In Quest of Competitive Catalysts for Nitrogenases and Other Metal Sulfur Enzymes

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Introduction

The inertness of the N_2 molecule has given the chemical element N its German and French names Stickstoff (suffocating matter) and Azote (from Greek "no life"). The N_2 molecule is nonpolar, has a negative electron affinity,[1] exhibits an ionization energy (15.58 eV) almost as high as that of argon (15.75 eV), and has a triple bond that is extremely stable toward dissociation (944 kJ/mol).[2] All of these properties readily explain why the Haber−Bosch process requires red-hot temperatures and high pressures (>500 °C, 200 bar) to form ammonia from N_2 and H_2.

Nevertheless, nature converts thousands of tons of molecular nitrogen into ammonia every day (an estimated 170×10^6 tons/year) at ambient conditions (20 °C, 1 bar) according to eq 1. Biological N_2 fixation through catalytic

$$N_2 + 8H^+ + 8e^- + 16\text{MgATP} \rightarrow 2NH_3 + H_2 + 16\text{MgADP} + 16PO_4^{3-} \quad (1)$$

action of the metal enzyme nitrogenase makes dinitrogen not a suffocating but in fact an essential element for all living matter. Three types of nitrogenases are known, containing Mo/Fe, V/Fe, or "Fe-only" centers.[3]

The extreme difference in reaction conditions between biological and industrial N_2 fixation, the question why the metal enzyme nitrogenase is so superior to Haber−Bosch catalysts, and the need of fixed nitrogen for human life make N_2 fixation a process whose significance may be second only to photosynthesis, the other fundamental synthetic process in nature.

The elucidation of the molecular structure and mode of action of nitrogenase was hoped to provide perspectives for the synthesis of low-molecular-weight functional models. Functional models with nitrogenase-like activity (termed "competitive catalysts" for the purpose of this review) are a dream of many chemists and the central issue of this Account.

More than 30 years ago, when cell-free nitrogenase[4] and metal dinitrogen complexes[5] had been isolated for the first time, this dream seemed close to coming true and a source of cheap fertilizer appeared within reach. In hindsight, this attitude was overly optimistic. Today, the structure of FeMo nitrogenase is known in great detail,[6] but the molecular mechanism by which nitrogenase catalyzes N_2 reduction is far from being understood. Synthetic efforts have yielded structural and functional models of nitrogenase,[7] but low-molecular-weight catalysts with nitrogenase-like reactivity are still unknown.

The Strategy of Bionics: Principles Instead of Blueprints

The X-ray structure determination and other results on nitrogenase, however, have settled an important question: Can low-molecular-weight competitive catalysts be compounds that at the same time mirror the structure, the spectroscopic properties, and the reactivity of the active centers of nitrogenase? Such compounds would duplicate the active centers and represent "ideal models".[8] "Ideal models" may indeed exist for enzymes that have very robust prosthetic groups, e.g., hemes. For nitrogenases and numerous other metal sulfur oxidoreductases, however, a statement can be made to the contrary: A functional model (and ultimately a competitive catalyst) *must structurally differ* from enzyme centers whose structural integrity and catalytic activity are warranted by the enzyme protein.

The FeMo cofactor (FeMoco) of FeMo nitrogenase (Figure 1) is a striking example. The FeMoco is considered the site where N_2 is activated and reduced. However, native FeMoco isolated from nitrogenases is short-lived in aqueous media ($\tau_{1/2} \sim 2$ h), and it *does not catalyze* N_2 reduction.[9] Thus, if chemists in their quest of competitive catalysts can conclude anything from unravelling the mysteries of nitrogenase, it is to search not for structural duplicates but rather for basic structure−function relationships of enzyme centers, in other words, to attempt to use *principles* and not *blueprints* (in the sense of dictatorial construction rules) of nature.

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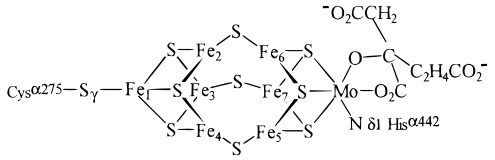


FIGURE 1. X-ray structural model of the FeMo cofactor of FeMo nitrogenase.

One of the most elementary structural principles of any metal complex is the type of donor atoms ligating the metal center(s). Donor atoms may differ in size, polarizability, electronegativity, charge, number of available lone pairs, and stability or instability in aqueous or nonaqueous media. All these features will influence the reactivity of a complex so that its properties can be expressed in terms of structure−function relationships.

Therefore, model complexes that are to combine structural *and* functional principles of metal sulfur ([MS]) oxidoreductases should exhibit sulfur-rich coordination spheres, vacant sites, Broensted acid−base properties, and redox activity. The last three features are pivotal for the reductive conversion of a substrate S into a product P through coordination, activation, and transfer of protons and electrons according to the general reductase reaction of eq 2. In the case of nitrogenases, it must be stressed

$$S + xH^+ + ye^- \rightarrow P \qquad (2)$$

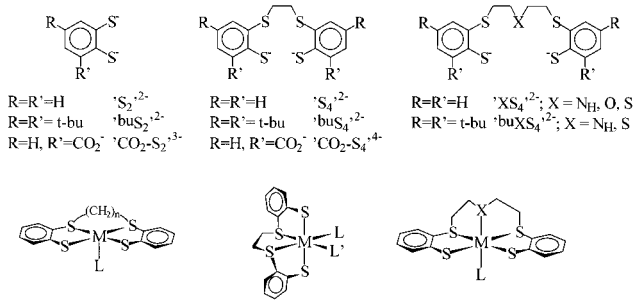
that the function and not the selectivity is the main concern. Nitrogenase is a rather unselective enzyme and catalyzes the reduction not only of N_2 but also of acetylene, nitriles, isonitriles, azide ion, and protons.[10] Thus, any complex that reacts with N_2 can be considered a nitrogenase model, but only if this complex catalyzes reaction 2 with nitrogenase-like efficiency will it be a competitive catalyst.

We began our search for such complexes with metal organic compounds such as $[C_5H_5Mn(CO)_2N_2]$,[10] and the results have now grown into a rather extensive coordination chemistry of transition metal complexes with sulfur ligands. The design of multidentate ligands to obtain stable complexes has been a major task.[11]

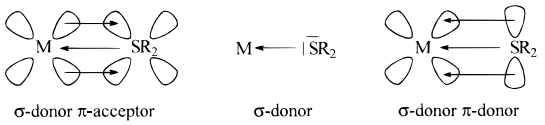
Sulfur Ligands and Complexes

Scheme 1 shows a few of these ligands, which are derived mainly from benzenedithiolate and its substituted congeners by template alkylations. These ligands bind numerous transition metals to give complex fragments, three of which are shown as representative examples. These complex fragments coordinate a large variety of coligands L or L′ which are relevant to N_2 fixation, the nitrate−ammonia interconversion, hydrogenase action, CO dehydrogenase action, and the biological sulfur cycle. Ranging from soft $\sigma-\pi$ ligands such as CO to hard ligands such as chloride or oxide, the nature of L and/or L′ indicates a

Scheme 1



Scheme 2. Bonding Modes of Sulfur Ligands Exemplified for a Thioether



remarkable electronic flexibility of the [MS] fragments (in this context, [MS] denotes a complex fragment whose metal coordination sphere is predominantly or exclusively made up of sulfide, thiolate, or thioether sulfur donors). Scheme 2 suggests the presence of sulfur donors to be the underlying cause for the electronic flexibility. Sulfide, thiolate, and thioether ligands can act as σ-donor, σ-donor π-acceptor, and, due to their lone pairs, also as σ-donor π-donor ligands. This versatility of sulfur ligands contrasts with the bonding mode of amines or phosphines, which act either as σ-donor or as σ-donor π-acceptor ligands. The actual bonding mode of sulfur donors will depend on the occupation of the metal orbitals. For example, formation of π-donor bonds can be expected when the metal center is electron deficient or in a high oxidation state.

π-Donation

An instructive example demonstrating the ability of thiolate donors to stabilize vacant coordination sites or electronically unsaturated metal centers via π-donation is the mononuclear Cr^0 anion $[Cr(CO)_3(S_2C_6H_4)]^{2-}$ (**1**)[12] (Scheme 3). Five-coordinate Cr^0 centers as in $[Cr(CO)_5]$ are usually very unstable.[13] The short average Cr−S distance (229.5 pm) indicates that stabilization of the Cr^0 center in $[Cr(CO)_3(S_2C_6H_4)]^{2-}$ is achieved by S⇉Cr π-donor bonds. These π-donor bonds can be "switched off/on" through coordination/decoordination of a sixth ligand as exemplified by the pair $[Cr(CO)_3(S_2C_6Cl_4)]^{2-}$ (**2**)/$[Cr(CO)_4(S_2C_6Cl_4)]^{2-}$ (**3**).[14] It has average Cr−S distances of 231.7 pm (**2**) and 242.0 pm (**3**), respectively, indicating that the formation of π-bonds shortens the bond by 10 pm. Likewise, Mo−S distances of 235.5 pm in $[Mo(CO)_2('^{bu}S_2')_2]$ (**4**) and $[Mo(CO)(PPh_3)('^{bu}S_2')_2]$ (**5**) (which are short in comparison to Mo−S (thiolate) single bonds as in $[Mo(CO)_2(PMe_3)('S_4')]$ (**6**) (253.3 pm)) indicate that in these Mo^{IV} complexes S⇉Mo π-donor bonds are effec-

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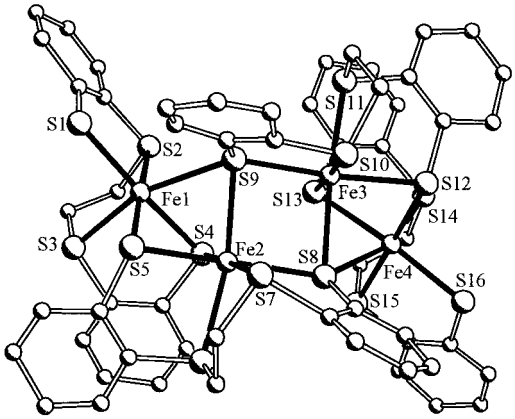
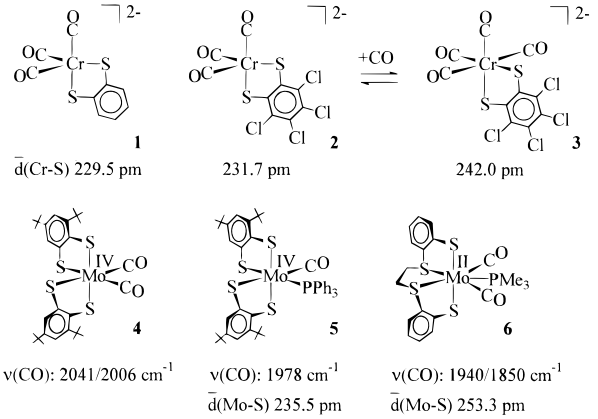


FIGURE 2. Molecular structure of [Fe('S_4')]$_4$ (7).

Scheme 3



tive.[15,16] They make the high-valent Mo^{IV} centers so electron rich as to behave like Mo^{II} or Mo^0 centers with regard to CO binding.

In summary, the (S⇉M) π-donation in these benzenedithiolate complexes does not differ from that in tetrathiomolybdate $[MoS_4]^{2-}$. It is not necessary to invoke a "noninnocent" behavior of the benzenedithiolate ligand.[15,17]

M−S−M Bridging via Sulfur Lone Pairs

Lone pairs on sulfur donors forming only σ-bonds make thiolate or sulfide bridging of complex fragments a recurrent motif in metal sulfur chemistry. This type of bridging is also found with the metal complex fragments of Scheme 1, which tend to dimerize or oligomerize in the absence of suitable coligands. An impressive example is the [Fe('S_4')] fragment. It has two vacant sites and tetramerizes in the solid state. The complicated structure of [Fe('S_4')]$_4$ (**7**) (Figure 2) is easily rationalized by the "explosion drawing" of Figure 3. Figure 3 shows that **7** contains four homochiral fragments. In THF solution, stepwise dissociation of **7** leads to coordinatively unsaturated [Fe('S_4')]$_2$ dimers and [Fe('S_4')] monomers. These may be detected and identified by coordination of CO yielding [Fe(CO)('S_4')]$_2$ (**8**) and [Fe(CO)$_2$('S_4')] (**9**).[18]

Structure and reactivity of [Fe('S_4')]$_4$ reveal a caveat for the discussion of polynuclear [MS] enzyme centers. Such centers may dissociate and, as a consequence, may exhibit quite different structures in the resting and in the turnover state of the enzyme.

The influence of the various X donors upon the structures of [M('XS_4')] complexes (X = O, S, N_H) can be drastic as shown by the series of [Ni('XS_4')] complexes in Figure 4. The structures range from achiral mononuclear [Ni('S_5')] (**10**),[19] via dinuclear [Ni('N_HS_4')]$_2$ (**11**) containing chiral [Ni('N_HS_4'] fragments,[20] to the completely different [Ni('OS_4')]$_2$ (**12**), in which O(C_2H_4)$_2$ bridges connect two cofacial [NiS_4] units.[19] The bridge length itself can also cause quite different structures as shown by the mononuclear [Ni('S_4−C_3')] (**13**)[19] and trinuclear [Ni('$^{tbu}S_4$')]$_3$ (**14**) complexes.[21] Significant are also the H_2S and μ-S_2 complexes [Ru(H_2S)(PPh_3)('S_4')] (**15**), [μ-S_2{Ru(PPh_3)('S_4')}$_2$] (**16**),[22] and [μ-S_2{Fe('S_4')}$_2$] (**17**)[23] (Figure 5). The X-ray structure analysis of the H_2S complex revealed strong S−H···S bridges between the H_2S protons and thiolate donors. The μ-S_2 bridges in **16** and **17** give rise to [M···S···S···M] 4-center 6-electron π-bonding (Figure 5d), which causes intense long-wave absorptions up to 1050 nm ($\epsilon \sim 14\,000$) in the UV−vis−near-IR spectra and up to six redox waves in the cyclic voltammograms. [Mo(NH_2O)(NO)('S_4')] (**18**)[24] and [Mo(N_2H_3)(NO)('S_4')] (**19**)[25] are rare examples of complexes showing the side-on binding mode of the NO reduction product NH_2O and the potential N_2 reduction intermediate N_2H_3 to sulfur-rich molybdenum sites.

High-Spin versus Low-Spin [MS] Complexes

The series of [Fe(L)(N_H'S_4')] complexes revealed the influence of the coligand L on structure, magnetism, and reactivity of [MS] complexes (Figure 6).[26,27] The five-coordinate [Fe('N_HS_4')] (**20**) is paramagnetic ($S = 2$) and has a distorted trigonal-bipyramidal structure and an average Fe−S(thiolate) distance of 230.6 pm, which is short in comparison to the average Fe−S(thioether) distance (254.0 pm). [Fe('N_HS_4')] (**20**) reversibly adds σ-donor ligands such as MeOH, N_2H_4, NH_3, or N_3^- to give paramagnetic ($S = 2$) six-coordinate complexes. All of these derivatives are labile and C_s symmetrical and exhibit long Fe−N (∼225 pm) and long Fe−S (∼240−260 pm) distances. In contrast, the addition of σ−π ligands such as CO, NO^+, and phosphines is irreversible and yields diamagnetic derivatives. These complexes are inert, have C_1 symmetry, and exhibit short Fe−N (∼207 pm) and short Fe−S (220−230 pm) distances. Thus, the change from σ

(15) Sellmann, D.; Grasser, F.; Knoch, F.; Moll, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1311.
(16) For Mo−S bond distances, see: Trnka, T. M.; Parkin, G. *Polyhedron* **1997**, *16*, 1031.
(17) Alvarez, S.; Vicente, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1985**, *107*, 6253.
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(20) Sellmann, D.; Fünfgelder, S.; Knoch, F. *Z. Naturforsch.* **1991**, *B46*, 1593.
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(23) Sellmann, D.; Mahr, G.; Knoch, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1477.
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(25) Sellmann, D.; Kern, W.; Pöhlmann, G.; Knoch, F.; Moll, M. *Inorg. Chim. Acta* **1991**, *185*, 155.
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(27) Sellmann, D.; Soglowek, W.; Knoch, F.; Ritter G.; Dengler, J. *Inorg. Chem.* **1992**, *31*, 3711.

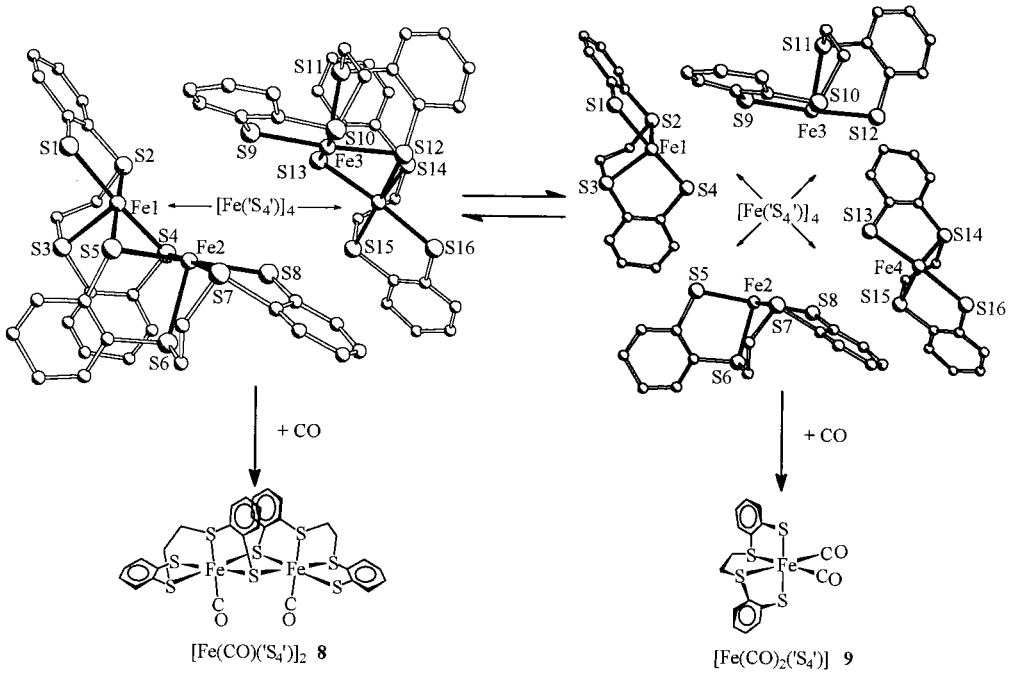


FIGURE 3. "Explosion drawing" of the [Fe('S_4')]$_4$ structure demonstrating the stepwise dissociation into two homochiral [Fe('S_4')] dimers and four homochiral [Fe('S_4')] monomers.

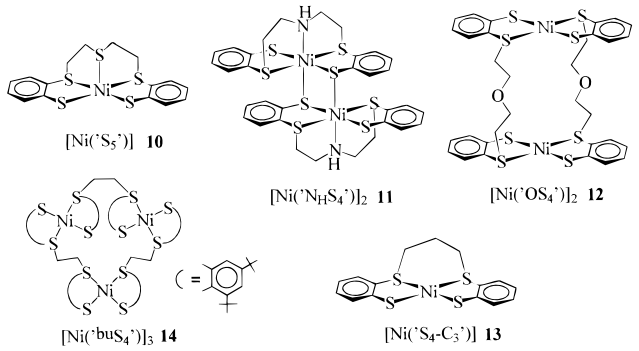


FIGURE 4. Molecular structures of nickel complexes.

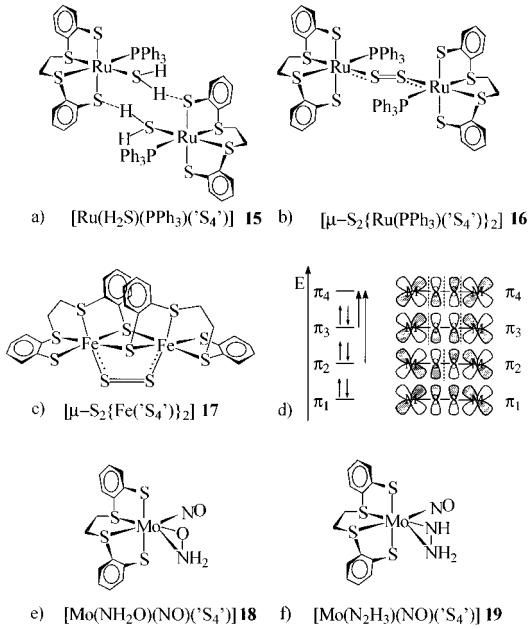


FIGURE 5. Molecular structures of H_2S and μ-S_2 complexes (a, b, and c), the 4c−6e π system of the [M$^{\cdots}$S=S$^{\cdots}$M] cores (d), and the η^2 side-on binding of NH_2O and N_2H_3 to [MS] cores (e and f).

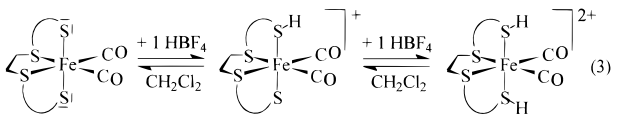
to $\sigma-\pi$ ligands results in a structural rearrangement, a spin-state change, and a concomitant shortening of the [Fe('N_HS_4')] core distances.

The electronic reason for these effects is the splitting and occupation of the frontier molecular orbitals in both types of complex, which is caused by the π-acceptor orbitals of the $\sigma-\pi$ ligands. For the high-spin complexes, four unpaired electrons result, two of which occupy the e*-orbitals that are antibonding with respect to the metal donor σ-bonds.

Coupling of Proton and Electron Flux

The reductase reaction of eq 2 stresses the coupling of proton and electron transfer. The study of protonations, isoelectronic alkylations, and redox reactions of [M(L)$_n$-('S_x')] complexes (M = Fe, Ru, Mo; L = CO, NO, 'S_x' = 'S_4'$^{2-}$, 'S_5'$^{2-}$, 'N_HS_4'$^{2-}$)[28] has shed light on the question of how primary protonation of metal sulfur sites influences the metal sulfur cores and small molecules bound to them, as well as the subsequent transfer of electrons. This is illustrated for the complexes [Fe(CO)$_2$('S_4')] (**9**) and [Fe(CO)('N_HS_4')] (**21**).[29]

In CH_2Cl_2 solution, the thiolate donors of both **9** and **21** can be protonated reversibly and in single steps by HBF_4, as shown in eq 3. The resultant thiol derivatives



(28) Cf.: Sellmann, D.; Hadawi, B.; Knoch, F. *Inorg. Chim. Acta* **1996**, *244*, 1996 and literature cited therein.

(29) (a) Sellmann, D.; Mahr, G.; Knoch, F.; Moll, M. *Inorg. Chim. Acta* **1994**, *224*, 45. (b) Sellmann, D.; Becker, Th.; Knoch, F. *Chem. Eur. J.* **1996**, *2*, 1092.

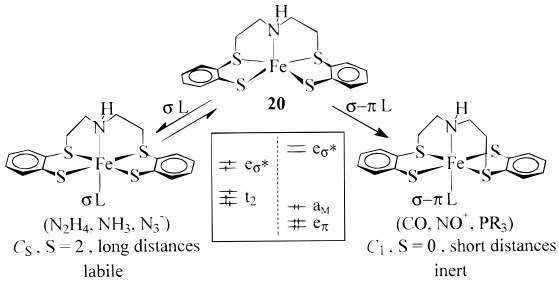
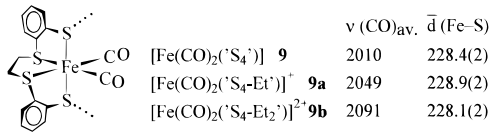
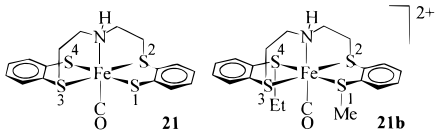


FIGURE 6. High-spin and low-spin [Fe(L)('N_HS_4')] complexes resulting from the different splitting and occupation of the frontier molecular orbitals (insert).

Table 1. ν(CO) Frequencies (cm^{-1}) versus FeS Distances (pm) in [$Fe(CO)_2$('S_4')] (9), [Fe(CO)('N_HS_4')] (21) and Their Alkylated Derivatives



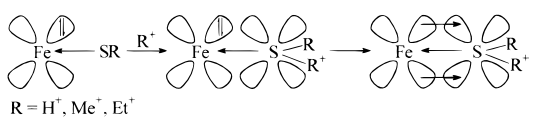
	ν (CO)av.	d̄ (Fe–S)
[$Fe(CO)_2$('S_4')] **9**	2010	228.4(2)
[$Fe(CO)_2$('S_4-Et')]+ **9a**	2049	228.9(2)
[$Fe(CO)_2$('S_4-Et_2')]2+ **9b**	2091	228.1(2)



	21	**21b**
ν (CO)	1954	2026
Fe(1)–C(1)	175.3(12)	177.2(12)
Fe(1)–N(1)	207.2(8)	203.4(9)
Fe(1)–S(1)	229.8(3)	227.1(4)
Fe(1)–S(2)	222.5(3)	224.5(4)
Fe(1)–S(3)	225.5(3)	224.4(4)
Fe(1)–S(4)	230.5(3)	229.1(4)

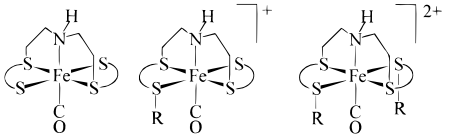
proved too labile to be isolated. However, the thiolate donors may also be alkylated by stepwise treatment with Me_3OBF_4 or Et_3OBF_4. The isoelectronic salts [$Fe(CO)_2$('S_4'-Et)]BF_4 (**9a**), [$Fe(CO)_2$('S_4'-Et_2)]$(BF_4)_2$ (**9b**), [Fe(CO)('N_HS_4'-Me)]BF_4 (**21a**), and [Fe(CO)('N_HS_4'-Me,Et)]$(BF_4)_2$ (**21b**) could be isolated and characterized by X-ray structure analysis.

In all cases, each step of protonation or alkylation increases the ν(CO) frequencies of the complexes by 35−40 cm^{-1}. The overall increase of the ν(CO) frequencies (∼80 cm^{-1}) is remarkably large. It reflects a considerable decrease of electron density at the Fe centers resulting in a weakening of the Fe−CO π-back-bonding, which led us to expect a correlation between ν(CO) frequencies and Fe−S distances. Table 1 shows that such a *correlation does not exist*. The Fe−S distances remain virtually invariant, and it should be noted that in the case of [$Fe(CO)_2$('S_4')] and its derivatives even the Fe−S(thiolate) and the Fe−S(thioether) distances are identical within standard deviations. To explain the invariance of Fe−S distances which strongly contrasts with the difference in electron density at the Fe centers as indicated by the large ν(CO) shifts, the following bonding scheme is suggested.



Protonation, and likewise alkylation, leads to a weakening of the respective S→Fe σ-bonds and an inductive withdrawal of electron density from the Fe centers. The newly formed thiol or thioether donors, however, have π-acceptor capability so that partial Fe−S π-back-bonding leads to a further decrease of electron density at Fe. However, the weakening of the Fe−S σ bonds and formation of the Fe→S π-back-bonds compensate each other so that the Fe−S distances remain invariant.

Table 2. Redox Potentials of [Fe(CO)('N_HS_4')] (21) and Its Protonated or Alkylated Derivatives (in V vs NHE, in CH_2Cl_2, v = 100 mV/s)



Redox couple			
Fe(II) / Fe(III)	+ 0.35 q	R = H : 0.98 q R = Et : 1.02 q	R = H : 1.46 i R = Et : n.o.
Fe(II) / Fe(I)	n.o.	R = Et : -1.34 i	R = Et : -0.54 q
Fe(I) / Fe(0)	n.o.	n.o.	-1.44 i

q = quasireversible; i = irreversible; n.o. = not observed; ⌒ ≙ 

While [$Fe(CO)_2$('S_4')] (**9**) and its derivatives proved electrochemically inert, the cyclic voltammograms of [Fe(CO)('N_HS_4')] (**21**) and its derivatives exhibit anodic and cathodic redox waves, the potentials and assignments of which are summarized in Table 2. The data of Table 2 reveal two important points. (1) Protonation and alkylation have identical consequences and anodically shift the redox potentials of corresponding redox couples by a remarkable 500−700 mV per protonation or alkylation step. (2) This makes the protonated (or alkylated) derivatives more difficult to oxidize, but easier to reduce than the parent complex so that the *irreducible* 18 valence electron (VE) complex [Fe(CO)('N_HS_4')] *becomes reducible upon alkylation*. For example, [Fe(CO)('N_HS_4'-Me,Et)]$^{2+}$ shows a quasi-reversible wave at the relatively mild reduction potential of −0.54 V, indicating the formation of the 19 VE monocation.

The data of Tables 1 and 2 allow the following conclusions: The invariance of Fe−S distances combined with the Broensted acid−base behavior and strong coupling of proton and electron flux is a genuine structure−function relationship of [MS] species. It may facilitate redox reactions for kinetic and thermodynamic reasons, and this may also be true for the active centers of [MS] enzymes, even if these centers have completely different structures.

Activation, Stabilization, and Reactivity of Small Molecules in [MS_n] Coordination Spheres

In the quest of competitive catalysts for nitrogenases and related enzymes, not only reactions of N_2 but also reactions of substrates such as CO, H_2, and NO with [MS] complexes are of considerable interest. All four molecules react with nitrogenases. The reactions of CO and H_2 provide further evidence for certain relationships between the [MS] enzymes nitrogenase, CO dehydrogenase, and hydrogenase. To be viable catalytically, metabolic reactions of these substrates in [MS] coordination spheres

have to form cyclic reaction sequences.[24,30] In view of its relevance to the N_2 fixation problem (cf. eq 1), such a sequence of H_2 reactions will be briefly described here.

Heterolytic H_2 Activation

Catalysis of the H^+/H_2 redox equilibrium and the D_2/H^+ exchange (with protons from H_2O) according to eq 4

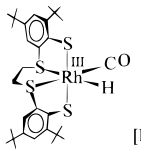
$$2\,H^+ + 2\,e^- \rightleftharpoons H_2 \qquad (4a)$$

$$D_2 + H^+ \rightleftharpoons HD + D^+ \qquad (4b)$$

characterize the reactivity of hydrogenases that contain [FeS] or [NiFeS] centers.[31] The structure of the [NiFeS] center in the hydrogenase isolated from *Desulfovibrio gigas* has been determined by X-ray structure analysis.[32] Reaction 4b requires the heterolytic cleavage of the strong H−H bond ($\Delta H = -436$ kJ/mol). If [MS] centers catalyze this heterolysis, plausible intermediates are metal hydride thiol species (eq 5). Low-molecular-weight complexes

$$\begin{matrix} M \\ | \\ S \end{matrix} + H_2 \longrightarrow \begin{matrix} M\cdots H \\ | \quad | \\ S\cdots H \end{matrix} \longrightarrow \begin{matrix} M-H^- \\ | \\ S-H^+ \end{matrix} \qquad (5)$$

with [FeS], [NiS], or [NiFeS] centers that catalyze reaction 4b and thus have particular significance as model compounds for hydrogenases have not yet been found. However, this catalysis can be achieved with [Rh(H)(CO)('^{bu}S$_4$')] (**22**).[33] [Rh(H)(CO)('^{bu}S$_4$')] (**22**) catalyzes the $D_2/$



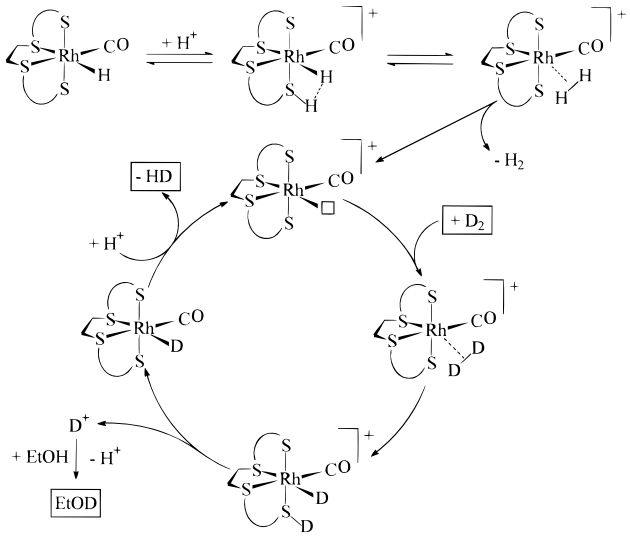
[Rh(H)(CO)('^{bu}S$_4$')] **22**

H^+ exchange according to eq 6, but only *if catalytic*

$$EtOH + D_2 \rightleftharpoons EtOD + HD \qquad (6)$$

amounts of Brönsted acids such as hydrochloric acid *are present*. This observation and supporting IR and ^{1}H NMR studies of the protonation of **22** and its PCy_3 derivative [Rh(H)(PCy_3)('^{bu}S$_4$')] (**23**) at temperatures between −50 and +20 °C[34] have corroborated the mechanism outlined in Scheme 4. Protonation of the Broensted-basic thiolate donors and subsequent release of H_2 yields the coordinatively unsaturated species [Rh(CO)('^{bu}S$_4$')]$^+$ which is the actual catalyst. Its vacant site is occupied by D_2, which is subsequently cleaved into D^+ and D^-. D^+ (from the thiol) exchanges with protons from EtOH to give EtOD plus H^+, which subsequently reacts with the D complex to regenerate the vacant site at the rhodium center. Thus, the key step, the heterolytic cleavage of D_2, is achieved by the concerted action of the Broensted-basic thiolate donor

Scheme 4. Heterolytic H_2 Cleavage Catalyzed by [Rh(H)(CO)('^{bu}S$_4$')] (22) in the Presence of Catalytic Amounts of Protons



and the Lewis-acidic Rh center of [Rh(CO)('^{bu}S$_4$')]$^+$ upon the D_2 molecule.

N_2 Fixation

CO, NO, and H_2 are highly reactive in comparison to the N_2 molecule. This further emphasizes why any reaction of N_2 occurring at ambient conditions (20 °C, 1 bar) is significant and potentially relevant to nitrogenase. A number of such reactions have been found over the past three decades. Most of these reactions have been reviewed[35] and comprise the formation of transition metal N_2 complexes, the conversion of the N_2 ligands into lower valent nitrogen derivatives by electrophilic,[36] nucleophilic[37] and radical attack,[38] the cleavage of N_2 into nitride ligands,[39] and even the reduction of N_2 in protic systems.[40] Yet, none of these reactions, each of which was considered a break-through at its time, has yielded an efficient catalyst for the reduction of N_2.

Likewise, the above-mentioned reactions of N_2 do not necessarily occur under nitrogenase-like mild conditions because the redox potentials have also to be taken into account. When alkaline metals are involved, the redox potentials are certainly not physiological. The participation of alkaline metals is frequently not evident because they are often involved in preceding steps, e.g., the synthesis of the N_2 complexes. Even $NaBH_4$ used as a reductant in aqueous media requires metallic sodium for its synthesis.

Thermodynamics clearly shows, however, that the reduction of N_2 under truly mild conditions including mild

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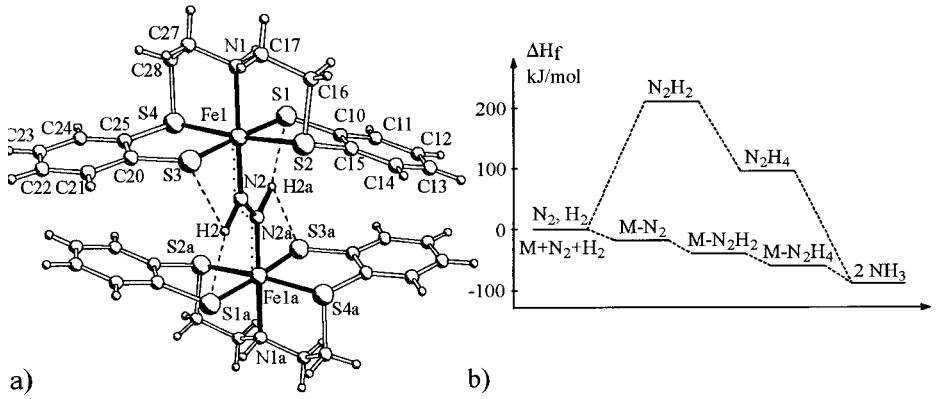


FIGURE 7. (a) Molecular structure of [μ-N_2H_2{Fe('N_HS_4')}$_2$] (24). Selected distances (pm): Fe1−N2, 186.7(4); N2−N2A, 130.0(7); S1A−H2, 220; H2−S3, 278; Fe1−S1, 231.8(2); Fe1−S2, 223.4(1); Fe−S3, 228.8(2); Fe1−S4, 225.1(1); Fe1−N1, 203.7(4). (b) Potential reaction coordinates for N_2 reduction in the absence and in the presence of metal sulfur complexes.

redox potentials should be possible. The reactions according to eq 7 are exergonic or require very moderate

$$N_2 + 3\,H_2 \longrightarrow 2\,NH_3 \quad \Delta G° = -16\ \text{kJ/mol} \qquad (7a)$$

$$N_2 + 6\,H^+ + 6\,e^- \xrightarrow{H_2O} 2\,NH_3 \quad E° = -280\ \text{mV (pH 7)} \qquad (7b)$$

$$2\,H^+ + 2\,e^- \xrightarrow{H_2O} H_2 \quad E° = -414\ \text{mV (pH 7)} \qquad (7c)$$

reduction potentials. In fact, eqs 7b,c demonstrate that it should be easier to electrochemically reduce dinitrogen than protons in neutral water. In this context it is worth noting that sulfur ligands are conspicuously absent in isolable metal N_2 complexes. In fact, only one metal N_2 complex with exclusively sulfur coligands has been described, whose synthesis, however, also needs metallic sodium.[41] Our search for such metal sulfur complexes has remained unsuccessful as yet. In this search, however, we have obtained diazene complexes which presumably are the first reduction products of N_2 complexes. Numerous results indicate that the $6H^+/6e^-$ reduction of N_2 to NH_3 in nitrogenases proceeds via successive $2H^+/2e^-$ steps.[42] Thus, the first step would lead to diazene, HN=NH, according to eq 8. This reaction can be consid-

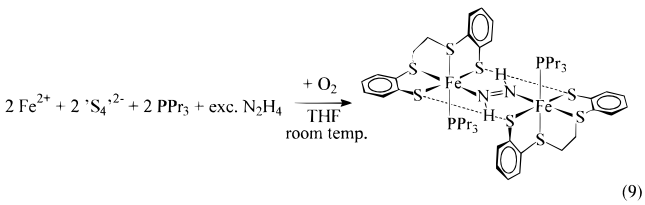
$$N_2 + 2H^+ + 2e^- \rightarrow HN{=}NH \quad E° = -1450\ \text{mV (pH 7)} \qquad (8)$$

ered the most difficult step because it requires 523 kJ/mol to break the "first bond" in the N_2 triple bond and diazene is extremely unstable in the free state ($\Delta H_f = +212$ kJ/mol).[6c,43]

Therefore, to avoid unsurmountably high barriers on the reaction coordinate from N_2 to NH_3, a suitable catalyst would not only have to activate inert N_2 but also have to stabilize the unstable N_2H_2. [FeS] diazene complexes have yielded a working hypothesis and a perspective as to how these problems might be solved.

[FeS] Diazene Complexes

The [Fe('N_HS_4')] fragment binds CO, N_2H_4, and NH_3. It also binds N_2H_2 resulting from oxidation of hydrazine to give the dinuclear complex [μ-N_2H_2{Fe('N_4S_4')}$_2$] (**24**) whose molecular structure is shown in Figure 7a.[44] [μ-N_2H_2{Fe('N_HS_4')}$_2$] (**24**) was the first N_2H_2 complex to prove that N_2H_2 can be stabilized by [MS_n] fragments that do not contain biologically objectionable metals or donor atoms, such as phosphine donors. The complex is diamagnetic and exhibits [Fe('N_HS_4')] core distances that are virtually identical with those of [Fe(CO)('N_HS_4')] (**21**). The N_2H_2 ligand has a *trans*-diazene structure, bridges two enantiomeric [Fe('N_HS_4')] fragments, and is stabilized by three major factors: (1) steric shielding, (2) strong 4c−6e π-bonds between Fe d-orbitals and the N_2H_2 π-system giving rise to the deep blue color of **24** (cf. Figure 5d), and (3) strong tricentric (bifurcated) NH···$(S)_2$ hydrogen bridges between the diazene protons and thiolate donors. While the first two stabilizing factors have also been observed in organometallic N_2H_2 complexes such as [μ-N_2H_2{$CpMn(CO)_2$}$_2$] or [μ-N_2H_2{$Cr(CO)_5$}$_2$],[45] the third factor is characteristic of [μ-N_2H_2{Fe('N_HS_4')}$_2$] (**24**) and related thiolate complexes. The N−H···S bridges alone can "neutralize" an estimated 70 kJ/mol of the positive ΔH_f of free diazene. In summary, even the first step on the reaction coordinate from N_2 to NH_3 could become exergonic (Figure 7b) so that the as yet hypothetical cycle of Scheme 5 needs not be out of reach. While insufficient solubility prevented a detailed investigation of the properties and, in particular, the redox behavior of **24**, this proved possible with the related complex [μ-N_2H_2{Fe(P^n-Pr_3)('S_4')}$_2$] (**25**), which is soluble and forms in high yields according to eq 9.[46] The X-ray crystal structure (schematically depicted in eq 9) and the spectroscopic properties showed that the N_2H_2 ligand of **25** is stabilized by the same



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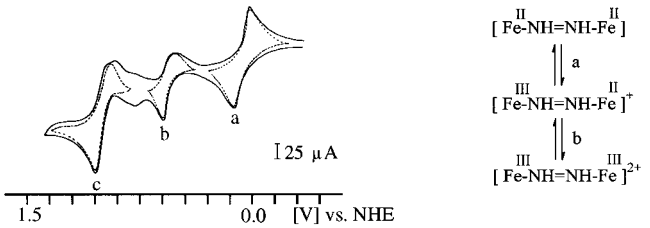
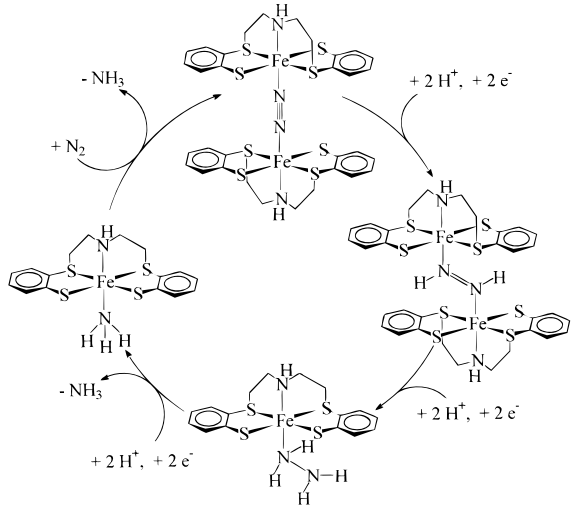


FIGURE 8. Cyclic voltammogram of [μ-N_2H_2{Fe(PPr_3)('S_4')}$_2$] (25) (in CH_2Cl_2, 20 °C, v = 100 mV/s) and assignment of redox waves and Fe oxidation states.

Scheme 5. Hypothetical Cycle for N_2 Fixation Catalyzed by [Fe('N_HS_4')] Fragments



three major effects as in [μ-N_2H_2{Fe('N_HS_4')}$_2$] (**24**). Further studies proved that the N_2H_2 protons exchange for D^+ from MeOD or D_2O via base catalysis, and that even the P^nPr_3 ligands can be substituted by P^nBu_3 under retention of the [Fe⋯NH═NH⋯Fe] chromophore.[47] Most importantly, [μ-N_2H_2{Fe(PPr_3)('S_4')}$_2$] (**25**) allowed cyclic voltammograms (CVs) to be recorded (Figure 8).[46a] The CV of [μ-N_2H_2{Fe(PPr_3)('S_4')}$_2$] (**25**) in CH_2Cl_2 at 20 °C exhibits three quasi-reversible redox waves a, b, and c in the anodic region. They can be assigned to the formation of the corresponding monocation (a), dication (b), and trication (c) with formal Fe oxidation states as indicated in Figure 8.

The intensity of the redox waves strongly depends on the temperature and the presence of protic solvents (MeOH) or bases (NaOMe). For example, at −70 °C in CH_2Cl_2, a fourth (irreversible) wave appears at 1330 mV; addition of MeOH causes this wave to disappear and wave b to increase.[47]

These results indicate that rapid and reversible protonation−deprotonation reactions of the N_2H_2 ligand are involved in the redox processes, leading to unequal intensity of the redox waves. The important point, however, is that [μ-N_2H_2{Fe(P^nPr_3)('S_4')}] (**25**) can be oxidized reversibly in two consecutive steps.

The reversible formation of the [μ-N_2H_2{Fe(P^nPr_3)('S_4')}$_2$]$^{2+}$ dication nourishes hope to achieve the reduction of N_2 under truly mild and catalytic conditions. A different rendering of the relevant core atoms of the dication (Fe, N_2H_2, S(thiolate) donors) shows that the dicationic diazene complex B and the diprotonated N_2 complex C are redox isomers (or valence tautomers) (Scheme 6). It must be stressed that species C and D are as yet hypothetical. However, it can be envisaged that B gives D via an intramolecular electron transfer from the diazene ligand to the Fe(III) centers of B, subsequent cleavage of NH with accompanying formation of S−H bonds, and final deprotonation of C.

The reversal of this sequence would convert D into A and allow the first $2H^+/2e^-$ reduction step of N_2 fixation. Important for this reversal is the 2-fold protonation of D to give C, in which all atoms necessary to form the neutral diazene complex A have already taken their positions. Reduction of C could then proceed either via the potential equilibrium between C and B or via direct uptake of electrons by C. In this respect, the anodic shift of redox potentials upon protonation (see above) is highly significant. It would make an otherwise irreducible 18-valence-electron complex (such as the N_2 complex D) reducible at relatively mild redox potentials.

To test this hypothesis the corresponding N_2 complexes are required. We have obtained evidence that such species form when [μ-N_2H_2{Fe(P^nPr_3)('S_4')}$_2$] (**25**) or the analogous Ru complex [μ-N_2H_2{Ru(PCy_3)('S_4')}$_2$] is oxidized by [Cp_2Fe]PF_6 or elemental iodine. The resultant products, however, have so far proved too unstable for unambiguous identification.[47]

The importance of Broensted-basic thiolate donors and their protonation for a reduction of dinitrogen complexes such as D is highlighted by the results of Collman and co-workers,[48] who have established a "retro N_2 fixation" pathway with the dinuclear porphyrinato complex [Ru_2(DPB)$(Im)_2$] (DPB = diporphyrinatobiphenylene tetraanion, Im = 1-*tert*-butyl-5-phenylimidazole). It allows the oxidation of two NH_3 ligands to give a μ-N_2 complex via three consecutive $2e^-$ oxidations, each of which is followed by base-induced withdrawal of $2H^+$. The reversal of these oxidations which would amount to N_2 fixation has proved impossible so far. One reason may be that the [Ru(porphyrinato)] fragments have no Broensted-basic centers whose initial protonation is necessary for the subsequent uptake of electrons. Against this background, thiolate complexes have considerable potential since they possess such centers.

Reflections on the Interaction of N_2 with the Nitrogenase Cofactors and with Molecular Dihydrogen under Standard Conditions

The way in which molecular N_2 interacts with the cofactors of FeMo, FeV, or FeFe nitrogenases on the molecular level remains an unsolved question.[49] Several models have been proposed for this interaction, most of which assume "closed" structures for the FeMoco in the resting and in

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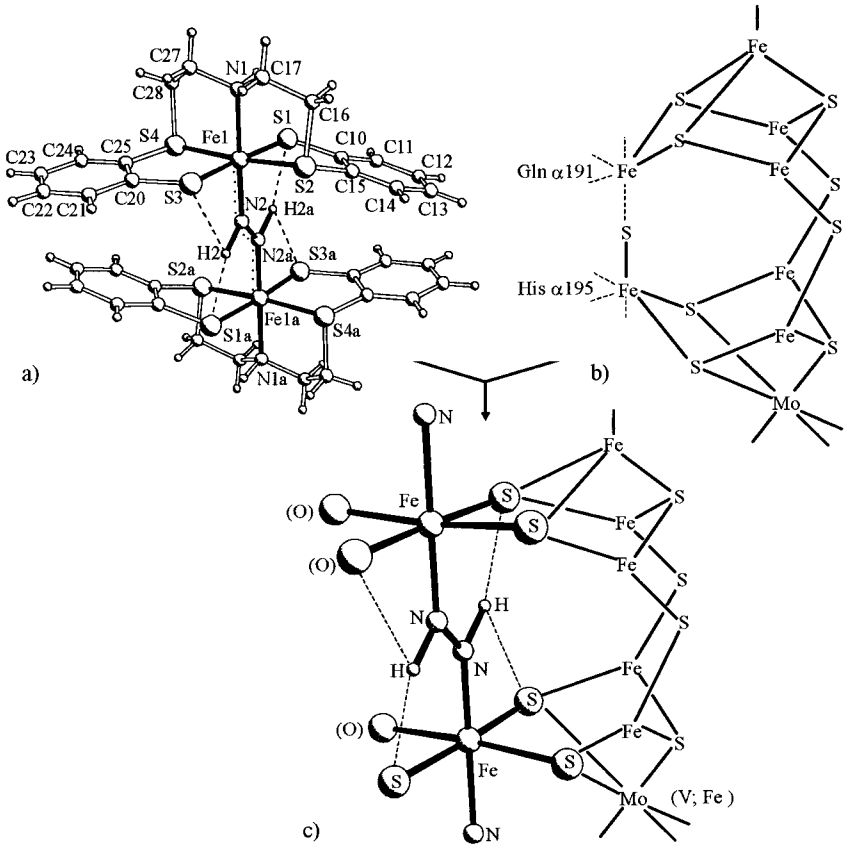
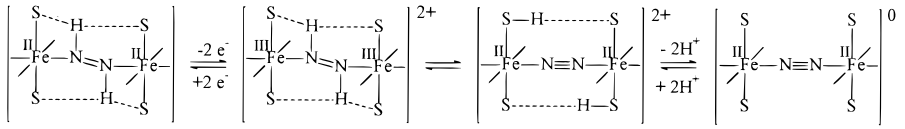


FIGURE 9. Model for the turnover states of the FeMo, FeV, or FeFe cofactors of nitrogenases stressing two unique six-coordinate Fe centers with suitable coordination spheres as binding sites for N_2 and its reduction products.

Scheme 6. Redox Isomerism of the $[\mu\text{-}N_2H_2\{Fe(PPr_3)('S_4')\}_2]^{2+}$ Ion



the turnover state of the enzyme.[50] Our alternative "open structure" model[49c] rests on the following observations: (a) the occurrence of "Fe-only" nitrogenases,[51] (b) the structures of the [FeS] diazene complexes exhibiting six-coordinate Fe centers, (c) the labile FeMoco with its three coordinate Fe centers, (d) the ready dissociation of thiolate complexes such as $[Fe('S_4')]_4$ (**7**), and (e) site-directed mutagenesis studies showing that the amino acids glutamine α191 and histidine α195 of nitrogenase are essential for enzyme activity.[52] These amino acids are located in close proximity to the FeMoco and, while not binding to it in the resting state, have N and O atoms that can potentially coordinate metals. Our model proposes that the FeMoco "opens" one of its Fe−S−Fe bridges when the enzyme changes from the resting to the turnover state. The two respective Fe centers coordinate N and O donors from the Gln α191 and His α195 residues and nearby H_2O molecules. The pentacoordination of the resulting unique two Fe centers is expected to favor the binding of N_2 and its reduction products, such as diazene. Figure 9 illustrates this model.

Imaginary removal of all carbon atoms from the $[\mu\text{-}N_2H_2\{Fe("N_HS_4")\}_2]$ complex (Figure 9a), replacement of three sulfur donors by O or N donors, and combination of the resulting core atoms with the "open" $[MoFe_7S_9]$ cluster (Figure 9b) results in the arrangement of Figure 9c. The two unique Fe centers and their donors are in the correct position to favor the binding of N_2 or N_2H_2 and the formation of the important hydrogen bridges. The remaining metal centers of the cofactor could serve as spacers for the unique Fe centers and as electron relays for electron transfer to facilitate $2e^-$ reduction steps. The Mo center may play a role in fine-tuning the redox potentials, and its substitution by vanadium or iron plausibly explains the occurrence of Fe/V and "Fe-only" nitrogenases.

Just as challenging as the catalytic reduction of N_2 by coupled H^+/e^- transfer would be the reduction by H_2

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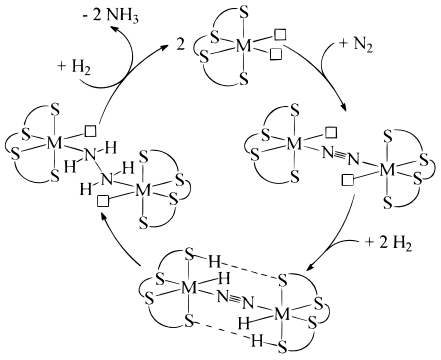
under mild conditions.[53] Equation 7a shows that thermodynamically this reaction is favored at lower rather than higher temperatures, but how does one activate N_2 and H_2 at the same time? The heterolytic activation of H_2 by [Rh(L)("$^{bu}S_4$")]$^+$ fragments (L = CO, PCy_3) and the exchange properties of the diazene complex [μ-N_2H_2{Fe(P^n-Pr_3)('S_4')}$_2$] make it appear worthwhile to search for [M('S_4')] derivatives that have two vacant sites, do not oligomerize, activate H_2 and N_2, and allow the formation of nitrogen hydrides by consecutive H^+/H^- or H^-/H^+ transfer steps, as suggested in Scheme 7. A primary H^- transfer followed by H^+ addition would be analogous to the reduction of the N_2 ligand in [$CpMn(CO)_2N_2$] by consecutive nucleophilic and electrophilic attack with $LiCH_3$ and protons.[37]

While Scheme 7 is so far still speculative, chemistry has seen more than one supposedly impossible reaction or compound become reality in the past.

Conclusion

Electronic flexibility that is frequently coupled with invariance of MS distances, vacant sites of coordination, activation or stabilization of small molecules, Broensted-basic thiolate donors, and the coupling of proton and electron flux has been stressed as pivotal for a potential reduction of N_2 by [MS] complexes under mild conditions. It may still be a long way before competitive catalysts for nitrogenase will be found, but the results described in this Account should give an idea why nature chooses a combination of metals and sulfur ligands to catalyze one of the most difficult chemical reactions under the mildest possible conditions.

Scheme 7. Hypothetical NH_3 Formation from N_2 and H_2 in the Coordination Sphere of [MS] Complexes



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