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# Sulfoxygenation of Active Site Models of [NiFe] and [FeFe] Hydrogenases – A Commentary on Possible Chemical Models of Hydrogenase Enzyme Oxygen Sensitivity

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The organometallic active sites in [NiFe]- and [FeFe]$H_2$ases are sensitive to oxygen in varying degrees. The microorganisms that utilize these enzymes for their hydrogen metabolism, and the enzymes themselves, have evolved from a reducing to an oxidizing environment in ways to avoid competition with oxygen, primarily by burying the active site machinery deeply within the protein matrix. In the case of [NiFe]$H_2$ase, biological studies indicate that repair mechanisms exist for reversible $O_2$-inhibition processes. This Microreview explores the possibility that S-oxygenation may represent reparable O-damaged enzyme active sites. Such S-oxygenation has precedent in chemical models for the terminal thiolate sulfur atoms of the nickel site in [NiFe]$H_2$ase as well as the bridging thiolate sulfur in the [FeFe]$H_2$ase active site. A discussion of the processes of $O_2$ damage leading to both reversible and irreversible enzyme inhibition, and reclamation of activity in the $H_2$ases, as explored by various biochemical assays and spectroscopic methods, is also presented.

## Introduction

Consistent with their chemical roles in the catalysis of $H_2$ production from protons and electrons, and the reverse of that reaction, that is, accessing the reducing power of $H_2$ through scission into $H^-$ and $H^+$, the diiron and nickel-iron hydrogenases, [FeFe]$H_2$ase and [NiFe]$H_2$ase, are typically air-sensitive. As expected, microorganisms that utilize these enzymes, in effect maintaining a microscopic $H_2$ economy, have evolved from their first appearance on a hydrogen-rich planet[1,2] in ways that avoid dioxygen. Some obvious strategies include (1) operating under anaerobic conditions such as in sediments of lakes and rivers; and (2) maintaining active sites deeply buried within the specific protein environments. The former include hydrogenases that function within methanogens (conversion of $CO_2$ and $H_2$ into $CH_4$), sulfate or sulfur reducers (to $H_2S$), ferric iron reducers ($Fe^{3+}$ to $Fe^{2+}$), and denitrifying bacteria ($NO_3^-$ to $N_2$).[1–3] Repair possibilities exist for reversible $O_2$-inhibition processes as seen in [NiFe]$H_2$ase; however, it is typically found and as-

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sumed to be general that the $O_2$ damage in [FeFe]$H_2$ase, once $O_2$ has gained access to the active site, is irreversible.[4,5] To realize the possibility of technological application of such well-designed base-metal molecular biocatalysts, or synthetic analogues of their active sites, for fuel cell electrodes,[2,6–8] the thermodynamic advantage of $O_2$ over $H_2$ or $H^+/e^-$ reactivity and its catalyst inhibition or deactivation properties must be addressed and ameliorated. As eloquently expressed by Armstrong et al., regarding small molecule biomimetics: "...a key issue is likely to be $O_2$ sensitivity, because it will be difficult to substitute the supramolecular protection that is provided by the protein environment to filter or neutralize attacks by this aggressor."[9]

Indeed, the processes of $O_2$ damage, leading to both reversible and irreversible enzyme inhibition, and reclamation of activity in the $H_2$ases, have been explored by various biochemical assays and spectroscopic methods.[3,10] Recent developments in electrochemical methods, particularly protein film voltammetry (PFV), for analysis of carbon electrodes imprinted with enzymes, has provided a new and exciting approach to establish key features of $O_2$ damage and repair possibilities.[9,11,12] Such PFV studies have the advantage of direct control of oxidation states at the electrode surface without requiring mediators, and thus catalytic activity can be directly recorded.[11] In addition, much knowledge is to be gained by the study of a few enzymes that are insensitive to $O_2$ and CO.[13]

The active sites of the known classes of hydrogenases are shown in Figure 1.[14] While [FeFe]$H_2$ase and [NiFe]$H_2$ases are bidirectional, the former is more regularly used within the hundreds of organisms that contain this enzyme as a hydrogen-producing catalyst, while the latter is most efficient as a $H_2$-uptake catalyst.[1] Possibly of significance is the position and orientation of the terminal cysteinyl sulfur atoms on nickel in the [NiFe]$H_2$ase active site at the end of a hydrophobic tunnel widely accepted as a gas-access channel.[15] In the case of [NiFeSe]$H_2$ase, incorporation of selenocysteine is at that terminal site, as shown in Figure 1.[16] [NiFeSe]$H_2$ase is known to be less air-sensitive than its all-sulfur [NiFe]$H_2$ase parent; however, the source of the greater resistance towards $O_2$ deactivation is still unclear, vide infra.[17]

Only the third hydrogenase, the monoiron or Hmd hydrogenase (the abbreviation stands for ***H***$_2$-forming ***m***ethylenetetrahydromethanopterin***d***ehydrogenase), is air-stable.[18] The metal site is not redox-active; its function is to bind/activate $H_2$ and assist in the delivery of a hydride to the optimally positioned methenyltetrahydromethanopterin (methenyl-$H_4$MPT$^+$) substrate.[19] It is known to be sensitive to superoxide and to copper(I).[20] It is very light-sensitive,[21] but it is not air-sensitive. While determinations of $O_2$ tolerance are affected by many factors, including the conditions under which the studies were performed, the typical generalization for the ranking of air-sensitivity in the hydrogenases is [Fe] << [NiFeSe] < [NiFe] << [FeFe].

In addition, air-sensitivity may vary according to the source and even the location of the hydrogenase. For example, membrane-bound [NiFe]$H_2$ase (MBH) in the Knallgas bacterium *Ralstonia eutropha* is known to be remarkably tolerant to $O_2$,[22] as is the MBH from *Ralstonia metallodurans CH34*.[6,7] The $O_2$-tolerant, $H_2$-sensor, or regulatory hydrogenase (RH) of *Ralstonia eutropha H16* (Re) is also capable of typical hydrogenase functions such as $H_2$ uptake, $H_2$ production and H/D exchange.[23] Recent results from in situ spectroscopic studies with the enzyme in its native environment find their active sites to be identical to those of typical [NiFe]$H_2$ases; however, they avoid the inactive redox levels shown in Figure 2 and discussed further below.[24] That is, they exist primarily in the reduced Ni-silent or Ni-C states; although $O_2$ lowers activity, $H_2$ can be produced in a sustainable manner even in the presence of $O_2$.

A question, of course, is the reason for the resistance to these diatomics that typically inhibit, reversibly deactivate, or irreversibly damage hydrogenases. Exploring a hypothesis that the atypical behavior results from restricted access of the larger diatomic compounds due to a difference in the amino acid residues that line the gas-access tunnel of regular $H_2$ases, as opposed to the sensors, Friedrich, Lenz, and co-workers prepared mutants of the RH enzyme in which the larger residues found along the RH tunnel were exchanged by smaller ones.[25] Such mutants with expanded cavities were found to lose activity in the presence of $O_2$, supporting the conclusion that the sensors were designed to block and prevent $O_2$ access to the active site. A further extensive specific amino acid mutation study by Liebgott et al. found a positive correlation of rates of CO diffusion along substrate tunnels in ten sources of [NiFe]$H_2$ases and two [FeFe]$H_2$ases with $O_2$ inhibition.[26] So now, the issue

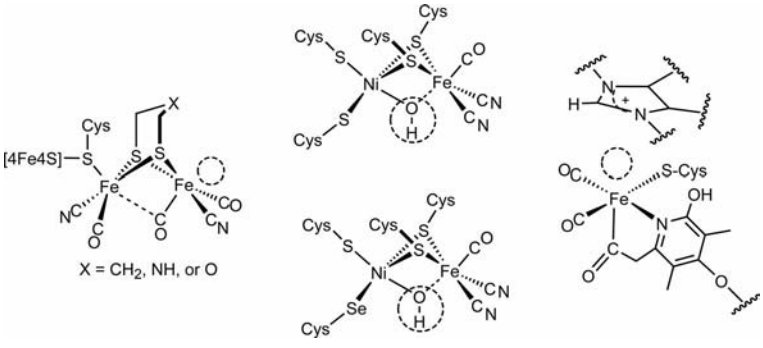



Figure 1. Active sites of [FeFe]$H_2$ase, [NiFe]$H_2$ase, [NiFeSe]$H_2$ase, and [Fe]$H_2$ase.

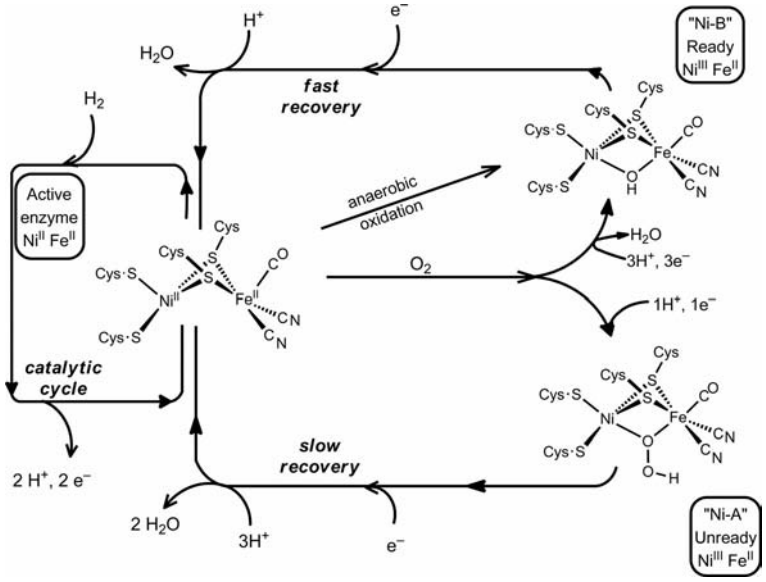



Figure 2. Cartoon of connected cycles for [NiFe]$H_2$ase. Reproduced from ref.[13] by permission of the Royal Society of Chemistry.

is as follows: when $O_2$ access to the active sites *does* occur, which chemical modifications are recoverable, and which are irreversible?

Historically the most well-studied hydrogenase, and the first for which protein crystallography and detailed vibrational spectroscopy elucidated the active site structure, is [NiFe]$H_2$ase.[27,28] Figure 2 is a cartoon of the various redox levels in the active site when inactivated by $O_2$ or when oxidized under anaerobic conditions, yielding the inactive enzyme in two forms: (1) the "Ready" $Ni^{III}Fe^{II}$ form, historically known as Ni-B, is capable of being quickly reactivated by reduction, requiring only one electron and one proton for recovery; and (2) the inactive "Unready" enzyme, Ni-A, also in the $Ni^{III}Fe^{II}$ redox level, would appear to need three electrons and three protons for the slow recovery of the active $Ni^{II}Fe^{II}$ enzyme.[9,13] The molecular significance of these oxidized states, as suggested in Figure 2, is that the ready state has a hydroxide bridge between the nickel and iron atoms and the unready state has a hydroperoxide bridge. Crystallographic evidence supports the former supposition; however, other possibilities for unready Ni-A are suggested from protein crystallography (Figure 3).[14] While the major form has a bridging hydroperoxide, Ni(μ-OOH)Fe, analogous to the Ni(μ-OH) of Ni-B, various levels of S-modification to sulfenates at the bridging thiolate position, or at a terminal position, the latter being O-bound, have been detected in various crystal habits.[14] Although some of these observations may be artifacts, perhaps resulting from radiation damage of the protein crystals, the connection between reactivation and oxygen level is so convincing as to suggest that the complicated recovery from oxygen damage lies at the active site.

One expects that [NiFeSe]$H_2$ase would provide clues as to how a single modification in the active site might affect the air-sensitivity of the enzyme. In fact, PFV studies of [NiFeSe]-$H_2$ase from *Desulfomicrobium baculatum* find it to be deacti-

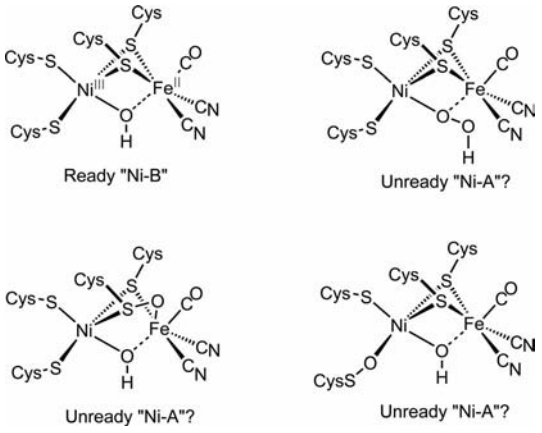



Figure 3. Structures of the active site of [NiFe]$H_2$ase in aerobically deactivated states, proposed by X-ray crystallography.[14]

vated by traces of $O_2$ for $H_2$ oxidation; however, for $H_2$ production, partial activity is retained even in 1% $O_2$, as shown in Equations (1) and (2), respectively.[17] The dichotomy in the direction of $O_2$ sensitivity is explained by the ability of the product of $O_2$ attack to be reductively activated at a potential almost as negative as that of the $2H^+/H_2$ couple.[17] Should this product contain a Se–O bond, rather than a stronger S–O bond or products from Fe-based oxygenation, the tolerance of [NiFeSe]$H_2$ase to $O_2$ exposure might be clarified.

$$H_2 \xrightarrow[\text{[NiFeSe]}]{\text{trace } O_2} 2\,H^+ + 2\,e^- \quad (1)$$

$$2\,H^+ + 2\,e^- \xrightarrow[\text{[NiFeSe]}]{1\%\ O_2} H_2 \quad (2)$$

## Nickel Sulfoxygenates as Models of Oxygen-Damaged [NiFe]$H_2$ase

There are a growing number of synthetic analogues of the [NiFe]$H_2$ase active site; however, to the best of our knowledge, none of them has been deliberately exposed to $O_2$ with a goal of isolating analogues of the O-damaged enzyme active site. Nevertheless, early studies by one of the authors and others have characterized S-oxygenates of *cis*-dithiolato derivatives of nickel complexes.[29–32] The bis(mercaptoethane)diazacycle $N_2S_2$ ligands have provided a useful scaffold for the synthesis of S-oxygenates, maintaining the integrity of the $NiN_2S_2$ binding in the coordination sphere (Figure 4). With diazacyclooctane as the $N_2$ portion of the ligand, and with judicious choice of oxygen atom source ($^3O_2$, $^1O_2$, or $H_2O_2$), all levels of S-bound oxygenates could be produced from the monosulfoxy to the bis(sulfone) or 4-oxy species, and these were structurally characterized. The more flexible acyclic $N_2S_2$ ligand shown in Figure 5 yielded the 6-oxy species, the bis(sulfate), requiring a *trans* arrangement of the O-bound species.[33]

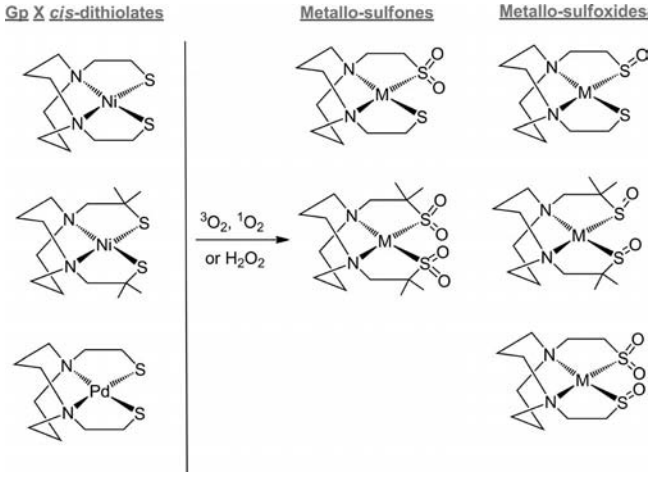



Figure 4. S-oxygenates derived from $MN_2S_2$ complexes. Adapted with permission from ref.[31]

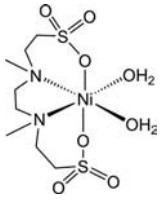
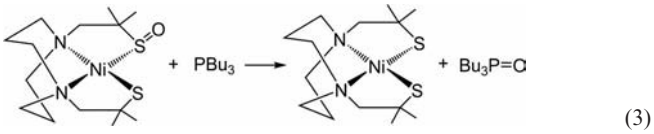


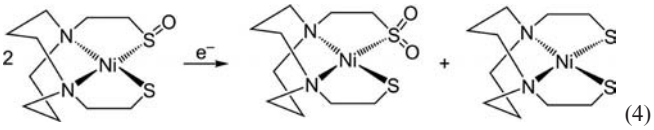
Figure 5. Fully S-oxygenated $NiN_2S_2$ complex becomes O-bound.[33]

While S-oxygenation up to the 4-oxy species had little effect on the structure or metric data of the $NiN_2S_2$ coordination sphere, there was, as expected, a significant difference in the electrochemical properties within the series. With each 2-oxygen gain, the reversible $Ni^{II/I}$ reduction couple was stabilized by 300 mV, spanning a range of 600 mV from the dithiolate to the bis(sulfone) complex.[29,31] Concomitantly the oxidation wave, irreversible for thiolato species, shifted negatively, maintaining an approximately 2 V difference between the oxidation and reduction events. For the bis(sulfone) species, the oxidation wave became completely reversible, signaling the possibility of a stable $Ni^{III}$ when the thiolato sulfur was no longer competitive for oxidation to disulfide.

Oxygen atom removal from the sulfoxides (or sulfenato complexes) was found to be possible with the strong oxygen atom acceptor P($n$Bu)$_3$, forming O=P($n$Bu)$_3$ and reclaiming the nickel dithiolate [Equation (3)].[34] Evidence for oxygen atom transfer was also seen in the reduction-promoted disproportionation reaction explored by electrochemistry [Equation (4)].[34] Such reductive activation that reverses oxygen "damage" to sulfur purports to be a reasonable model of the repair processes that are a part of the [NiFe]-$H_2$ase cycle.




(3)




(4)

As further discussed below, related group 8 S-oxygenates have been prepared from oxidative addition of cyclic thiosulfinates to $Pt^0$ compounds or by photooxidation of dithiolato platinum(II) complexes with $O_2$.[35,36]

At this point, it should be mentioned that some active site S-oxygenations are known to be required for the activity of at least a couple of enzymes: nitrile hydratase and thiocyanate hydratase.[36,37,38] In these cases a tripeptide motif, Cys-Ser-Cys, assumes an $N_2S_2$ tetradentate binding array within the protein, and post-translational S-modification renders the *cis*-dithiolates into a sulfoxide and sulfenate, presumably enhancing the electrophilicity of the Fe or

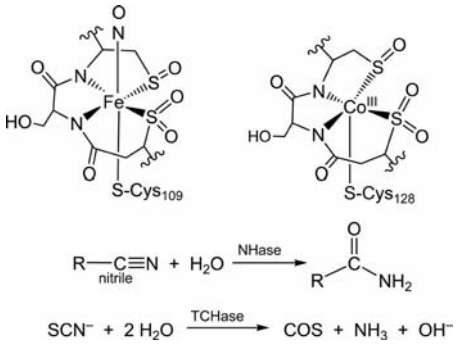



Figure 6. Active sites of nitrile hydratase and thiocyanate hydratase. Both exist in Fe and Co forms.

Co metal centers and their ability to bind the substrates, nitrile or thiocyanate.[39] In addition, the sulfoxy units are proposed to orient, via H-bonding, the reactive water molecules so as to efficiently perform the required hydrolyses (Figure 6). Model studies have found stable S-oxygenates of both Fe and Co analogues as well as those of ruthenium.[39–41]

## Air-Sensitivity Studies of [FeFe]$H_2$ases

As [FeFe]$H_2$ases are the most active of the hydrogenases for proton reduction to $H_2$, it is reasonable that they should be the most air-sensitive. Thus considerable effort has been expended on understanding the source of their $O_2$ sensitivity, especially in the photosynthetic green algal organism *Chlamydomonas reinhardtii*. Stripp, Happe, Armstrong and co-workers investigated the mechanism of $O_2$ attack, known from XAS studies to destroy the 4Fe-4S portion of the active site H-cluster, leaving the 2Fe subsite intact.[42] By clever and informative PFV experiments, it was shown that the presence of CO, known to bind to the 2Fe subsite, but not known to attack iron-sulfur clusters in proteins, actually protected [FeFe]$H_2$ase from $O_2$ damage and inhibition. This implied that binding of $O_2$ to the 2Fe subsite must precede 4Fe-4S cluster destruction. Whether the activation of $O_2$ to reactive oxygen species as shown in path A of Figure 7 or a polarization effect, path B, resulted in the degradation of the 4Fe-4S cluster is unknown.

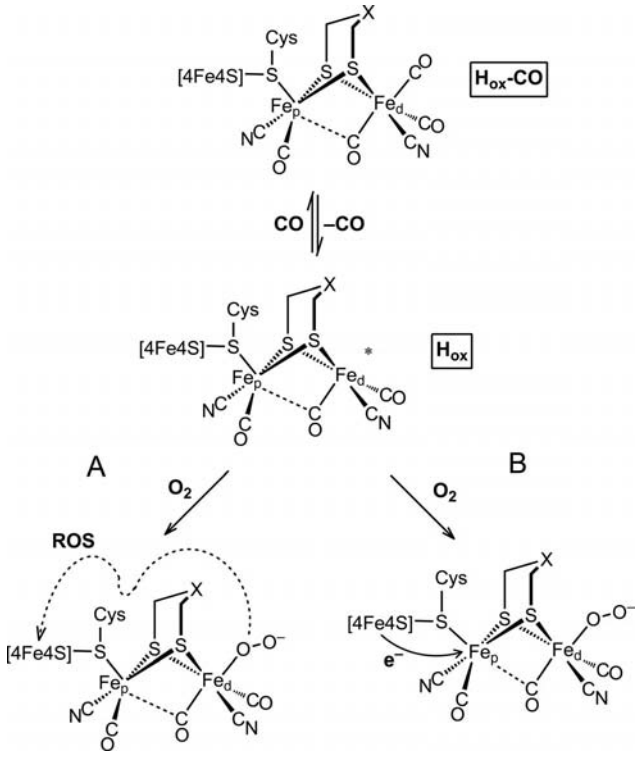



Figure 7. Cartoon of possible mechanisms for $O_2$ damage of the 4Fe-4S subsite in the H-cluster of [FeFe]$H_2$ase. Modified with permission from ref.[42]

A theoretical investigation of this process revealed that $O_2$ binding at the open, distal iron site of the 2Fe subsite, as shown in Figure 7, was the thermodynamically most feasible structure, rather than as a peroxo species bridging the two iron atoms, as appears to be the case with [NiFe]-$H_2$ase.[43] This computational result is consistent with the binding of CO and its competitive inhibition of $O_2$ damage. These results also accounted for the experimental observation that the redox level of the H-cluster influenced the extent of oxygen damage. That is, in the oxidized, inactive $Fe^{II}Fe^{II}$ level, obtained by anaerobic oxidation, the damage to the enzyme from oxygen exposure is less severe and it is reversible!

## The [FeFe]$H_2$ase Models and S-Oxygenates

As of this writing, some 300 structures of complexes that are purported models of the 2Fe subsite of the [FeFe]$H_2$ase active site have been deposited in the Cambridge Structural Database.[44] Most of these are in the $Fe^IFe^I$ redox level and are derivatives of the classic (μ-SRS)[Fe(CO)$_3$]$_2$ compound as a readily accessible and easily modifiable precursor to substituted complexes that are more "like" the active site (Figure 8).[44]

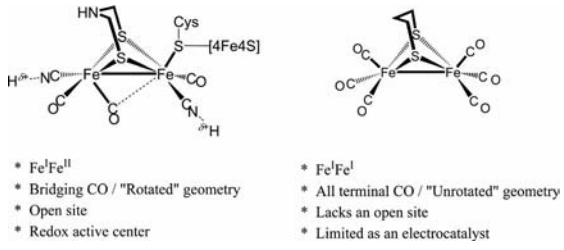



Figure 8. The versatile (μ-SRS)[Fe(CO)$_3$]$_2$ precursor to $Fe^IFe^I$ models of the [FeFe]$H_2$ase active site.

Only a handful of [FeFe]$H_2$ase active site models have achieved the "rotated" or "inverted" structure and the mixed $Fe^IFe^{II}$ valency of the as-isolated enzyme active site (Figure 9).[45–49] These are found to be very fragile com-

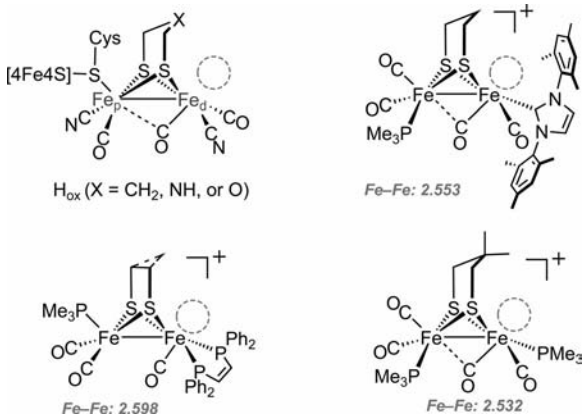
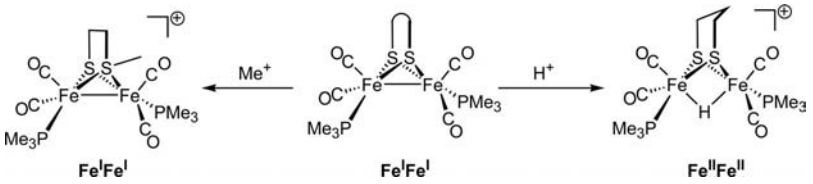



Figure 9. The [FeFe]$H_2$ase enzyme active site structure and a selection of "rotated" synthetic analogues of the $Fe^IFe^{II}$ mixed-valent diiron subsite of the $H_{ox}$ cluster.




Scheme 1.

pounds that are both thermally sensitive and highly susceptible to $O_2$ degradation; thus far, products from exposure to $O_2$ have not been identified. Nevertheless, as found for the nickel dithiolates described above, products of oxygen atom addition are found for S- and Se-containing analogues of the (μ-SRS)$Fe^{I}Fe^{I}$-CO complexes.

Explorations of the chemical reactivity of (μ-SRS)$[Fe(CO)_3]_2$ that re-emerged after the discovery of the diiron subsite in [FeFe]$H_2$ase indicated multiple possibilities for reactions with electrophiles. For example, Darensbourg and co-workers found that protonation of the electron-rich (μ-pdt)$[Fe(CO)_2PMe_3]_2$ engaged the electron density of the Fe–Fe bond generating the oxidative addition product, the bridging hydride, $Fe^{II}$(μ-H)$Fe^{II}$. However, alkylation proceeded at sulfur, yielding the bridging thioether and retaining the iron atoms in the +1 oxidation state (Scheme 1).[50,51] Hence, expectations for reaction with oxygen atom sources were explored by theory and experiment.

Preliminary DFT computations predicted that, for the all-CO diiron complex, S-oxygenation should be approximately 10 kcal/mol less favored by thermodynamics than the μ-O species shown in Figure 10.[52] This prediction was inconsistent with literature precedent by Messelhäuser et al., who found a μ-sulfoxide species upon reaction of (μ-edt)$[Fe(CO)_3]_2$ with the oxygen atom source, *m*-chloroperbenzoic acid (*m*-CPBA).[53] Further DFT calculations on a series of (μ-pdt)$[Fe(CO)_2L]_2$ complexes revealed in all cases the μ-oxo species to be thermodynamically favored, sometimes, as in the case of phosphane-substituted derivatives, as much as 17 kcal/mol over the S-oxygenate. Only for the (μ-H)$[Fe^{II}]_2^+$ species of Scheme 1 was the S-oxy species predicted and experimentally verified. It should be noted that the calculations were carried out with the B3LYP functional and with modified LANL2DZ basis sets for Fe and S and D95 for other atoms. Use of B3LYP/cc-PPVDz& LANL2DZ or replacement of B3LYP with TPSS gave similar results, again with the (μ-O)$Fe^{II}_2$ product of lower energy. A recent, expanded exploration of functional and basis sets by M. B. Hall and C. Liu[80] finds the specific oxygenate isomer to be much more sensitive to the computational settings than previously observed. In fact, in selected combinations of functional and basis set, the S-oxygenate is found to be the thermodynamically favored product.

Four S-oxy products within the series were structurally characterized, (Figure 11).[52] The minor differences relative to the dithiolate precursors are discussed below.

Similar bridging S-oxygenates of diironhexacarbonyl have been derived by reaction of dimethyldioxirane (DMD) with the bicyclic dithiolate shown in Scheme 2.[35,54–61] An

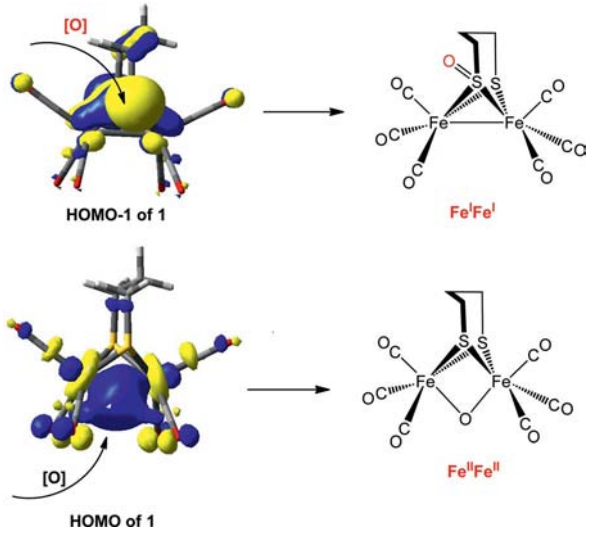



Figure 10. The frontier orbitals of (μ-pdt)$[Fe(CO)_3]_2$ (**1**) and stick drawings of the **1**-O isomers. Adapted with permission from ref.[52]

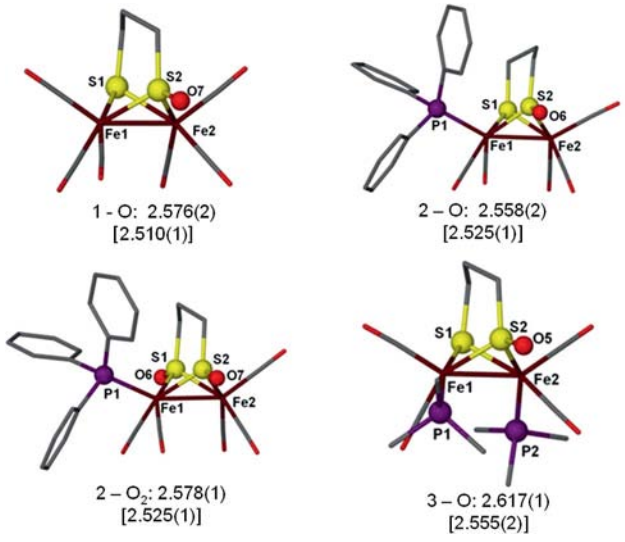
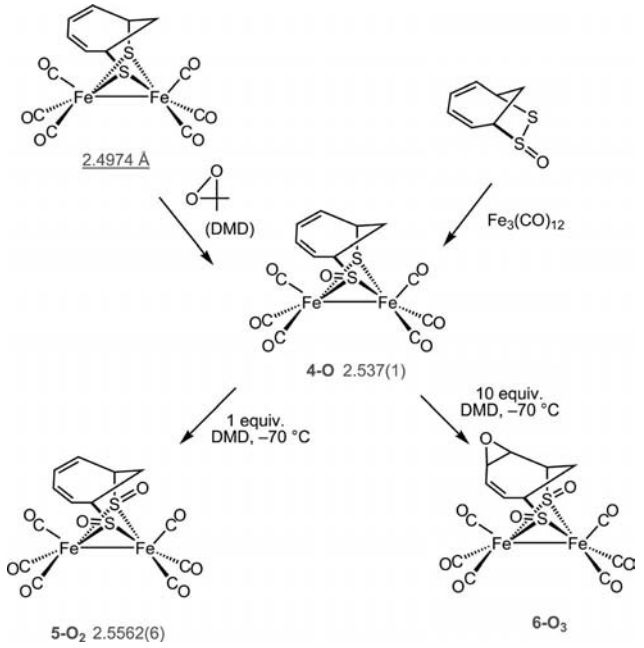



Figure 11. Structures of S-oxygenated derivatives of {μ-S$(CH_2)_3$S}-$[Fe(CO)_2L]_2$. Fe–Fe distances (Å) under each structure with Fe–Fe distances in the parent dithiolate in parentheses. Adapted with permission from ref.[52]

alternate route to **4**-O (Scheme 2), developed by Windhager et al., utilized oxidative addition of 7,8-dithiabicyclo[4.2.1]-nona-2,4-diene-7-*exo*-oxide (**12**) to $Fe_3(CO)_{12}$.[54] Side products included the μ-dithiolate (μ-SRS)$[Fe(CO)_3]_2$ complex

(15%) and $Fe_3(CO)_9S_2$. Further reaction with DMD produced the disulfinato (**5**-$O_2$) complex or the disulfinatooxirane (**6**-$O_2$).




Scheme 2. Oxidative addition of 7,8-dithiabicyclo[4.2.1]nona-2,4-diene-7-*exo*-oxide to $Fe_3(CO)_{12}$. Reactions of sulfenato-thiolato complexes with DMD. Fe–Fe distances from XRD molecular structures are given below each compound.

The work described in Scheme 2 was presaged by observations that addition of RS–SR or RS–S(=O)R reagents to a $Pt^0$ source as well as $Fe_3(CO)_{12}$ yielded oxidized-metal bound dithiolates.[62–70] Scheme 3 presents such results for the cyclic disulfide. Furthermore, the platinum(II) dithiolate could be S-oxygenated by reactive oxygen species in a manner similar to (μ-SRS)$[Fe(CO)_3]_2$, yielding sulfenato species and retaining the integrity of the coordination sphere. Such reactions illustrate the similar redox and chemical potential (sulfophilicity) of $Pt^0$ and suitably ligated $Fe^0$ compounds, the latter requiring two iron atoms with CO as stabilizing ligand for the $Fe^I$(μ-SRS)$Fe^I$ product. As a goal of these biomimetic studies is to follow Nature's guide for the preparation of base-metal molecular catalysts "as good as platinum" in $H_2$ production,[71] the analogous reactivity of a single $Pt^0$ and a cluster of $Fe^0$ is of no small significance.

The 1,2,4-trithiolane cyclic disulfide also oxidatively adds to $Pt^0$ and likewise to the iron(0) carbonyl clusters, $[Fe_2(CO)_9]$ and $[Fe_3(CO)_{12}]$, yielding the sulfur–dithiolate (sdt) complexes $[S(CH_2S)_2Pt^{II}(PPh_3)_2]$ and $[(\mu\text{-}SCH_2SCH_2S)\{Fe^I(CO)_3\}_2]$.[67–70,72,73] The latter complex offered the opportunity to observe S-oxygenation distributions for the thioether bridgehead sulfur atoms vs. the μ-thiolate sulfur atoms. With DMD as oxygen atom source, all levels of S-O products shown in Figure 12 were realized with maximum yields obtained for **7a** (98% when reacted with 1 equiv. of DMD) and **7b** (75%). With 3 equiv. of DMD, all of **7a** was converted to **7b**, **7c**, and **7d**.

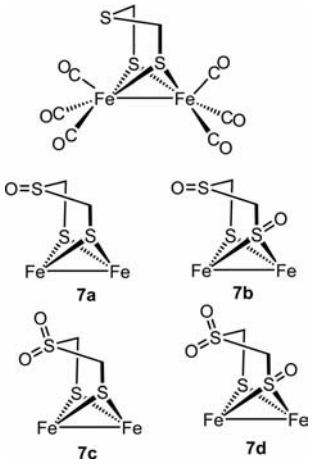
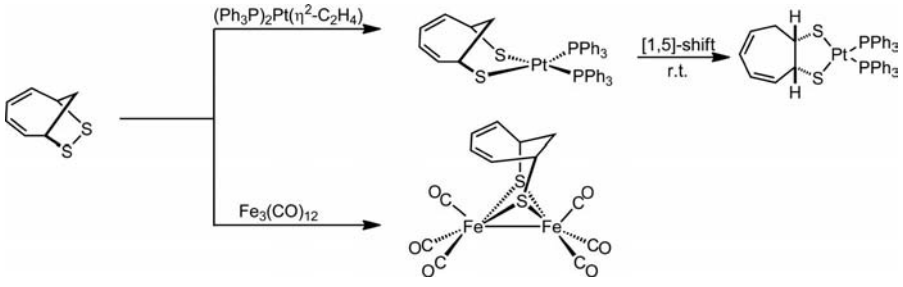



Figure 12. Products of the reaction of (μ-$SCH_2SCH_2S$)$[Fe(CO)_3]_2$ with varying numbers ($x$ = 1–4) of equivalents of DMD.

An effect of the interesting dicyclohexyl derivative (Figure 13) is that S-oxygenation occurred exclusively on the bridgehead sulfur, the product being the sulfone, regardless of the stoichiometry of the added DMD.[74] Figure 13 shows this reaction and an end-on view (down the Fe–Fe bond vector) of the unique S-to-S bridged diiron complex.

## Properties of Diiron Sulfoxygenates

While formation of bridging sulfoxides at the μ-thiolato sites of (μ-SRS)$[Fe(CO)_3]_2$ does not disturb the overall integrity of the coordination spheres, it has a lengthening effect on the Fe–Fe bonds, of 0.03 to 0.05 Å per added oxygen atom (e.g., see Figure 11).[52] The $Fe^I$–$Fe^I$ bond length of complex **3**-O is even longer than the $Fe^{II}$··$Fe^{II}$ distance




Scheme 3. Oxidative addition of 7,8-dithiabicyclo[4.2.1]nona-2,4-diene to $(Ph_3P)_2Pt(\eta^2\text{-}C_2H_4)$ and $Fe_3(CO)_{12}$.

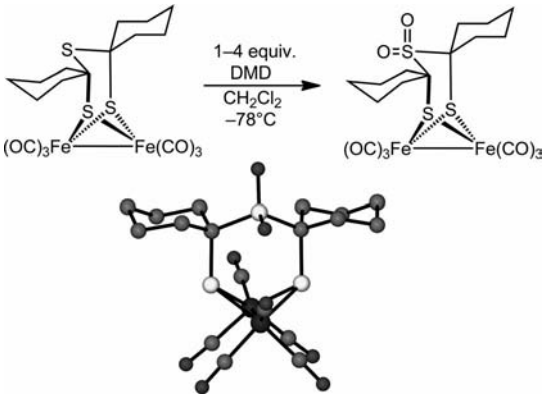



Figure 13. Reaction of hexacarbonyl{bis[($\mu^2$–1-thiolato-S,S′-1-pentamethylenemethyl)sulfide]}diiron with 1–4 equiv. of DMD.

in (μ-H)(μ-pdt)[$Fe^{II}(CO)_3PMe_3]_2^+$ (2.578 Å).[75] The lengthening of the Fe···Fe distance is accompanied by a slight decrease of the Fe–S(=O) distance.

DFT computations combined with variable-temperature NMR spectroscopic studies (Figure 14) were used to explore the effect of S-oxygenation on the intramolecular CO site exchange in (μ-pst)$[Fe(CO)_3]_2$.[76] Earlier variable-temperature $^{13}C$ NMR spectroscopic studies of the (μ-pdt)$[Fe(CO)_3]_2$ parent complex demonstrated that the individual $Fe(CO)_3$ units were rotors interchanging apical and basal CO units as shown in Scheme 4.[77] Interestingly, the calculated transition-state structure for this rotation, which agreed well with the experimentally determined activation barrier, bore a strong resemblance to the "rotated" active site, including a semibridging CO.

DFT computations further predicted that the activation barrier to the intramolecular exchange process would be influenced by several factors including the nature and position of the bridgehead atom in the S-to-S linker. Substitution of CO by better donor ligands stabilized the transition state by delocalization of the Fe–Fe bond density onto the semibridging CO.[78,79] A logical extension of this conclu-

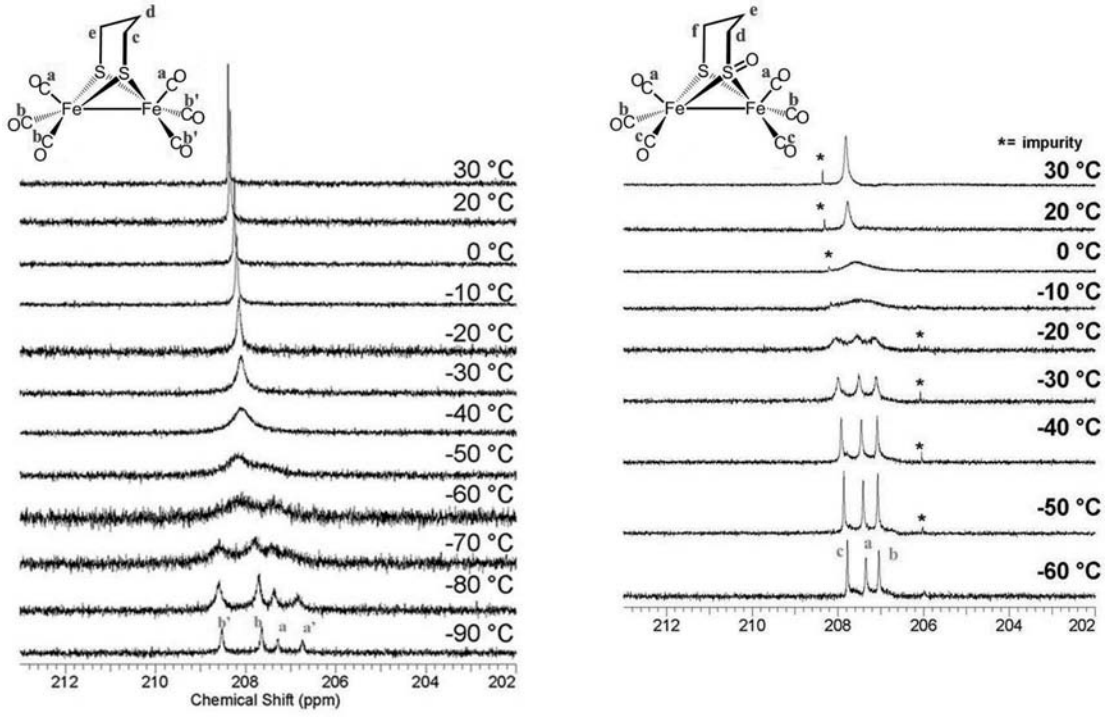
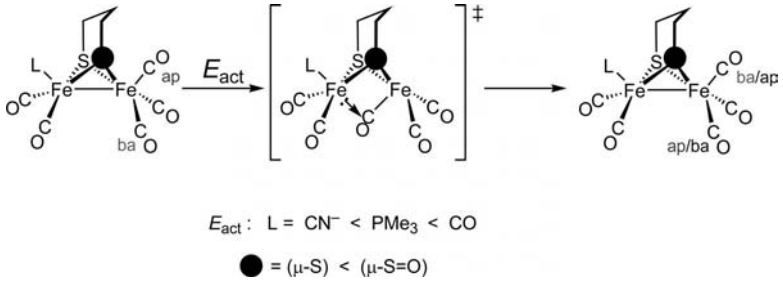



Figure 14. Comparison of variable-temperature $^{13}C$ NMR spectra in $CD_2Cl_2$ solvent.




Scheme 4. Intramolecular CO site exchange in the $Fe(CO)_3$ rotor, showing the DFT-optimized structure of the "rotated" transition state. Adapted with permission from ref.[76]

sion is that replacement of CO by a poorer donor ligand should raise the $E_{act}$ barrier to rotation. While such an experiment cannot easily be performed {$NO^+$ substitution on the hexacarbonyl to form a stable (μ-pdt)[$Fe(CO)_3$][$Fe(CO)_2$-NO]$^+$ has not yet been realized}, the S-oxygenates have such an effect of diminishing electron density from the iron atoms, as implicated by ν(CO) values. Thus the higher barrier to apical/basal CO exchange in (μ-pst)[$Fe(CO)_3$]$_2$ {$\Delta G^{\ddagger}_{exptl.}$ ($\Delta G^{\ddagger}_{calcd.}$) = 10.7 (14.0) kcal/mol, as compared to (μ-pdt)[$Fe(CO)_3$]$_2$ [$\Delta G^{\ddagger}$ = 8.6 (11.9) kcal/mol]} was consistent with this analysis of the (μ-SRS)$Fe_2$ core electronic structure and its response to its electronic environment.[76]

The flexibility of the (μ-SRS)$Fe_2$ structure is undoubtedly vital to its adaptation in the [FeFe]$H_2$ase enzyme active site. It is also of importance for ligand-substitution reactions in (μ-pst)[$Fe(CO)_3$]$_2$. Despite the coordinative saturation of the $Fe^I$ units in (μ-pdt)[$Fe(CO)_3$]$_2$, ligand exchange with good nucleophiles such as $CN^-$ and $PMe_3$ follows a second-order rate expression, implicating an expanded coordination sphere in which nucleophilic attack is concurrent with rotation (Figure 15) and the overall barrier to CO/L exchange is a combination of the barriers to nucleophilic attack and $Fe(CO)_3$ rotation.[76]

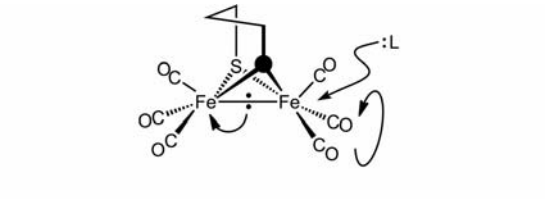
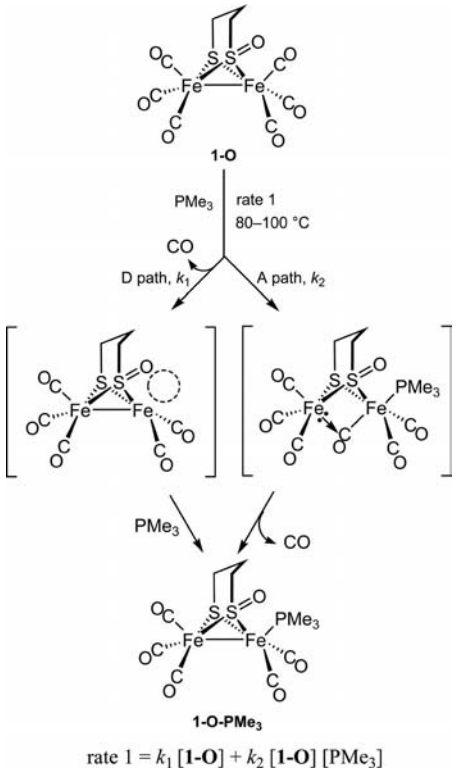



Figure 15. Representation of the interplay of $Fe(CO)_3$ rotation, nucleophilic attack at iron, and Fe–Fe bond density shift. Adapted with permission from ref.[76]

As S-oxygenation increases the electrophilicity of the iron atoms, the barrier to nucleophilic attack should be lowered; at the same time, the $Fe(CO)_3$ rotational barrier is, as described above, increased in the S-oxygenate complex **1**-O. To define these competing effects, kinetic studies of CO/L substitution processes were carried out with complex **1**-O; Scheme 5 summarizes the results.[76] Whereas the first CO/$PMe_3$ exchange could be monitored in a 20 to 50 °C range for complex **1**, with **1**-O, reactions within a reasonable time frame required temperatures of 80 °C or higher. In this temperature regime, both associative and dissociative paths were observed (Scheme 5). Thus, the higher barrier to rotation must be invoked to account for the sluggish reactivity of **1**-O relative to that of **1**. This result is verified in $CN^-$/CO substitution reactions. The better nucleophilicity of $CN^-$ over $PMe_3$ is well demonstrated here, and the overall kinetic expression and substitution pattern are the same for both; harsher conditions than those for similar reactions with the (μ-pdt)[$Fe(CO)_3$]$_2$ complex are required for (μ-pst)[$Fe(CO)_3$]$_2$.[76] Again, the conclusion is that the greater rotational barrier and lower flexibility of the sulfoxygenate complex **1**-O, verified in the NMR spectroscopic studies of Figure 11, must overwhelm the increased electrophilicity that governs nucleophilic attack of the incoming ligand.




Scheme 5. Reprinted with permission from ref.[76]

It should be noted that, although thermally accessed CO/L exchange is difficult in the sulfoxygenates, $PPh_3$ derivatives have been made through oxidatively induced CO dissociation, that is, addition of $Me_3N$–O results in loss of $CO_2$ and the creation of an open site for exogenous ligand binding.[54] Shown in Figure 16 are products of such reactions yielding $PPh_3$ substituted sulfenato and stable acetoni-

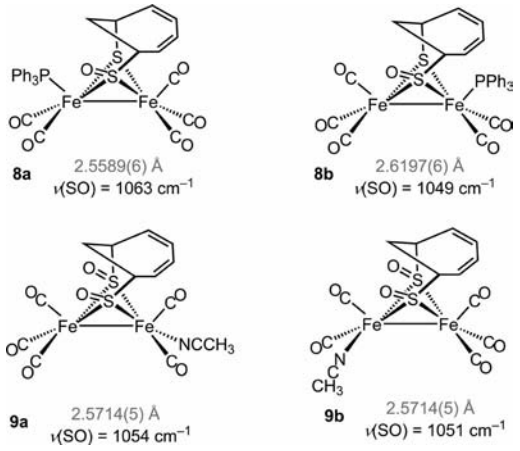



Figure 16. Products of substitution reactions of μ,μ′-(4,6-cycloheptadiene-1-sulfenato-3-thiolato)hexacarbonyldiiron with triphenylphosphane and acetonitrile. Fe–Fe distances from XRD molecular structures and ν(SO) values ($cm^{-1}$) are given below each compound.

trile derivatives of disulfenato complexes. Note the *trans* effect of the $PPh_3$ ligand on the ν(SO) value in complex **8b** relative to that of **8a**.[54]

## Oxygen Removal from the Sulfoxygenates

As with the sulfoxygenates of the nickel complexes described earlier, deoxygenation is of significance as a possible repair mechanism of oxygen-damaged active sites. For complex **1**-O, typical oxygen atom acceptors such as $PPh_3$ or $PMe_3$ had no effect at ambient temperatures and, as described, phosphane/CO substitution occurred at higher temperatures.[76] Whether the lack of oxygen atom removal by $PR_3$ (including $PtBu_3$) signals a large kinetic barrier or a thermodynamic preference is not known. However, events in the cyclic voltammogram of **1**-O suggested that **1**-O converted to **1** on repeated scans of the reduction events. Hence, bulk chemical reduction of **1**-O was examined by using $Cp^*_2Co$ as reductant with the result that, in the presence of trace amounts of $H_2O$, **1**-O could be returned to its precursor dithiolate form. Bulk electrolysis was consistent with this result as were similar studies with **2**-O, **2**-$O_2$, and **3**-O, defined in Figure 11. A possible mechanism involving proton-coupled electron transfer was offered.[52]

## Concluding Remarks

Synthetic inorganic chemists are reticent to expose their hard-earned air-sensitive molecules to $O_2$; nevertheless, the need to understand recovery processes for oxygen-damaged active sites suggests such experiments, and the identification of reaction processes and products could be valuable. In rudimentary thiolate-containing models of [NiFe]- and [FeFe]$H_2$ase active sites we have noted that discrete S-oxygenates result from controlled reaction with reactive oxygen species. Both terminal and bridging thiolates are susceptible to oxygen atom attack. The oxygen atom capture products are stable; they have properties that reflect the change in the oxidation state of sulfur, yet the Ni–S or Fe–S bonds and the integrity of the coordination spheres are maintained. Reduction-induced deoxygenation of the S-oxygenates has been demonstrated, indicating that thiolates could serve a double purpose in such enzyme active sites: as versatile ligands they can (1) bridge the 2-metal constructs apparently required to mediate the 2-electron processes of hydrogen reactivity; and (2) protect the site from irreversible metal oxidation. Furthermore, sulfur atoms positioned in model complexes as distal thioethers appear to be more oxophilic than bridging thiolates.

## Acknowledgments

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