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Thiolate-Bridged Iron–Nickel Models for the Active Site of [NiFe] Hydrogenase

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Hydrogenases catalyze the reversible oxidation of H_2, which is crucial for the anaerobic metabolism of microorganisms. They attract growing interest in connection with H_2-based energy systems. [NiFe] hydrogenase is the most common type among the currently known hydrogenases, and its active site consists of an "organometallic" Fe–Ni complex supported by cysteinyl thiolate ligands. This review presents an overview of the synthesis, properties, and reactions of thiolate-bridged iron–nickel complexes that model the active site of [NiFe] hydrogenase.

1. Introduction

The biological production and uptake of H_2 are promoted by hydrogenases, which are present in a variety of microorganisms from bacteria and archaea to eukarya.[1] Currently, three major families are known, namely [NiFe], [FeFe], and [Fe] hydrogenases, which are classified by their active sites. The active sites of all three hydrogenase types possess an "organometallic" (carbonyl)iron moiety. Figure 1 shows the protein structure of [NiFe] hydrogenase. The active sites of [NiFe][2] and [FeFe] hydrogenases[3] consist of dinuclear carbonyl/cyanide complexes having two bridging cysteinyl thiolate ligands. In particular, the dinuclear core of [FeFe] hydrogenase has a cysteine linkage to an [Fe_4S_4] cluster. [NiFe] and [FeFe] hydrogenases promote both the oxidation of H_2 ($H_2 \rightarrow 2H^+ + 2e^-$) via heterolysis of H_2 ($H_2 \rightarrow H^+ + H^-$) and the reduction of H^+ ($2H^+ + 2e^- \rightarrow H_2$); however, their functionality differs in that [NiFe] hydrogenase tends to take up H_2 while [FeFe] hydrogenase more often facilitates H_2 production.[4] In contrast to [NiFe] and [FeFe] hydrogenases, the active site of [Fe] hydrogenase is a mononuclear (carbonyl)iron complex, supported by a cysteinyl thiolate and a guanylylpyridinol (GP) moiety which serves as an N,C-ligand.[5] [Fe] hydrogenase has no iron-sulfur cluster required for electron-transfer, and thus [Fe] hydrogenase promotes neither the oxidation of H_2 nor the reduction of H^+, but splits H_2 in a heterolytic manner.[6]

[NiFe] hydrogenase, which is the most prevalent family, was structurally identified first in 1995 for the enzyme from *Desulfovibrio gigas* (*D. gigas*).[7] Since then, several additional [NiFe] hydrogenases from the organisms *Desulfovibrio vulgaris Miyazaki F* (*D. v. Miyazaki F*),[8] *Desulfovibrio fructosovorans* (*D. fructosovorans*),[9] and *Desulfovibrio desulfuricans* (*D. desulfuricans*)[10] have been reported. A variant class of [NiFe] hydrogenase from *Desulfomicrobium*

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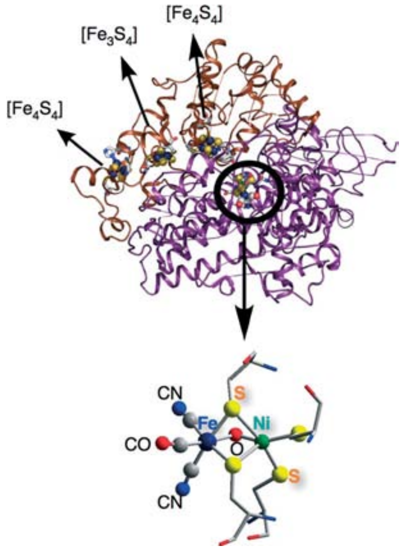


Figure 1. [NiFe] hydrogenase and its active site. Structural data was taken from the PDB entry 2FRV.[7b] This figure was drawn by using computer programs PyMol (top) and Mercury (bottom).

baculatum (*Dm. baculatum*) containing a nickel-bound selenocysteine has also been crystallographically characterized.[11] Purified [NiFe] enzymes have been found to crystallize roughly in two states as well as an inhibited form,[12] and the representative active sites are shown as schematic diagrams in Figure 2. While there are some differences between these active sites, they all feature a dinuclear $(CN)_2(CO)Fe–Ni$ complex with two bridging thiolates and two nickel-bound terminal thiolates. The oxidized (inactive) form shown in Figure 2a has a third bridging ligand X, which has been suggested to be an oxygeneous ligand (^-OH, O^{2-}, ^-OOH, or H_2O). The assignment of X as ^-SH or S^{2-} has also been proposed.[13] This ligand (X) is missing in the reduced (active) form (Figure 2b), and instead there is a bridging hydride ligand or a metal–metal bond. The Fe–Ni distance for the oxidized form is 2.8–2.9 Å, which indicates the absence of Fe–Ni bonding, while that for the reduced form is 2.5–2.6 Å. The oxidized and reduced forms can be interconverted upon exposure of the oxidized form to H_2 or treatment of the reduced form with O_2.[14] The CO-inhibited form shown in Figure 2c possesses an additional nickel-bound CO ligand, which has been identified on the basis of crystallographic[8c] and spectroscopic studies.[15] This form does not occur naturally, but deserves interest because the coordination site for CO may also serve as the binding site for H_2 during catalysis. In fact, a possible H_2 channel in [NiFe] hydrogenase is directed toward the nickel atom of the active site.[16] It should be noted that various states such as the EPR-active *Ni-A*, *Ni-B*, *Ni-C*, and *Ni-L* states and the EPR-silent *Ni-SU*, *Ni-SIr*, *Ni-SIa*, and *Ni-R* states[17] have been found as a result of spectroscopic studies of purified proteins.[18]

The active site of [NiFe] hydrogenase has attracted considerable attention from inorganic and organometallic chemists, and thus a number of thiolate-bridged Fe–Ni complexes have been synthesized to date. While several excellent reviews of the properties of the model complexes have appeared,[19] this Microreview will focus on the synthesis of relevant thiolate-bridged Fe–Ni complexes. Recent progress toward understanding the function of [NiFe] hydrogenase by using structural mimics will also be addressed.

2. Synthesis of Thiolate-Bridged Fe–Ni Complexes

The active site of [NiFe] hydrogenase consists of some key components, namely an iron atom with CO and CN ligands, a nickel atom, and thiolate ligands. Thus mixing of these components in an appropriate manner would possibly lead to the formation of the structural analogues of the active site. However, synthetic reactions for models are not as simple as one might imagine and often give rise to multiple products. There are two major difficulties, and one is the high affinity of both iron and nickel toward thiolates (and cyanides). When thiolates are simply mixed with iron and nickel precursors, thiolates may link not only iron to nickel but also iron to iron or nickel to nickel, which leads to a random arrangement of the metals. The other difficulty arises from the tendency of thiolate ligands to bridge metals. Thiolate may keep reacting with metals one after another, forming cluster complexes or metal–thiolate polymers. In order to avoid such difficulties, some precursor thiolate complexes of iron and nickel have been prepared. The synthetic approaches described below are classified on the basis of precursor type.

2.1. Precursor Nickel Complexes Having a Chelating Dithiolate Ligand

An effective way to selectively connect iron to nickel with thiolate ligands is to employ preformed metallothiolate complexes as ligands. However, homoleptic Ni^{II} thiolates tend to form multinuclear compounds $\{Ni(\mu\text{-}SR)_2\}_n$ with square-planar NiS_4 geometry.[20] Anionic Ni^{II} complexes $[Ni(SR)_4]^{2-}$ are also known;[21] however, their thiolate li-

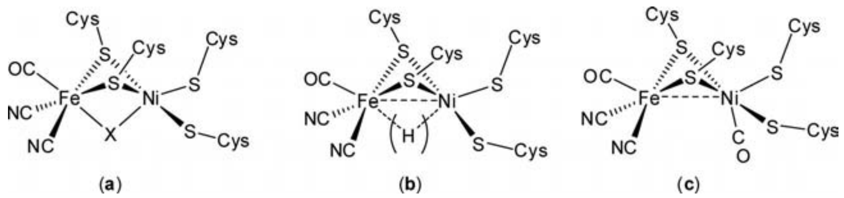


Figure 2. Schematic diagrams of oxidized (a), reduced (b), and CO-inhibited (c) forms of the active site of [NiFe] hydrogenase.

gands are often labile, dissociating in DMF or DMSO to generate thiolate anions and $[Ni(SR)_x(solv)_{4-x}]^{(x-2)-}$ (x = 2, 3).[22] In this regard, chelating thiolate ligands that have slower ligand exchange rates, particularly tetradentate or tridentate ligands, are useful because they remain intact long enough for the desired reaction to occur. Thus, various Ni^{II} complexes carrying a multidentate dithiolate ligand have been used as precursors for complexation with iron. An advantage of these nickel complexes is the spatial arrangement of the sulfur lone pairs that is suitable for capturing other metals. Figure 3 shows some of the precursor Ni^{II} complexes that have been employed, and Scheme 1 shows two of the resulting complexes formed with Fe^{II}.[23]

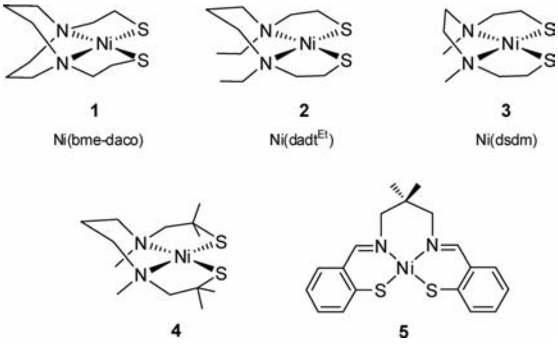
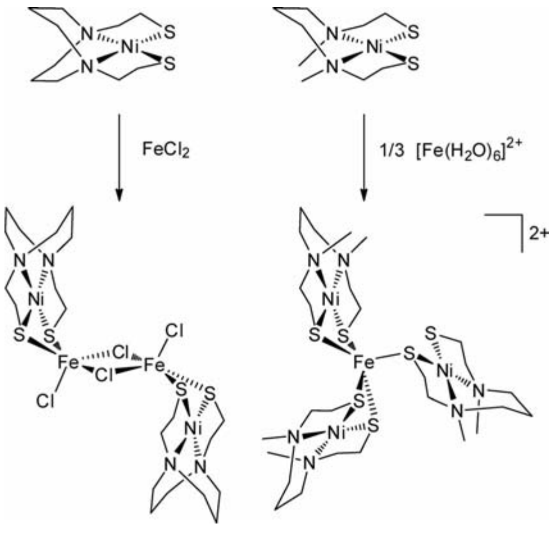


Figure 3. Ni^{II} complexes having a tetradentate N_2S_2 ligand.



Scheme 1. Complexation of [Ni(N_2S_2)] complexes with iron.

2.1.1. Precursors of thelNi(N_2S_2)] Type

Soon after the first crystallographic analysis of [NiFe] hydrogenase, a thiolate-bridged (carbonyl)iron–nickel complex (compound **6**, Figure 4) was prepared by Darensbourg's group by the reaction of [Ni(bme-daco)] {**1**; bme-daco = *N*,*N*′-bis(mercaptoethyl)-1,5-diazacyclooctane} with $Fe_2(CO)_9$.[24] One of the sulfur atoms of the [Ni(bme-daco)] complex bridges to the iron atom in a trigonal-bipyramidal geometry, suggesting retention of the Fe^0 state. Exposure of this dinuclear complex to ^{13}CO results in as much as 50% CO exchange within a few hours, while the dissociation of [Ni(bme-daco)] from iron is relatively slow (a $t_{1/2}$ of days) in the presence of excess PPh_3 or CO. A similar synthetic approach using Ni^{II} complexes having a tetradentate N_2S_2 ligand was also employed by Pohl et al.[25] They reacted [Ni(dadt^{Et})] (**2**; dadt^{Et} = *N*,*N*′-diethyl-3,7-diazanonane-1,9-dithiolate) with $[Fe(CO)_2(NO)_2]$ and isolated $[(NO)_2Fe(dadt^{Et})Ni]$ (**7**). In contrast to complex **6**, both sulfur atoms of Ni(dadt^{Et}) in **7** bridge the two metals, and the iron atom is tetrahedral with two terminal NO ligands. The different bridging modes of the Ni(N_2S_2) units between complexes **6** and **7** also dramatically affect their Fe–Ni distances [3.76(1) Å for **6** and 2.797(1) Å for **7**]. Chemical oxidation of these dinuclear complexes results in decomposition.

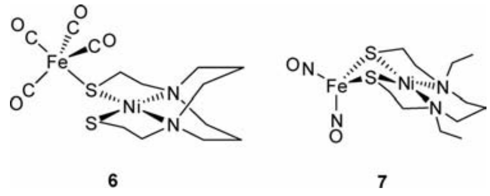


Figure 4. [NiFe] hydrogenase mimics prepared from [Ni(bme-daco)] or [Ni(dadt^{Et})].

Bouwman and co-workers treated [Ni(dsdm)] {**3**; dsdm = *N*,*N*′-dimethyl-*N*,*N*′-bis(mercaptoethyl)ethylenediamine} with $Fe_2(CO)_9$ or $K[FeH(CO)_4]$,[26] which resulted in products that vary dramatically depending on the iron reactants. Treatment of [Ni(dsdm)] with $Fe_2(CO)_9$ gives rise to complex $[\{(CO)_3Fe\}_2Ni(dsdm)]$ (**8**) with a triangular Fe_2Ni framework (Figure 5), while the reaction with $K[FeH(CO)_4]$ leads to a complete reshuffling of ligands between metals to form complex $[(CO)_3Ni–Fe_2(dsdm)_2–Ni(CO)_3]$

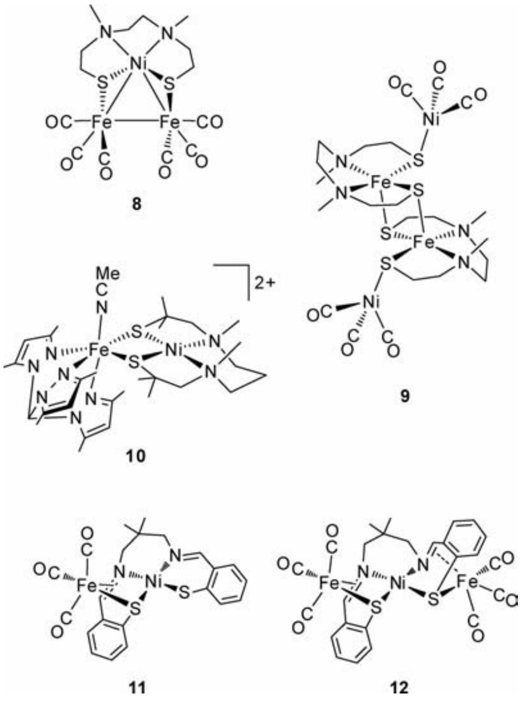


Figure 5. Structures of complexes **8**–**12**.

(**9**). Recently Ogo and co-workers reacted the *N*,*N*′-dimethyl-*N*,*N*′-bis(2,2-dimethyl-2-mercaptoethyl)-1,3-propanediamine complex of nickel with a triaquairon complex having a tris(3,5-dimethylpyrazolyl)methane ligand in acetonitrile, to produce dinuclear complex **10** having an acetonitrile ligand on iron (Figure 5).[27] This complex was found to be unstable in the presence of water, splitting into the nickel and iron precursors. Schröder et al. prepared a N_2S_2 ligand of the Schiff base type, tsalen {tsalen = *N*,*N*′-ethylenebis(thiosalicylideneiminato)}, by using Zn^{2+} as a template metal, and reacted its nickel complex [Ni(tsalen)] with $Fe_2(CO)_9$ to produce Ni–Fe and Fe–Ni–Fe complexes [$(CO)_3$Fe(tsalen)Ni] (**11**) and [{$(CO)_3Fe$}$_2$(tsalen)Ni] (**12**), respectively (Figure 5).[28] In these complexes, $Fe^0(CO)_3$ units are bound to the tsalen ligand through one bridging thiolate sulfur atom and one C=N imine π bond. This results in the loss of planarity of the conjugated π-system of tsalen and elongation of the C=N bond from 1.293(3) Å [Ni(tsalen)] to 1.398(3)–1.399(4) Å (**11**, **12**), showing significant π back-donation from the $Fe^0(CO)_3$ unit.

2.1.2. Precursors of the [Ni(N_2S_3)] and [(dppe)Ni(pdt)] {dppe = 1,2-bis(diphenylphosphino)ethane, pdt = 1,3-propanedithiolate} Types

The Schröder group employed a Ni^{II} complex having a pentadentate N_2S_3 ligand [‘N_2S_3’ = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-mecracptoethyl)bis(aminoethyl)sulfide] as precursor, producing the dinuclear complex [CpFe(‘N_2S_3’)Ni]$^+$ (**13**; Cp = η^5-C_5H_5) (Figure 6).[29] Interestingly, the Ni–Fe distance [2.539(4) Å] is comparable to that in the reduced form of [NiFe] hydrogenase (2.5–2.6 Å), indicating some interaction between the nickel and iron centers. In the same paper, they also reported a Ni^{II} dithiolate complex, [(dppe)Ni(pdt)] (**14**), which serves as a versatile precursor for Fe–Ni model complexes of the reduced form of [NiFe] hydrogenase.[28] For example, treatment of **14** with $(CO)_3$Fe(benzylideneacetone) results in the formation of [$(CO)_3$Fe(pdt)Ni(dppe)] (**15**), which is thermally unstable in solution and is converted gradually into [$(CO)_2$Fe(pdt)(dppe)Ni(CO)] (**16**) upon heating (Figure 6). Complex **14** also reacts with [CpFe$(CO)_2$I] to give [Cp(CO)Fe(pdt)Ni(dppe)]$^+$ (**17**). Among these dinuclear complexes, **15** is structurally closest to the hydrogenase active site. Its Fe–Ni distance [2.4666(6) Å] and acute Fe(μ-S)$_2$Ni dihedral angle (80.3°) are somewhat comparable to those of the active site in the reduced form, 2.5–2.6 Å and 89–98°, respectively. The short Ni–Fe distance in **15** suggests direct Ni–Fe bonding, which also fits with the observed diamagnetism. Indeed, a bonding combination of Ni and Fe d orbitals was found to be doubly occupied according to theoretical calculations.[29]

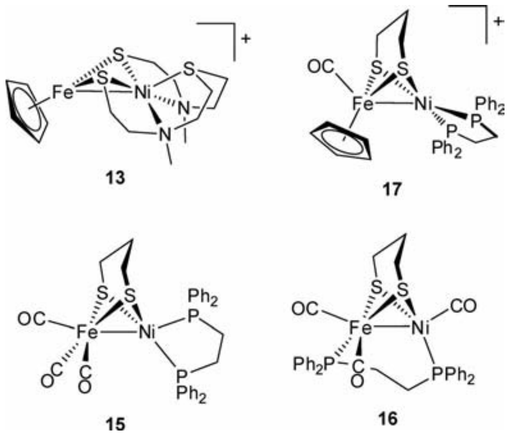


Figure 6. Dinuclear Fe–Ni complexes derived from Ni(‘N_2S_3’) or [(dppe)Ni(pdt)] precursors.

2.1.3. Precursors of the Ni(S_4) Type

Nickel(II) complexes carrying a tetradentate S_4 ligand (Figure 7) are more relevant precursors than those with S_2N_2 ligands, as the nickel atom of the active site is surrounded by four cysteinyl thiolate ligands. Bouwman et al. reacted nickel complex [Ni(xbsms)] {**18**; xbsms = α,α′-bis(4-mercapto-3,3-dimethyl-2-thiabutyl)-*o*-xylene} with $FeCl_2$, $Fe_2(CO)_9$, [Fe$(CO)_2(NO)_2$], and [Fe$(CO)_4I_2$], and obtained the four Fe–Ni complexes [Ni(xbsms)FeCl(μ-Cl)$_2$FeCl(xbsms)Ni] (**23**), [$(CO)_4$Fe(xbsms)Ni] (**24**), [$(NO)_2$Fe(xbsms)Ni] (**25**), and [$(CO)_2I_2$Fe(xbsms)Ni] (**26**), respectively (Figure 8),[30] although only Ni–Fe–Fe–Ni complex **23** was crystallographically characterized. A cationic (carbonyl)iron–nickel complex **27** having a Cp ligand on Fe was prepared by Schröder et al. by the reaction of the bis(2-mercaptoethyl)-1,2-dimercaptoethane complex of Ni^{II} (compound **19**) with CpFe$(CO)_2$I followed by treatment with NH_4PF_6 (Figure 9).[28] The analogous complex, [Cp(CO)Fe(xbsms)Ni]$^+$ (**28**), was recently prepared by Artero and co-workers, using [Ni(xbsms)] as the precursor (Figure 8).[31] On the other hand, a team of chemists in the UK including Schröder found that complex [$(CO)_6Fe_2$-{$(RC_6H_3S_2)_2(CH_2)_3$}Ni] (**29**) with a triangular Fe_2Ni framework is formed by the reaction of [Ni{$(RC_6H_3S_2)_2(CH_2)_3$}] (**20**; R = CH_3, H) with $Fe_3(CO)_{12}$ (Figure 9).[32] Similarly, Sellmann and co-workers used Ni(‘S_4’) {**21**; ‘S_4’ = 1,2-bis(2-mercaptophenylthio)ethane} and Ni(‘$S_4C_3Me_2$’) {**22**; ‘$S_4C_3Me_2$’ = 1,3-bis(2-mercaptophenylthio)-2,2-dimethylpropane} as precursors for the analogous Fe_2Ni complexes [$(CO)_6Fe_2$(‘S_4’)Ni] (**30**) and [$(CO)_6Fe_2$(‘$S_4C_3Me_2$’)Ni] (**31**), respectively (Figure 9).[33] The Ni–Fe [2.4789(9)–2.5038(4) Å] and Fe–Fe distances [2.6050(7)–2.6435(9) Å] for **29**–**31** are short, indicating Ni–Fe and Fe–Fe bonding interactions. The Ni–Fe distances are comparable to those determined for the reduced form of [NiFe] hydrogenase (2.5–2.6 Å), and the Fe–Fe distances are slightly shorter than that for [{$(CO)_3Fe$}$_2$Ni(dsdm)] (**8**) [2.6617(8) Å].[25] Chemical reduction of **29** with Cp_2Co (or electrochemical reduction of **29**) leads to the formation of [**29**]$^-$, which is EPR active and shows an interaction between the unpaired electron and the nickel nucleus upon ^{61}Ni (I = 3/2) enrichment.

Liaw, Darensbourg, and their co-workers found that the dimeric nickel complex bearing S_3 ligands [Ni(tpdt)]$_2$[34] {tpdt = 3-thiapentanedithiolate, $S(CH_2)_2S(CH_2)_2S$} reacts with [$(NO)_2$Fe$(SePh)_2$]$^-$ in the presence of NO_2^- to produce dinuclear complex [$(NO)_2$Fe(tpdt)Ni(NO)] (**32**) (Fig-

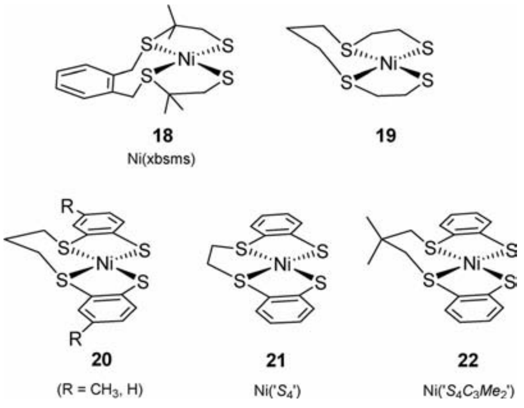


Figure 7. Ni^{II} complexes having a tetradentate S_4 ligand.

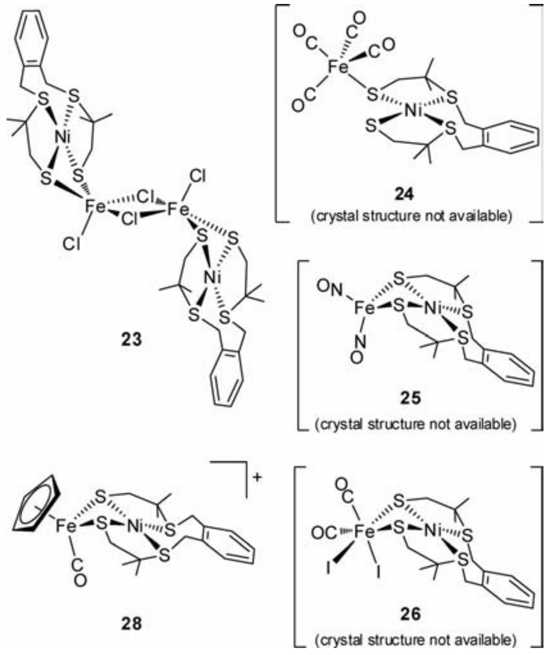


Figure 8. Iron–nickel complexes derived from the precursor [Ni(xbsms)].

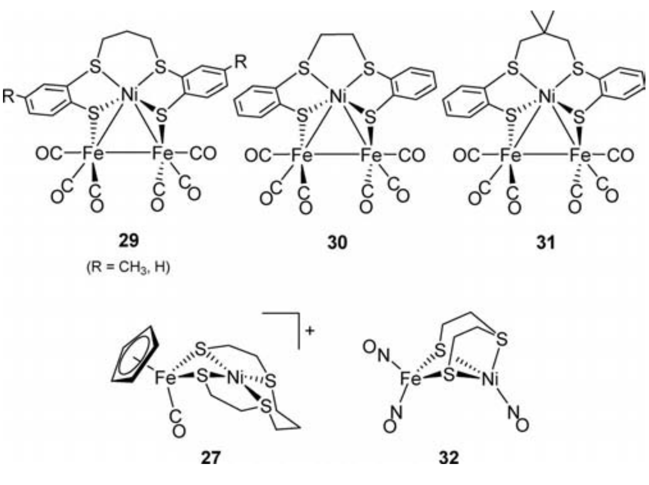
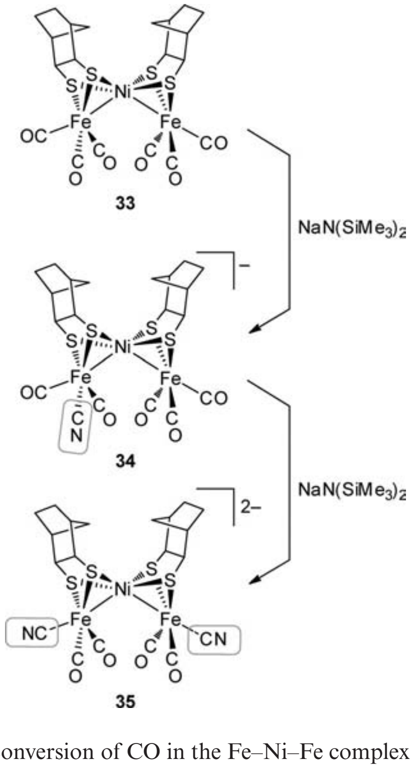


Figure 9. Iron–nickel complexes derived from nickel complexes with an S_4 or S_3 ligand.

ure 9).[35] The iron and nickel atoms in **32** have distorted tetrahedral geometries, and the Fe–Ni distance is 2.8001(6) Å. The cyclic voltammogram of **32** displays quasi-reversible oxidation and reduction processes at 0.69 V and –0.97 V vs. Ag/Ag^+, respectively. Complex **32** has an odd number of electrons and is EPR active. Its EPR signal at $g = 2.021$, indicative of the $S = 1/2$ state, is lost upon chemical oxidation with 1 equiv. of Ce^{IV}.

Homoleptic, bis(dithiolate) complexes of nickel provide a monomeric $Ni(S_4)$ environment, which would be useful for the preparation of hydrogenase models. We prepared dithiolate-bridged Fe–Ni–Fe trinuclear carbonyl complex $[(CO)_3Fe(ndt)Ni(ndt)Fe(CO)_3]$ (**33**) (ndt = norbornane-*exo*-2,3-dithiolate) by the reaction of the bis(dithiolate) complex $[Ni(ndt)_2]^{2-}$[36] with $Fe(CO)_4I_2$.[37] This reaction involves complicated redox processes, since the formal Fe^{I}–Ni^{II}–Fe^{I} oxidation state of product **33** differs from the Ni^{II} and Fe^{II} states of the precursors. One or two CO ligands in **33** can be converted into CN in a stepwise manner by treatment with 1 or 2 equiv. of $NaN(SiMe_3)_2$, giving rise to the mono- or bis(CN) complexes **34** or **35**, respectively (Scheme 2). In contrast to the above-mentioned trinuclear Fe_2Ni complexes having an Fe–Fe bonding interaction, the large separations of the two iron atoms in **33**–**35** [Fe–Fe, 3.899(2)–4.002(2) Å] exclude direct Fe–Fe interaction, while the short Fe–Ni distances [2.4328(7)–2.464(1) Å] show Fe–Ni bonding.



Scheme 2. Conversion of CO in the Fe–Ni–Fe complex **33** into CN.

2.1.4. A Precursor of the $Ni(N_6S_3)$ Type

Kersting et al. have designed a nonadentate amine–thiolate hybrid ligand N_6S_3 {[N_6S_3 = *N*,*N*′,*N*′′-tris(2-thio-3-aminomethyl-5-*tert*-butylbenzyl)]-1,1,1-tris(aminomethyl)-

ethane}[38] and used it to generate a mononuclear nickel complex $[Ni(N_6S_3)]^-$, which was further treated with $FeCl_2$ and was then exposed to air to give Fe^{III}–Ni^{II} dinuclear complex $[\{Fe(N_6S_3)Ni\}]^{2+}$ (**36**) (Figure 10).[39] The crystal structure of **36** reveals a C_3-symmetric complex with a $(N)_3Fe(\mu\text{-}SR)_3Ni(N')_3$ core. The octahedral metal centers are separated by 3.030(1) Å, and there is no Fe–Ni bonding. The assignment of low-spin Fe^{III} in **36** is supported by the Mössbauer spectrum, where a single quadrupole doublet appears at an IS (isomer shift) value of 0.32 mm/s with a QS (quadrupole splitting) of 1.83 mm/s at 77 K. The cyclic voltammogram of **36** displays reversible oxidation and reduction processes at 0.45 and –0.43 V vs. SCE, respectively.

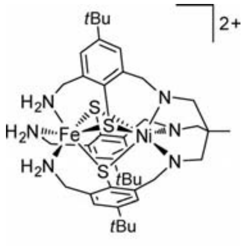


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Figure 10. Complex cation of $[Fe(N_6S_3)Ni]^{2+}$.

2.2. Thiolate Complexes of (Carbonyl/Cyanide)iron as Precursors

An alternative approach to the synthesis of thiolate-bridged Fe–Ni complexes is to use a thiolate complex of an (carbonyl/cyanide)iron to link to nickel. Particularly, iron complexes with two thiolate ligands would serve as useful synthons as two sulfur atoms can link to nickel as a chelating ligand. Whereas (carbonyl/cyanide)iron complexes can be regarded as "classical", most of those bearing thiolate ligands have appeared in the past 15 years, and selected examples are described below (Figure 11).

Koch and co-workers used the tetradentate PS_3 ligand [PS_3 = tris(2-phenylthio)phosphane] for the preparation of an octahedral Fe^{II} complex $[(PS_3)Fe(CO)(CN)]^{2-}$ (**37**), in which a CN ligand is located *trans* to phosphorus.[40] Rauchfuss et al. developed the anionic thiolate/carbonyl/cyanide complexes of Fe^{II}, $[Fe(SPh)_2(CN)_2(CO)_2]^{2-}$ (**38**) and $[Fe(bdt)(CN)_2(CO)_2]^{2-}$ (**39**; bdt = 1,2-benzenedithiolate), from sequential treatment of $FeCl_2$ with NaSPh or Na_2bdt and $(Et_4N)(CN)$ in CO-saturated CH_3CN.[41] Liaw and co-workers synthesized various six-coordinate and five-coordinate thiolate/carbonyl/cyanide complexes of Fe^{II}, such as $[Fe(CO)_2(CN)\{S(C_6H_4)NH\}]^-$ (**40**), $[Fe(CO)_2(CN)_2\{S(C_5H_4N)\}]^-$ (**41**), and $[Fe(CO)_2(CN)\{S(CH_2)_2S(CH_2)_2S\}]^-$ (**42**),[42] by the oxidative addition of disulfide (RS–SR) or cyanogen bromide (BrCN) to the Fe^0 compound $[Fe(CO)_4(CN)]^-$. Sellman et al. designed the S_3 ligand $^-S(C_6H_4)S(C_6H_4)S^-$[43] and prepared the dinuclear iron complex $[Fe(CO)_2\{S(C_6H_4)S(C_6H_4)S\}]_2$ (**44**), from which the monomeric thiolate/CO/CN complex $[Fe(CO)(CN)_2(S_3)]^{2-}$ (**43**) was obtained.[44]

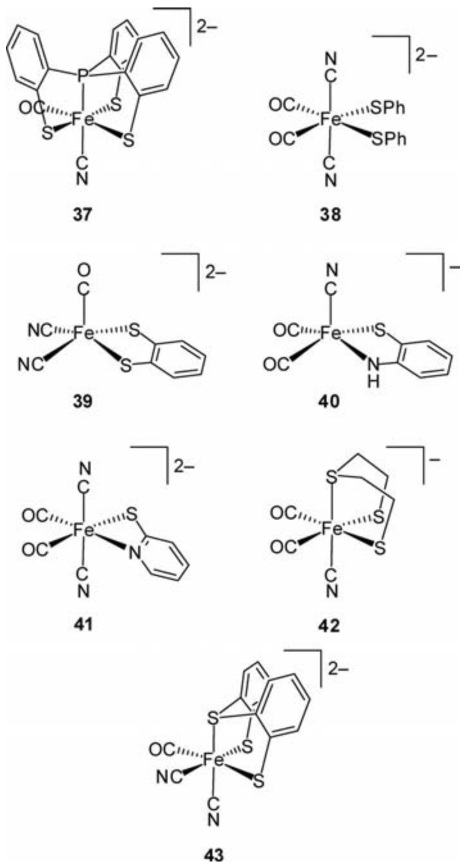
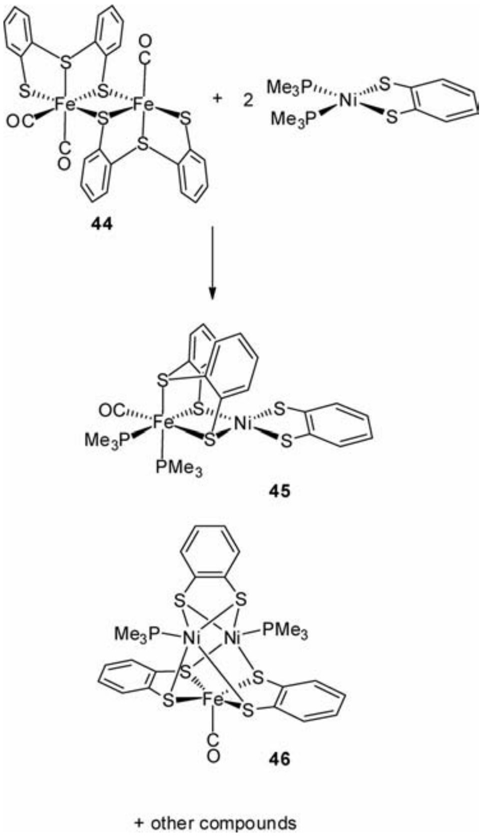


Figure 11. Selected examples for (carbonyl/cyanide)iron–thiolate complexes.

2.2.1. *[Fe(CO)₂{S(C₆H₄)S(C₆H₄)S}]₂ as Precursor*

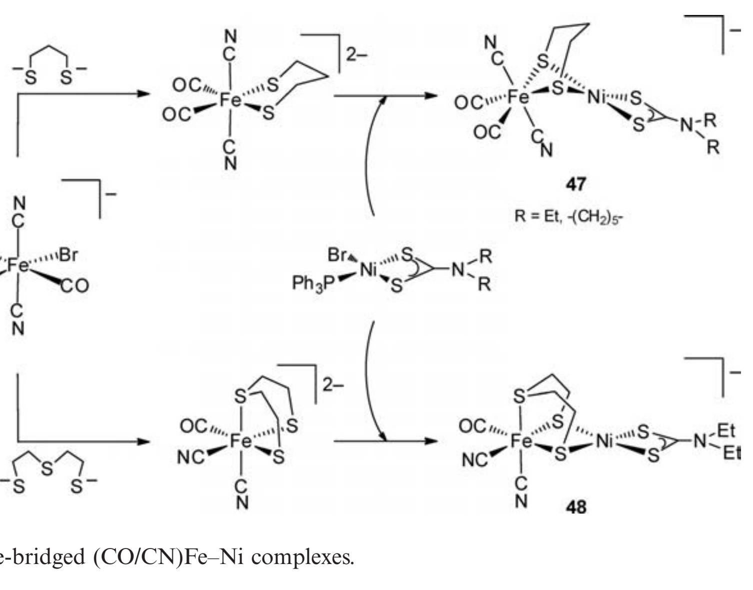
Dinuclear (carbonyl)iron complex **44** was subjected to further reaction with $[Ni(PMe_3)_2(bdt)]$ (Scheme 3),[45] and Sellman et al. successfully crystallized the Fe–Ni dinuclear complex $[(CO)(PMe_3)_2Fe\{S(C_6H_4)S(C_6H_4)S\}Ni(bdt)]$ (**45**) and the $FeNi_2$ trinuclear complex $[(CO)Fe(bdt)_2\{Ni(PMe_3)\}_2(bdt)]$ (**46**) among multiple products. The nickel atom of **45** is surrounded by four thiolate ligands in an essentially planar geometry, while the iron atom is pseudo-octahedrally coordinated by two thiolates, two PMe_3, one CO, and one thioether. The small $Fe(\mu\text{-}S)_2Ni$ dihedral angle of 11.40(6)° in **45** suggests that the four-membered $Fe(\mu\text{-}S)_2$-Ni ring is close to planar. Trinuclear complex **46** consists of a square-pyramidal $(CO)Fe(bdt)_2$ fragment, which is connected to two $Ni(PMe_3)$ fragments that are linked through a bdt ligand. The Fe–Ni and Ni–Ni distances are 2.569(1)–2.623(1) and 2.405(1) Å, respectively, and are indicative of metal–metal bonding. Complex **46** is redox-active, and three quasireversible redox waves appear at –1.071, –0.095, and 0.844 V vs. NHE, which are assigned as the $[\mathbf{46}]^{0/-}$, $[\mathbf{46}]^{0/+}$, and $[\mathbf{46}]^{+/2+}$ couples, respectively. Complex **46** can be protonated as described below (section 3, reactions of model compounds).



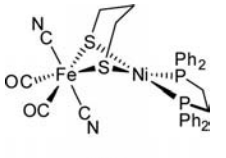
Scheme 3. The reaction of $[Fe(CO)_2\{S(C_6H_4)S(C_6H_4)S\}]_2$ with $[Ni(PMe_3)_2(bdt)]$.

2.2.2. *(CO/CN)Fe–Dithiolate Complexes as Precursors*

Inspired by the above-mentioned Fe^{II} carbonyl/cyanide/thiolate complexes (Figure 11), we prepared an iron precursor having a pdt (1,3-propanedithiolate) ligand, $[Fe(CO)_2(CN)_2(pdt)]^{2-}$, by the reaction of $[Fe(CO)_3(CN)_2Br]^{-}$[42b] with pdt^{2-}. This preformed iron complex was found to react with $[Ni(PPh_3)Br(S_2CNR_2)]$ (S_2CNR_2 = dithiocarbamate) to give the dithiolate-bridged (CO/CN)Fe–Ni complexes $[(CO)_2(CN)_2Fe(pdt)Ni(S_2CNR_2)]^-$ (**47**) (Scheme 4).[46] An extension of this synthetic approach using the *S*$_3$ ligand tpdt $[^-S(CH_2)_2S(CH_2)_2S^-]$ led to the formation of $[(CO)(CN)_2Fe(tpdt)Ni(S_2CNEt_2)]^-$ (**48**), in which the iron atom possesses two CN and one CO ligands.[47] An analogous approach was taken by Jiang et al., who used *fac,cis*-$[Fe(CO)_3(CN)_2I]^-$ instead of *mer,trans*-$[Fe(CO)_3(CN)_2Br]^-$ for sequential reactions with thiolates and with $[Ni(dppe)Cl_2]$ to obtain $[(CO)_2(CN)_2Fe(SR)_2Ni(dppe)]$ $\{(SR)_2$ = pdt (**49a**) or $(SEt)_2$ (**49b**)$\}$ (Figure 12).[48] The structures of **47** and **48** reveal that the iron and nickel atoms are in octahedral and square-planar geometries, respectively, and that the two sulfur atoms of the dithiolate ligand bridge the two metals. The bending angle of the $Fe(S)_2Ni$ rhombus is different between **47** (52.5–54.4°) and **48** (14.7°), and the more planar **48** leads to a longer Fe–Ni distance 3.2960(5) Å than that in **47** [3.0364(8)–3.0587(6) Å]. The Fe–Ni distances for **47**, as well as the Fe–S_{bridge} (av. 2.337–2.338 Å) and Ni–S_{bridge} (av. 2.111–2.213 Å) distances, are comparable to those found in the oxidized forms of [NiFe] hydrogenases from *D. gigas* and *D. fructosovorans.* The infrared spectrum of **48**, in which two CN bands and one CO band appear at 2094, 9083 (CN), and 1944 cm^{-1} (CO) (Figure 13), resembles closely that of the *Ni-A*, *Ni-B*, and *Ni-SU* states of *Allochromatium vinosum* hydrogenase,[49] verifying the assignment of a $(CN)_2(CO)Fe^{II}$ moiety in the active site of [NiFe] hydrogenase. This reproduction of the CN/CO bands also indicates that the octahedral Fe^{II} center in the active site has electronic properties similar to those in **48**. As complexes **47** and **48** show important structural/spectroscopic features, they have been recognized as the structural models closest to [NiFe] hydrogenase thus far reported.[19h,50]



Scheme 4. Synthesis of dithiolate-bridged (CO/CN)Fe–Ni complexes.



49a

Figure 12. Thiolate-bridged [(CO/CN)Fe–Ni] complex **49a**.

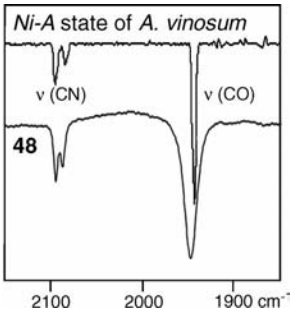
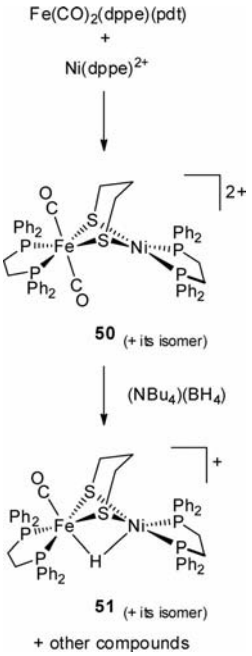


Figure 13. CN/CO bands for *A. vinosum* hydrogenase[48] (top) and **48** (bottom) in the IR spectrum.

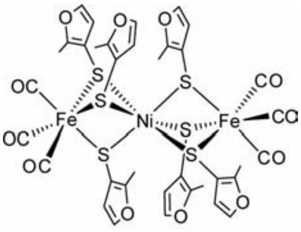
2.2.3. $Fe(CO)_2(dppe)(pdt)$ and $[Fe(CO)_3\{S(C_4H_2O\text{-}2\text{-}CH_3)_3\}]^-$ as Precursors

A recent report by Rauchfuss et al. described the synthesis of the pdt-bridged Fe–Ni complex $[(dppe)(CO)_2Fe(pdt)Ni(dppe)]^{2+}$ (**50**) from the reaction of $[Fe(CO)_2(dppe)(pdt)]$[51] with $Ni(dppe)^{2+}$ (Scheme 5).[52] This dinuclear complex was further treated with NBu_4BH_4 to give a complex mixture, in which isomers of the hydride-bridged complex $[(dppe)(CO)_2Fe(pdt)(H)Ni(dppe)]^+$ (**51**) were observed in the electrospray ionization mass (ESI-MS) and ^1H NMR spectra. It is interesting to note that hydride complex **51** is more robust than dicationic complex **50**. Complex **51** was alternatively prepared by the reaction of Schröder's model complex $[(CO)_3Fe(pdt)Ni(dppe)]$ (**15**)[29] with HBF_4 followed by replacement of two CO ligands on iron with dppe under irradiation.



Scheme 5. [(dppe)Fe(pdt)Ni(dppe)] models **50** and **51**.

Liaw and co-workers prepared the monomeric thiolate/carbonyl complexes *fac*-$[Fe(CO)_3(SR)_3]^-$ (R = 2-benzothiazoyl, 2-thienyl, 2-methyl-3-furyl) through the oxidative addition of disulfides to $[HFe(CO)_4]^-$.[53] In contrast to the thermally unstable complex *fac*-$[Fe(CO)_3(SPh)_3]^-$,[54] these (carbonyl)iron–thiolate complexes are stable at room temperature. One of these complexes, $[Fe(CO)_3\{S(C_4H_2O\text{-}2\text{-}CH_3)_3\}]^-$, was found to react with Ni^{2+} to produce the Fe–Ni–Fe complex $[[(CO)_3Fe\{S(C_4H_2O\text{-}2\text{-}CH_3)_3\}_3]_2Ni]$ (**52**) (Figure 14). This trinuclear complex shows C_3 symmetry, and a threefold axis runs through the Fe–Ni–Fe vector. The central nickel atom is in a slightly distorted octahedral geometry, and the mean Fe–Ni distance is 3.121 Å.



52

Figure 14. Fe–Ni–Fe complex **52**.

2.2.4. $[Fe(NS_3)(L)]^-$ (L = CO, NO) Complexes as Precursors

Early structural analogues of the active site of [NiFe] hydrogenase were reported by Evans et al., who used $[Fe(NS_3)(CO)]^-$ or $[Fe(NS_3)(NO)]^-$ $\{NS_3$ = tris(ethylthiolato)amine$\}$ in the reactions with $[Ni(dppe)Cl_2]$, $[Ni(dppp)Cl_2]$ {dppp = 1,3-bis(diphenylphosphino)propane}, the DMSO solvate of $NiCl_2$, or $[Ni(PPh_3)_2Cl_2]$.[55] From these reactions under a CO or N_2 atmosphere, they obtained the dinuclear Fe–Ni complexes $[(CO)_2Fe(NS_3)NiCl(P\text{^}P)]$ (**53a**; P^P = dppe, **53b**; P^P = dppp) and $[(NO)Fe(NS_3)NiCl(dppe)]$ (**54**), and the Fe–Ni–Fe complex $[\{(CO)Fe(NS_3)\}_2Ni]$ (**55**) (Figure 15). They also prepared $[(CO)Fe(NS_3)NiCl(SCH_2CH_2S)]$ or its polymer, by treatment of in situ generated **55** with $HSCH_2CH_2SH$, although the product was not fully characterized because of its insolubility. Similarly, the formation of $[(CO)Fe(NS_3)Ni(S_2CNiPr_2)]$ or its polymeric form has also been suggested for the reaction of $[Fe(NS_3)(CO)]^-$ with $[Ni(PPh_3)Cl(S_2CNiPr_2)]$. These dithiolate-bridged dinuclear Fe–Ni complexes (or their polymers) feature a $Ni(S_4)$ environment, which is essential for the nickel site of [NiFe] hydrogenase. The Fe–Ni distances for dinuclear Fe–Ni models **53a**, **53b**, and **54**, ranging from 3.0216(5) to 3.3638(9) Å, are longer than that for the Fe–Ni–Fe complex **55** [2.6372(11) Å]. The Mössbauer spectra of **53a** and **53b** are almost identical with an IS (isomer shift) value of 0.07 mm/s and QS (quadruple splitting) of 0.56 mm/s, and are consistent with octahedral low-spin Fe^{II}.

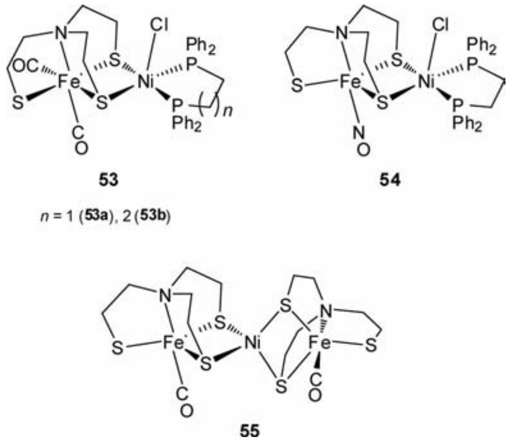


Figure 15. Fe–Ni and Fe–Ni–Fe complexes derived from [Fe(NS_3)(CO)]$^-$ or [Fe(NS_3)(NO)]$^-$.

2.2.5. A [Fe(N_3S_3)]$^-$ Complex as Precursor

A Fe^{III} complex bearing a hexadentate amine–thiolate ligand N_3S_3 [1,4,7-tris(4-*tert*-butyl-2-mercaptobenzyl)-1,4,7-triazacyclononane], [Fe(N_3S_3)],[56] has also been used to complex nickel. Wieghardt and co-workers synthesized [Fe(N_3S_3)Ni(N_3S_3)Fe]$^{2+}$ (**56**) (Figure 16), which exhibits multiple oxidation states [Fe(N_3S_3)Ni(N_3S_3)Fe]$^{+/2+/3+/4+}$.[57] The intermediate state [Fe(N_3S_3)Ni(N_3S_3)Fe]$^{3+}$ ([**56**]$^+$) was synthesized by the reaction of Fe(N_3S_3) with the triazacyclononane complex of Ni^{III}, while the chemical oxidation of **56** with CH_3SO_3H/PbO_2 yields [**56**]$^{2+}$. In complex **56**, both Fe^{III} and Ni^{II} are octahedral, and the Fe–Ni distance is 3.054(1) Å, while oxidation to [**56**]$^+$ leads to slight shortening of the Fe–Ni distance to 3.002(1) Å. The Mössbauer and XANES spectra for **56** indicate that the two Fe atoms have an oxidation state of approximately +2.66, which renders the oxidation state of Ni as +2.66. This fractional oxidation state suggests that there are d electrons in orbitals delocalized over the cluster.

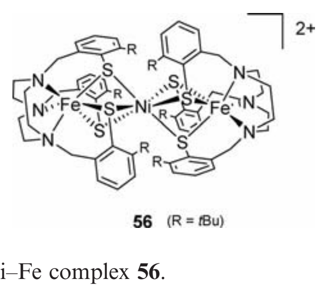


Figure 16. Fe–Ni–Fe complex **56**.

2.3. One-Pot Self-Assembly Reactions

All the synthetic approaches noted above employ either nickel–thiolate or iron–thiolate precursors, which were isolated and then used for complexation with their counterparts. On the other hand, we have recently found that the one-pot reaction of $Fe(CO)_4Br_2$, thiolates, and $[Ni(EtOH)_4Br_2]$ yields new structural models of the active site of [NiFe] hydrogenase.[58] The reaction of $[Ni(EtOH)_4Br_2]$ with a 1:2–3 mixture of $Fe(CO)_4Br_2$ and NaSPh generated the linear trinuclear Fe–Ni–Fe complex $[\{(CO)_3Fe(SPh)_3\}_2Ni]$ (**57**), while the analogous reaction using NaS*t*Bu instead of NaSPh gave rise to the tetranuclear Fe–Ni–Ni–Fe complex $[[(CO)_3Fe(StBu)_3Ni]_2(Br)_2]$ (**58**) (Figure 17). It is notable that complex **58** and the dinuclear Fe–Ni derivatives described below are thermally unstable and need to be manipulated below –40 °C.

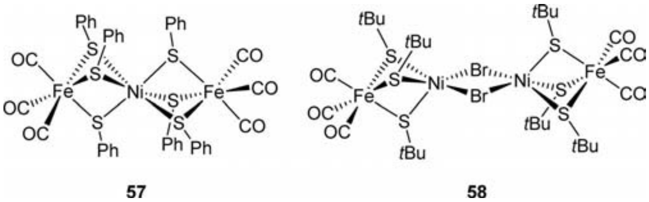
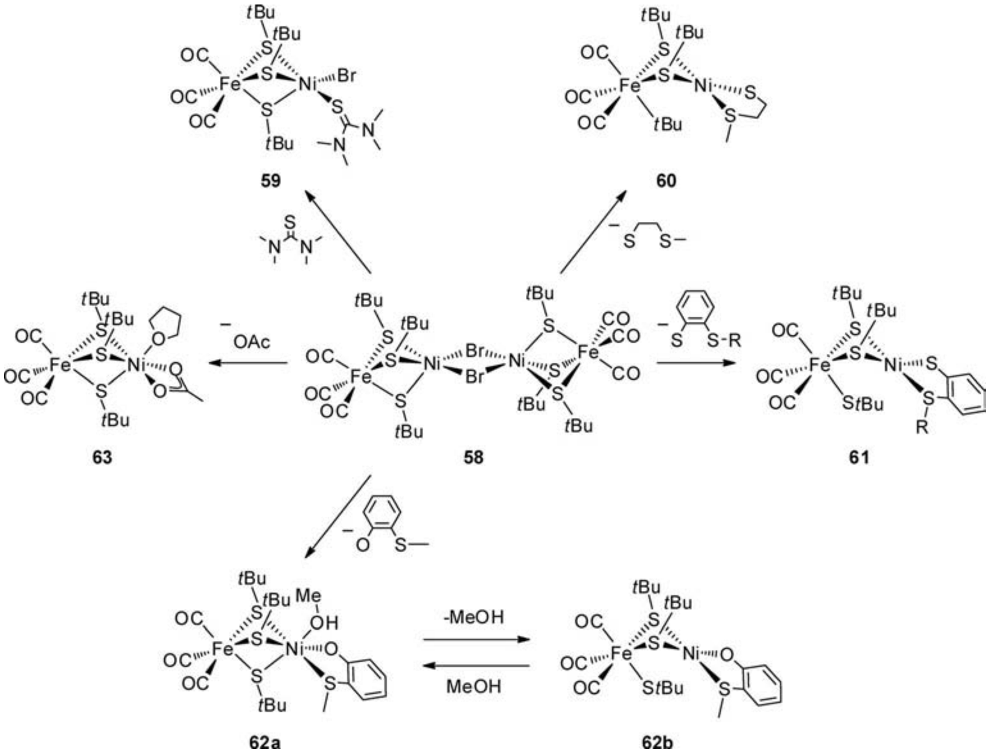


Figure 17. Fe–Ni–Fe and Fe–Ni–Ni–Fe complexes **57** and **58**.

Complex **58** can be seen as a dimeric form of thiolate-bridged $(CO)_3Fe^{II}–Ni^{II}$ species weakly bridged by bromides in the middle. Indeed, complex **58** is converted into Fe–Ni dinuclear complexes in the presence of various sulfur-donating ligands (Scheme 6). For example, treatment of **58** with tetramethylthiourea (tmtu) splits the Fe–Ni–Ni–Fe framework into two Fe–Ni units, forming the tmtu adduct $[(CO)_3Fe(StBu)_3Ni(tmtu)Br]$ (**59**). This complex is relevant to the oxidized form of [NiFe] hydrogenase in that an octahedral iron and a distorted square-pyramidal nickel atom are linked by three bridging ligands. The reactions of **58** with thioether–thiolate hybrid ligands $NaS(CH_2)_2SCH_3$ or $NaS(C_6H_4)SR$ (R = CH_3, *t*Bu) provided a series of Fe–Ni complexes $[(CO)_3(tBuS)Fe(StBu)_2Ni\{S(CH_2)_2SCH_3\}]$ (**60**) or $[(CO)_3(tBuS)Fe(StBu)_2Ni\{S(C_6H_4)SR\}]$ (**61**; R = CH_3, *t*Bu), respectively. Coordination of the thioether–thiolate hybrid ligand at Ni disrupts the tris-bridging thiolate arrangement, so that the Fe and Ni atoms in **60**–**61** are bridged by only two thiolate ligands, leaving one thiolate bound to Fe as a terminal ligand. The Ni atom is coordinated by four sulfur donors in a somewhat distorted square-planar geometry. The Fe–Ni distances for **60** and **61** [3.2344(7) and 3.2877(7) Å] are longer than that for **59** [3.1442(13) Å]. Dinuclear $(CO)_3Fe–Ni$ complexes with an octahedral Ni^{II} center, **62a** and **63**, are available from the reactions of **58** with 2-methylthiophenolate [$^-O(C_6H_4)SCH_3$] or acetate. The methanol ligand on the nickel atom of **62a** is labile, and it is removed under reduced pressure to afford **62b**, in which the nickel atom is nearly square-planar. This geometric change at the nickel site is reversible, and thus **62a** is regenerated upon addition of methanol to **62b**. As found in complexes **59**–**63**, the coordination geometry of Ni varies among four-, five-, and six-coordinate, and the reversible coordination of methanol occurs at the Ni site, while the Fe atom retains octahedral geometry. This raises the possibility that the flexible coordination mode of Ni may be important for H_2 accommodation and activation by [NiFe] hydrogenase.



Scheme 6. Synthesis of thiolate-bridged $(CO)_3Fe–Ni$ complexes from **58**.

3. Reactivity of Model Complexes Relevant to [NiFe] Hydrogenase

Representative reactions relevant to the function of [NiFe] hydrogenase are (a) the heterolytic splitting of H_2 ($H_2 \rightarrow H^+ + H^-$), (b) the oxidation of H_2 ($H_2 \rightarrow 2H^+ + 2e^-$), and (c) the reduction of H^+ ($2H^+ + 2e^- \rightarrow H_2$). However, none of the thiolate-bridged Fe–Ni complexes noted above have been reported to activate H_2. Thus, reactions (a) and (b) still remain targets for further investigation. With regard to (c), the complexes in Figure 18 have been shown to serve as catalysts for the electrochemical reduction of H^+.

The trinuclear $FeNi_2$ complex **46** reported by Sellmann et al. in 2004 is the first model to achieve proton reduction, although hydrogen production was not observed at that time, but rather the one-electron oxidation of **46** upon treatment with HBF_4 was noted.[45b] Later in 2007, the reduction of H^+ catalyzed by a CH_2Cl_2 solution of **46** was reported,[59] and H_2 evolution was observed with low activity (TON $< 0.1\ h^{-1}$) during electrolysis at –0.48 V vs. NHE. Schröder and co-workers used trinuclear Fe_2Ni complex **29**[32] as a catalyst for the electrochemical reduction of H^+.[60] A CH_2Cl_2 solution of **29** shows a reversible one-electron reduction process at –1.31 V vs. Fc/Fc^+ in the cyclic voltammogram. At an applied potential of –1.64 V vs. Fc/Fc^+, complex **29** consumed an average of 13 e/mol h (TON = 6 h^{-1} for H_2 production) in the presence of 50 mM trifluoroacetic acid (TFA). This activity is as high as those reported for [FeFe] hydrogenase models;[61] however, **29** gradually degrades when electrolysis is continued for more than 1 h. On the basis of DFT calculations and spectroscopic evidence, the SOMO of $[\mathbf{29}]^-$ containing the unpaired electron was suggested to be delocalized over the Ni and the two Fe atoms, implicating metal-based protonation during catalysis.

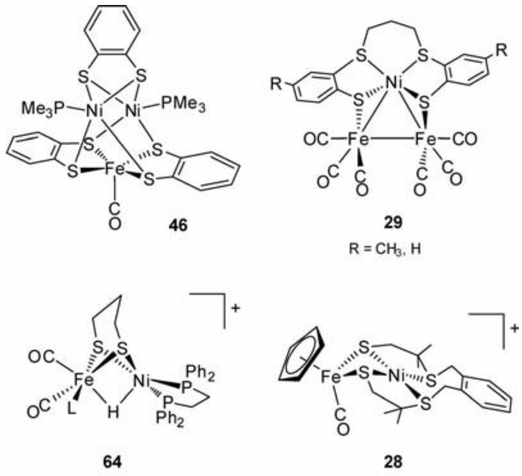
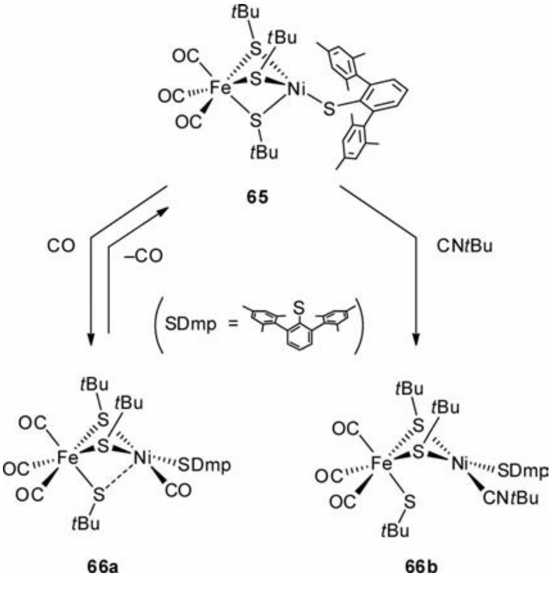


Figure 18. [NiFe] hydrogenase models that catalyze the electrochemical reduction of H^+.

The first dinuclear Fe–Ni complex to achieve proton reduction was $[(CO)_3Fe(pdt)(H)Ni(dppe)]^+$ (**64a**), which was prepared by Rauchfuss et al. by protonation of **15**[29] with HBF_4.[52] Complex **64a** was alternatively prepared by protonation of **15** with $H_2/B(C_6F_5)_3$, where an approach analogous to “Frustrated Lewis Pair”[62] was applied. The structures of **64a** and **b** reveal a hydride ligand bridging between the octahedral Fe and square pyramidal Ni, analogous to a possible structure of the active site in the *Ni-R* state. A catalytic current due to proton reduction by a CH_2Cl_2 solution of **64a** was observed near –1.37 V vs. Fc/Fc^+ in the presence of TFA. The hydrogen evolution was assessed by the cathode current in the cyclic voltammogram. Artero and coworkers reported that a DMF solution of **28** displays a reversible reduction process at –1.43 V vs. Fc/Fc^+, and a TON of 5 h^{-1} for H_2 production from the protons of TFA was sustained for four hours.[31] They proposed a dinuclear Fe–Ni complex lacking CO but having a bridging hydride as a key intermediate, on the basis of the acid-dependent behavior in the cyclic voltammogram and DFT calculations of possible models.

Another important property of the active site of [NiFe] hydrogenase is its reversible inhibition by CO.[15] In the CO-inhibited form of hydrogenase from *D. v. Miyazaki F*, the exogenous CO binds to nickel, but this CO can be liberated upon flushing with N_2[15a] or by white light irradiation at 20 K,[15c] to recover catalytic activity. We synthesized a dinuclear complex having a bulky thiolate, $[(CO)_3Fe(StBu)_3Ni(SDmp)]$ {**65**; Dmp = 2,6-di(mesityl)phenyl}, from the reaction of Fe–Ni–Ni–Fe complex **58** with NaSDmp at –40 °C.[63] The nickel site of **65** was found to bind CO at –40 °C to give the adduct $[(CO)_3(tBuS)Fe(StBu)_2Ni(CO)(SDmp)]$ (**66a**), the molecular structure of which was identified by X-ray crystallography (Scheme 7). Its Ni–CO band appearing at 2055 cm^{-1} is comparable to those observed for the CO-inhibited form of [NiFe] hydrogenases from *C. vinosum* and *D. fructosovorans*.[15c,15d] The CO ligand on nickel dissociates under reduced pressure to regenerate **65**, demonstrating the reversible binding of CO. The nickel site of **65** also binds CN*t*Bu, while the coordination of CN*t*Bu is irreversible.



Scheme 7. Reactions of **65** with CO or CN*t*Bu.

4. Conclusion and Perspectives

Since the elucidation of the structure of [NiFe] hydrogenase in the mid 1990s, considerable effort has been devoted to chemical synthesis of the active site. The difficulty in connecting heterogeneous metal ions by thiolate ligands has resulted in fewer model complexes for [NiFe] hydrogenase than for the homogeneous [FeFe] hydrogenase. However, the recent progress summarized in this review has led to successful model synthesis by using nickel–thiolates, iron–thiolates, or one-pot reactions, and has provided good structural models including $Fe(SR)_2Ni$ complexes carrying both CO and CN on iron. Although these results are encouraging, it still remains a challenge to model the reactivity of [NiFe] hydrogenase. Some model complexes catalyze the electrochemical reduction of H^+, and a recent model complex reproduces the reversible CO inhibition of the active site. However, none of the models exhibit any reactivity toward H_2, suggesting that the models reported thus far lack some important features. Features present in [NiFe] hydrogenase but are so far lacking in most of the structural models are the distorted coordination geometry of Ni with terminal thiolate ligands and the enigmatic ligand X between Fe and Ni. Further work on synthetic analogues will be required to uncover the secrets of [NiFe] hydrogenase.

Acknowledgments

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