^\circ\text{C}$; yield: 85%. $^1\text{H NMR}$ (CDCl_3): δ 7.28–8.29 (4H, dd, C_6H_4), 5.54 (4H, s, NCH_2Cl). HR-EIMS: Calc. for $\text{C}_8\text{H}_8\text{Cl}_2\text{N}_2\text{O}_2$, m/z 233.995973. Found: 233.996283. **2f**: Colorless oil; yield: 70%. $^1\text{H NMR}$ (CDCl_3): δ 5.24 [s, 4H, $\text{N}(\text{CH}_2\text{Cl})_2$], 3.24 (t, 2H, $\text{CH}_2\text{CH}_2\text{N}$), 2.76 (t, 2H, CH_3SCH_2), 2.18 (s, 3H, CH_3SCH_2).

‡ **3a**: Red crystals after chromatography on silica gel and recrystallization from hexanes; yield: 58%. Anal. Calc. for $\text{C}_{11}\text{H}_9\text{Fe}_2\text{NO}_6\text{S}_2$: C, 30.94; H, 2.12; N, 3.28. Found: C, 30.84; H, 1.97; N, 3.43%. $^1\text{H NMR}$ (C_6D_6): δ 5.22 (m, 1H, $\text{CH}_2=\text{CH}$), 4.77 and 4.66 (ddq, 2H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 2.55 (s, 4H, NCH_2S), 2.38 (d, 2H, $\text{NCH}_2\text{CH}=\text{CH}_2$). IR (hexanes): ν_{CO} 2076, 2038, 2003, 1999 cm^{-1} . **3b**: Red crystals from hexanes; yield: 58%. Anal. Calc. for $\text{C}_{12}\text{H}_{13}\text{Fe}_2\text{NO}_6\text{S}_2$: C, 32.53; H, 2.96; N, 3.16. Found: C, 32.42; H, 3.10; N, 3.20%. $^1\text{H NMR}$ (CD_3CN): δ 3.29 (br, 4H, NCH_2S), 0.97 (s, 9H, CH_3). IR (hexane): ν_{CO} 2074, 2036, 2003, 1995 cm^{-1} . **3c**: Red crystals from hexanes; yield: 31%. $^1\text{H NMR}$ (CD_3CN): δ 3.12 (s, 3H, CO_2CH_3), 2.85 (s, 4H, NCH_2S), 2.68 (s, 2H, $\text{NCH}_2\text{CO}_2\text{CH}_3$). IR (hexane): ν_{CO} 2076, 2044, 2037, 2004, 1996 cm^{-1} , ν_{ester} 1752 cm^{-1} .

§ **4a**: An orange solution of 0.150 g (0.35 mmol) **3a** in 10 mL of MeCN was treated with 0.026 g (0.35 mmol) ONMe_3 in MeCN. The resulting red-purple solution was evaporated and the product crystallized from cold hexane. Yield: 45%. Anal. Calc. for $\text{C}_{10}\text{H}_9\text{Fe}_2\text{NO}_5\text{S}_2$: C, 30.10; H, 2.27; N, 3.51. Found: C, 29.94; H, 2.10; N, 3.41%. $^1\text{H NMR}$ (C_6D_6): δ 4.17 (m, 1H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 3.69 and 3.06 (dd, 2H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 3.07 and 2.40 (s and AA'BB', 4H, NCH_2S), 2.77 and 1.48 (dd and dd, 2H, $\text{NCH}_2\text{CH}=\text{CH}_2$). IR (hexanes): ν_{CO} 2062, 2009, 1998, 1982, 1967 cm^{-1} . **4f**: Dark red crystals from hexanes; yield: 32%. Anal. Calc. for $\text{C}_{10}\text{H}_{11}\text{Fe}_2\text{NO}_5\text{S}_3$: C, 27.71; H, 2.54; N, 3.23. Found: C, 27.78; H, 2.55; N, 3.23%. $^1\text{H NMR}$ (CD_3CN): δ 4.10 and 4.01 (dd, 4H, $\text{SH}_2\text{CNCH}_2\text{S}$), 3.12 (b, 4H, $\text{NCH}_2\text{CH}_2\text{SMe}$), 2.66 (s, 3H, SCH_3). IR (hexane): ν_{CO} 2053, 1990, 1970, 1943 cm^{-1} .

¶ *Crystal data* for **4a** $\text{C}_{10}\text{H}_9\text{Fe}_2\text{NO}_5\text{S}_2$, $M = 399.0$, monoclinic, $P2_1/n$, $a = 10.7450(13)$, $b = 9.4727(11)$, $c = 14.1176(16)$ \AA , $\beta = 91.324(2)^\circ$, $V = 1436.6(3)$ \AA^3 , $T = 193$ K, $Z = 4$, max. min. transmission: 0.9990, 0.7248, $D_c = 1.845$ g cm^{-3} , 11960 reflections collected, 3222 unique, $R_{\text{int}} = 0.0763$, $R_1 = 0.0384$, $wR_2 = 0.0548$ [$I > 2\sigma(I)$]. For **4f** $\text{C}_{20}\text{H}_{22}\text{Fe}_4\text{N}_2\text{O}_{10}\text{S}_6$, $M = 866.16$, monoclinic, $P2_1/n$, $a = 17.341(11)$, $b = 10.489(7)$, $c = 18.338(12)$ \AA , $\beta = 110.020(12)^\circ$, $V = 3134(3)$ \AA^3 , $T = 193$ K, $Z = 4$, max. min. transmission: 0.9918, 0.7477, $D_c = 1.863$ g cm^{-3} , 28546 reflections collected, 7566 unique, $R_{\text{int}} = 0.0489$, $R_1 = 0.322$, $wR_2 = 0.0709$ [$I > 2\sigma(I)$].

CCDC reference numbers 163360 and 163361. See <http://www.rsc.org/suppdata/cc/b1/b104195a/> for crystallographic data in CIF or other electronic format.

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