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Review

Catalysis of the electrochemical H_2 evolution by di-iron sub-site models

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Contents

Abstract

A short non-exhaustive overview of hexacarbonyl dithiolate di-iron species and of their substituted derivatives relevant to the chemistry of the di-iron sub-site of the hydrogenase enzymes is presented. Although few detailed electrochemical studies have been reported until now, we discuss the use of di-iron organometallic species as catalysts for the electrochemical reduction of protons. Finally, we propose targets for the synthesis of more efficient biomimetic catalysts.

Keywords: Hydrogenase; Electrocatalysis; Proton reduction; Di-iron sub-site models; Biomimetic catalysts; Bioorganometallic chemistry

1. Introduction

The need for new energy sources as an alternative to fossil fuel and the necessity to cut down the release of greenhouse gases make molecular hydrogen the ideal energy resource for the future. The efficient production of molecular hydrogen, as well as its oxidation to protons and electrons (Scheme 1), offer a major challenge for the scientific community.

In biological processes, both hydrogen uptake and production are catalyzed by metalloenzymes called hydrogenases (H_2ases) [1], which differ by their metal content, either nickel and iron ([NiFe] H_2ases) or only iron (Fe-only H_2ases). The determination of the crystal structures of both classes of en-

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$$2\,H^{+} + 2\,e \rightleftharpoons H_2$$

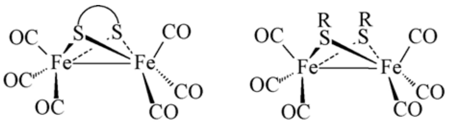
Scheme 1. Electrochemical hydrogen uptake and production.

zymes [2–5] constituted a decisive breakthrough revealing that their active sites are organometallic in nature, and of a type for which there is no precedent in biology. This provided tracks for chemical models of the active sites of the enzymes and led to a renewed interest in the chemistry of homo- and hetero-binuclear organometallic iron compounds. Structural models related to the [NiFe] H_2ases are reviewed in the contribution of Bouwman and Reejdik (this issue), while several review articles concerning the chemistry of synthetic models of the Fe-only H_2ases have already appeared [6–10].

In order to set up a chemical strategy to design biomimetic models (or bio-inspired catalysts, see the contribution by Artero and Fontecave in this issue), it is necessary to identify the actual proton binding site(s) within the active site, as well as the keys of the enzyme's efficiency. The structurally characterized active sites, the so-called H-cluster, of Fe-only H_2ases from two different organisms [3–5] are strikingly similar (Scheme 2).

The H-cluster consists in a di-iron assembly, the di-iron sub-site $[2Fe]_H$, which is connected to a Fe_4S_4 cluster via a cysteinyl bridge. The coordination sphere of the iron centers of the $[2Fe]_H$ sub-site is completed by terminal diatomic ligands CO and CN, and by a dithiolate bridge. The carbonyl found in a bridging position in the crystal of the CpI H_2ase adopts a terminal coordination mode at the iron center most distant from the Fe_4S_4 cluster (that is distal Fe or Fe_d as opposed to proximal Fe or Fe_p for the iron center closest to the Fe_4S_4) in the DdH H_2ase (Scheme 2). The differences between the two crystal structures (nature of the linking chain R in the S–R–S dithiolate bridge, presence or absence of an aqua ligand at Fe_d, terminal versus bridging coordination of one carbonyl) were assigned either to the different redox state of the as-crystallized enzymes or to the different resolution of the crystal structures [5,12,13]. The crystal structure of the CO-inhibited form of the CpI H_2ase was also obtained [11,14], showing that the exogenous carbonyl occupies the site where the H_2O is bound in the oxidized CpI (Scheme 2(b) and (c)).

In this article, we will present a short non-exhaustive overview of di-iron hexacarbonyl dithiolate species and of their substituted derivatives which have been considered as relevant to the di-iron sub-site chemistry. The reader is also directed towards the reviews by Evans and Pickett [9], Rauchfuss [10] and Darensbourg et al. [6–8,15]. Electrochemical studies are expected to provide information on several aspects of the reactivity of model complexes. First, electrochemistry gives access to the potentials of the electron transfer processes; in case the coordination sphere of metal centres is altered by ligand substitution, this allows one to estimate the relative electronic effects of the substituting ligands. Electron-transfer steps can trigger different types of reactions, such as metal–ligand bond cleavage generating a substrate-binding site, rearrangements of the coordination sphere of the metal centres resulting in a different reactivity of the compounds. Among other electrochemical techniques, cyclic voltammetry is a powerful tool to investigate the mechanisms of processes involving coupled electron-transfer and chemical (for example, protonation) steps. Also, measurements of the reduction peak current of a model complex in the presence of increasing concentrations of acid allows the detection of a catalytic proton reduction process. Although few detailed electrochemical studies have been reported until now, several di-iron organometallic species have been tested as catalysts for the electrochemical reduction of protons. These studies including protonation and reduction behavior will be presented in the third section. In the last section, we propose targets for the synthesis of more efficient biomimetic catalysts.



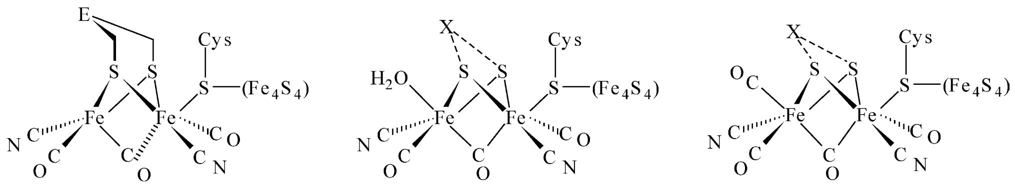
(A) (B)

Scheme 3. Di-iron(I) hexacarbonyl precursors.

2. Di-iron sub-site models

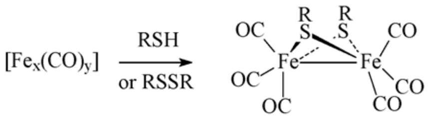
2.1. Hexacarbonyl dithiolate species

Main biomimetic models of the bimetallic sub-site in Fe-only H_2ases derive from di-iron(I) hexacarbonyl precursors including either one dithiolate bridge or two thiolate bridges [16].

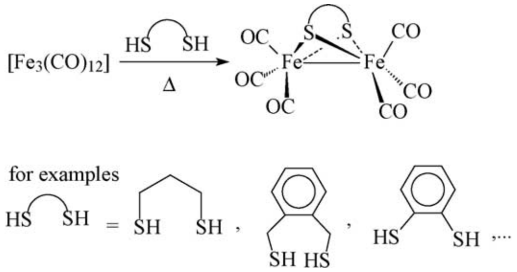


(a) (b) (c)

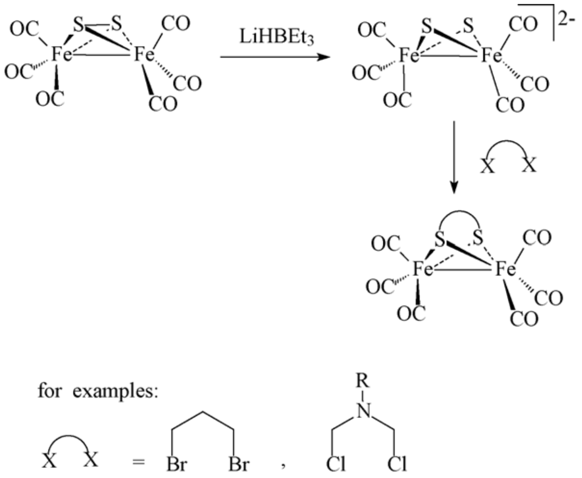
Scheme 2. Schematic representations of the H-cluster of the Fe-only hydrogenase from (a) D. desulfuricans (DdH) [4,5], (b) C. pasteurianum (CpI) [3] and (c) the CO-inhibited form of CpI [11]. In (a) $E = CH_2$ or NH [4,5], while in (b) and (c) X was originally taken to be either H_2O or an arrangement of unidentified light atoms [3,11].



Scheme 4. Syntheses of di-iron(I) dithiolate compounds.



Scheme 5. Preparation of [(μ-S_2R)$Fe_2(CO)_6$] by using dithiol HS–R–SH and [$Fe_3(CO)_{12}$].



Scheme 6. Preparation of complexes [(μ-SR)$_2Fe_2(CO)_6$] and [(μ-S_2R)$Fe_2(CO)_6$] by alkylation with organic halides.

The coordination geometry around each Fe atom can be described as a distorted pyramid supplemented by a metal–metal bond. Normal electron counting rules require the presence of a Fe^I–Fe^I single bond. The individual values of the Fe–Fe distance fall in the narrow range of 2.5 Å. Various isomers are known for thiolate-bridged systems in form B (Scheme 3). They differ in the mutual orientation (syn or anti) of the organic groups on the bridging S atoms. Evidently, such isomers do not exist when the two thiolate bridges are replaced by one dithiolate bridge (Scheme 3, form A). In addition to this isomerism, a fluxional process consisting in apical/basal CO exchange arises in solution and the dithiolate bridge (form A) may exhibit a stereochemical nonrigidity [17] (Scheme 3A and B).

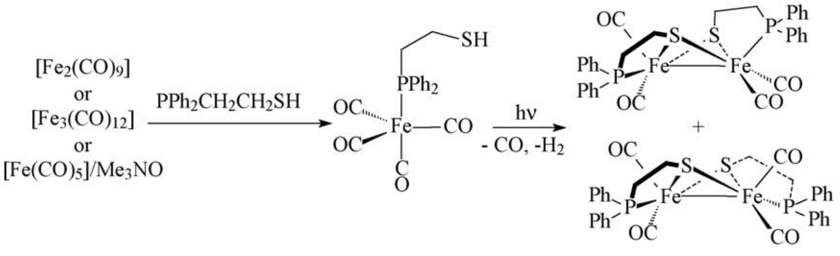
Syntheses of these di-iron(I) dithiolate compounds involve reactions of usual iron(0) carbonyl precursors of general formula [$Fe_x(CO)_y$] = ([$Fe(CO)_5$], [$Fe_2(CO)_9$] or [$Fe_3(CO)_{12}$]) with dialkyldisulfide or monothiol to give thiolate-bridged compounds [(μ-SR)$_2Fe_2(CO)_6$] (Scheme 4) [18].

Similar procedures with dithiol HS–R–SH and [$Fe_3(CO)_{12}$] afford the dithiolate complexes [(μ-S_2R)$Fe_2(CO)_6$] [18]. By reacting [$Fe_3(CO)_{12}$] with the tripodal dithiol thioether $MeC(CH_2SH)_2CH_2SR$ (R = Me or Ph), Pickett and coworkers have synthesized the pentacarbonyl derivative [{$RSCH_2C(Me)(CH_2S)_2$}$Fe_2(CO)_5$] which is one of the rare analogues of the di-iron sub-site featuring a {2Fe3S} core with differentiated iron centers [19] (Scheme 5).

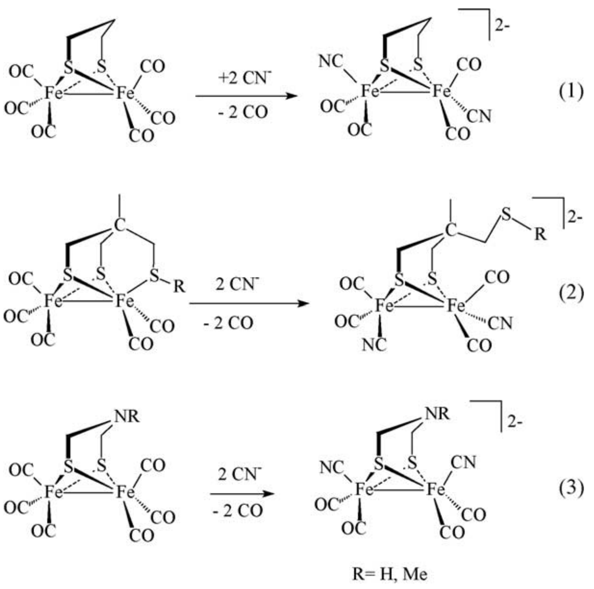
Complexes [(μ-SR)$_2Fe_2(CO)_6$] and [(μ-S_2R)$Fe_2(CO)_6$] have also been prepared by alkylation, with organic halides, of the sulfur atoms in the dianionic species [(μ-S)$_2Fe_2(CO)_6$]$^{2-}$ obtained by reducing [(μ-S_2)$Fe_2(CO)_6$] [20,21]. Rauchfuss and coworkers have used this sulfur-alkylating method with dichloroamine $RN(CH_2Cl)_2$ to synthesize functionalized azadithiolate bridged systems [22]. A straightforward procedure using [(μ-SH)$_2Fe_2(CO)_6$], RNH_2 and CH_2O has been also reported [23] (Scheme 6).

2.2. Substitution reactions and cyanide derivatives

The substitution of various good σ-donor ligands, such as phosphine (PR_3) or isocyanide (RNC) for one CO on each Fe atom yields mono- and disubstituted derivatives: [(μ-SR)$_2Fe_2(CO)_5$(L)] and [(μ-SR)$_2Fe_2(CO)_5(L)_2$]. The incoming ligand in monosubstituted species lies in the apical position (*trans* position relative to the Fe–Fe bond). The disubstituted complexes may exist as four isomers, depending on the relative position (basal or apical) of the two substituting ligands [24–26]. Reaction of phosphine-tethered thiol $Ph_2PCH_2CH_2SH$ with {$Fe(CO)_4$} sources ([$Fe(CO)_5$], [$Fe_2(CO)_9$] or [$Fe_3(CO)_{12}$]) afforded the complex [($PPh_2CH_2CH_2SH$)$Fe(CO)_4$]. Photolytic transformation of the latter gave the tetracarbonyl bimetallic compound



Scheme 7. Reaction of phosphine-tethered thiol $Ph_2PCH_2CH_2SH$ with {$Fe(CO)_4$} sources.

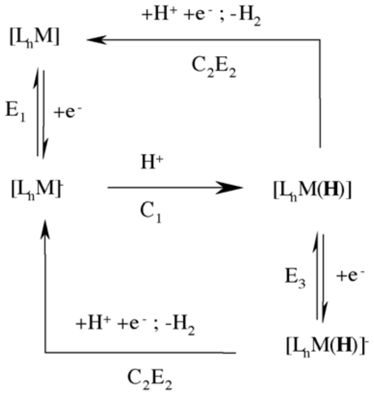


Scheme 8. Substitution of CN^- for CO in di-iron complexes (1) with propanedithiolate bridge [28–30], (2) with functionalized propanedithiolate bridge [31], (3) with azadithiolate bridge [23,32].

$[(\mu\text{-}PPh_2CH_2CH_2S)_2Fe_2(CO)_4]$ as a mixture of two isomers (Scheme 7) [27].

Recent extensions of this reactivity to cyanide (CN^-) allowed the synthesis of the closest dicyanide analogues of the di-iron sub-site (Scheme 8).

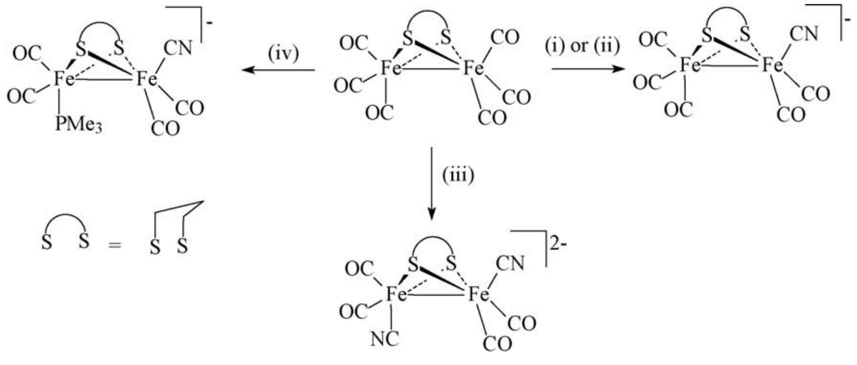
The associative substitution of two CN^- for carbonyls in the compound $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$ yields the dianion $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CN)_2]^{2-}$ (Scheme 9, path (iii)). It has been proposed that the reaction proceeds through the formation of carbonyl-bridged intermediates [18]. The monosubstituted cyanide derivative $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_5(CN)]^-$ can be obtained only by indirect synthesis; that is either via initial replacement of one carbonyl by MeCN in the presence of Me_3NO and then substitution of this labile molecule by CN^- (Scheme 9, path (i)) [18] or via the transformation of one CO into CN^- by treatment of $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$ by $(SiMe_3)_2N^-$ (Scheme 9, path (ii)) [29]. Cyanation reaction of $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$ in the presence of trimethylphosphine affords the complex $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CN)(PMe_3)]^-$ (Scheme 9, path (iv)) [18]. More recently, Pickett and coworkers have reported spectroscopic evidences of the formation of carbonyl-bridged intermediates during the cyanation of the {2Fe3S} system $[\{MeSCH_2C(Me)(CH_2S)_2\}Fe_2(CO)_5]$ [33].



Scheme 10. Heterolytic hydrogen production by transition metal complexes.

3. Catalysis of electrochemical proton reduction by di-iron complexes

Long before any report on the structure of the active center of H_2ases, transition-metal hydride complexes attracted interest because of their possible role in a low-energy route to H_2 evolution [34–40]. Catalytic cycles based on this concept are summarized in Scheme 10. Regardless of the metal involved, the hydrogen production is usually suggested to proceed through an attack of the metal hydride by protons (Scheme 10, steps C_2E_2). Besides, this latter step most probably involves a simultaneous proton and electron transfer [41], analogous with the Heyrovsky step for H_2 evolution in heterogeneous electrocatalysis [42]. An homolytic hydride coupling (analogous with the Tafel step) is also sometimes assumed, but its occurrence is not favored in the case of a mono-



Scheme 9. Cyanation reactions of $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$: (i) Me_3NO, MeCN, CN^-; (ii) $(SiMe_3)_2N^-$); (iii) 2 equiv. CN^-; (iv) CN^-/PMe_3.

hydride homogeneous catalyst [38]. Similarly, no significant amount of molecular H_2 is expected to be produced upon the release of the radical species $H^{\bullet}$ from the hydride complexes.

According to the literature on transition metal catalyzed H_2 production, hydride complexes can be generated via either a chemical route (Scheme 10, step C_1) or an electrochemical route (Scheme 10, steps E_1 and C_1). Although not always explicitly mentioned in the corresponding works, these two routes were also successful in producing either stable or transient hydride species from di-iron units mimicking the active center of the Fe-only H_2ases. Analogy with the mechanism involved in H_2 formation by transition metal H_2ases is attractive and has been recently discussed on the basis of density functional theory (DFT) studies [9,10,41,43–45].

3.1. *Effects of ligands in terminal position*

Soon after the report on the structure of the Fe-only H_2ases [3], several research groups independently reported the synthesis of the propanedithiolate complex $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CN)_2]^{2-}$ as a CO-inhibited model for the $[2Fe]_H$ sub-site [28–30]. Pickett and coworkers further noted that this dianion is soluble and stable in water, although it does not catalyze the electrochemical proton reduction in aqueous electrolyte (4.0 < pH < 8.4) [28]. More interestingly, Rauchfuss and coworkers reported that the dicyanide species reacts readily with protons in organic solvent to afford some molecular H_2 and insoluble material [30], while Darensbourg and coworkers observed a transiently stable bridging hydride species $[(\mu\text{-}H)(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CN)_2]^-$ under similar experimental conditions [46].

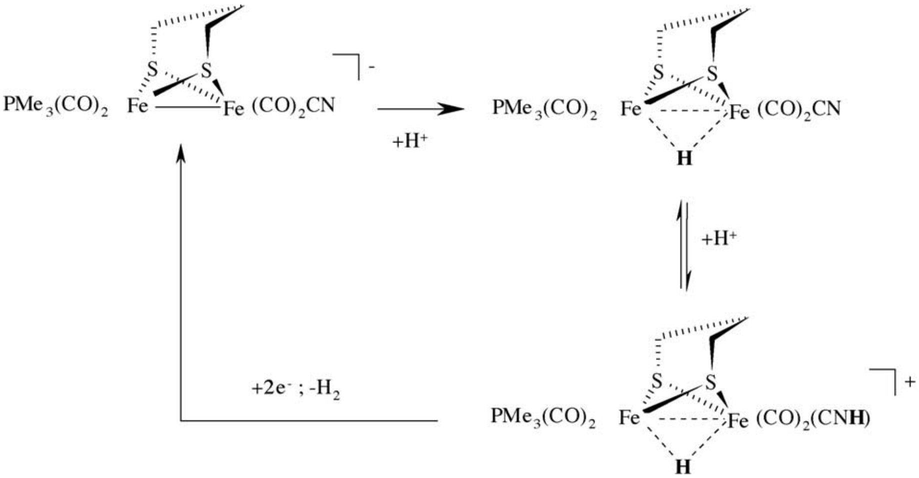
Thus by analogy with the mechanism elucidated by Koelle for $[CpCo(PR_3)_2]$ based catalysts (Scheme 10, steps C_1, E_3 and C_2E_2) [34], protonation of $[(\mu\text{-}SR_2)Fe_2(CO)_4L_2]$ complexes could possibly afford hydride intermediates, the reduction of which could initiate catalysis of the electrochemical proton reduction.

Table 1
Primary reduction potential of di-iron complexes and their protonated forms (0 V vs. NHE ∼ −0.2 V vs. $Fc^{+/0}$)

Compound	E_p^{red} (V) vs. $Fc^{+/0}$	Reference
$[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$	−1.66	[50]
$[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(PMe_3)(CN)]^-$	−2.64	[47]
$[(\mu\text{-}H)(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(PMe_3)(CN)]$	−1.63	[47]
$[(\mu\text{-}H)(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(PMe_3)(CNH)]^+$	−1.48	[47]
$[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(PMe_3)_2]$	−2.36	[48,50]
$[(\mu\text{-}H)(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(PMe_3)_2]^+$	−1.45	[48]
$[(\mu\text{-}S_2C_4H_6)Fe_2(CO)_6]$	−1.44	[52]
$[(\mu\text{-}S_2C_2H_4NR)Fe_2(CO)_6]$	−1.56	[54,55]
$[\{\mu\text{-}S_2C_2H_4N(H)R\}Fe_2(CO)_6]^+$	−1.16	[54,55]

This possibility was demonstrated in a subsequent study by Rauchfuss and coworkers [47]. They reported that the anion $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CN)(PMe_3)]^-$, a less reducing species than the dicyanide complex, is an efficient and rugged catalyst for electrochemical H_2 evolution. Bulk electrolysis at ca. −1.7 V versus $Fc^{+/0}$ of a $MeCN + Bu_4NBF_4$ solution containing a catalytic amount of the cyanide/phosphine complex and excess sulfuric acid as a proton source produced molecular hydrogen with a Faradaic yield close to 100%. This result provided the first link between organometallic models and the catalytic activity of Fe-only H_2ases. As established from spectroscopic data, catalysis by the cyanide/phosphine derivative involves protonation firstly at the metal–metal bond forming a stable and well-characterized bridging hydride and secondly at the cyanide ligand. Notably, the bridging hydride complex is reduced at a potential about 1 V less negative than the anion (Table 1), in agreement with the shifts in ν_{CO}. Cyclic voltammetry experiments further suggested that the reduction of $[(\mu\text{-}H)(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CNH)(PMe_3)]^+$ regenerates the anion without the intermediary of the bridging hydride species (Scheme 11).

Catalytic activities of structurally related species were examined in a following study by Rauchfuss and coworkers



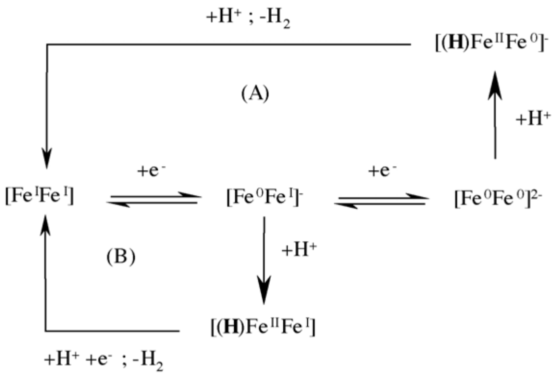
Scheme 11. Proposed mechanism for H_2 production by $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(CN)(PMe_3)][BF_4]$ (from [47]).

[48]. As anticipated from the work of Poilblanc [26,49], the bisphosphine [(μ-$S_2C_3H_6$)$Fe_2(CO)_4(PMe_3)_2$] protonates at the Fe–Fe bond to form a stable bridging hydride [46]. This complex also catalyzes the electrochemical proton reduction in organic solvent but seems less active than the cyanide/phosphine complex [48]. This difference was attributed to a slower kinetics of protonation at the Fe–Fe bond in the case of the bis-phosphine derivative. Catalysis by di-iron units appears thus quite sensitive to the electronic effects caused by the replacement of one PMe_3 by CNH. This result points to a possible role for the cyanide ligand, a common ligand in the two major families of H_2ases. The assumption of an intra-molecular coupling of the hydridic (Fe_2H) and protic (Fe–CNH) centers is attractive, but the easily protonated cyanide ligand (i.e., the kinetic site of protonation) may as well serve as a proton relay for a rapid protonation of the di-iron center (i.e., the thermodynamic site of protonation). Since protonation at the cyanide/phosphine compound occurs at the Fe–Fe bond first, an other explanation for the superior catalytic activity of this complex as compared to the bisphosphine derivative is that protonation at CN^- transforms this ligand to CNH, that is a better π-acceptor ligand than PMe_3, leading to weaker Fe(μ-H)Fe bonds and possibly to an increase of the kinetics of the proton/hydride coupling reaction.

3.2. Electrochemical reactivity of the Fe–Fe bond

As described in Scheme 10 (steps E_1 and C_1), transition metal hydride complexes active for proton reduction catalysis can be generated through an electrochemical route. For example, Savéant and coworkers demonstrated that hydrogen evolution by iron porphyrins begins with reduction of the catalyst down to the Fe^0 redox state followed by its protonation to a transient Fe^{II}–H species. H_2 production proceeds subsequently through proton/hydride coupling [39].

Similarly, Darensbourg and coworkers provided evidence for catalytic H_2 production upon electrochemical reduction of di-iron dithiolate complexes [(μ-S_2R)$Fe_2(CO)_4L_2$] (L = CO or PMe_3) in organic solution containing weak acid (i.e., acetic acid) as a proton source [50]. Experiments were carried-out in CO-saturated solutions to slow down the well-known decomposition of the [(μ-SR)$_2Fe_2(CO)_6$] and [(μ-S_2R)$Fe_2(CO)_6$] complexes upon reduction [51]. The hexacarbonyl complexes are assumed to exhibit two successive one-electron reduction events between −1.6 and −2.2 V versus $Fc^{+/0}$. Catalysis takes place after the second reduction step and thus presumably involves the reaction of an Fe^0Fe^0 intermediate with protons (Scheme 12). For the bisphosphine derivatives, the Fe^0Fe^0 redox state is not accessible within the solvent window. However, catalysis takes place after the first one-electron reduction step at ca. −2.3 V versus $Fc^{+/0}$, involving thus an Fe^0Fe^I intermediate species (Scheme 12). No reaction of the neutral bisphosphine complexes with protons from acetic acid was observed, contrary with the study by Rauchfuss in which stronger acids were used (see above). Nevertheless, a plot of the reduction peak current against the acetic acid concentration indicates that the bis-phosphine complexes have a greater catalytic activity than the hexacarbonyl complexes. This result is consistent with both an enhanced stability of the Fe^0Fe^I intermediate and a faster reaction of the latter with protons when two CO ligands are replaced with better electron-donating ligands such as PMe_3. Finally, it is worth mentioning that catalysis of H_2 production upon electrochemical reduction of [(μ-S_2R)$Fe_2(CO)_4L_2$] complexes in weak acid solution takes place at potentials negative to −2 V versus $Fc^{+/0}$, which preclude these systems from any applications even in light driven cycles [35].



Scheme 12. Proposed mechanism for H_2 production by (A) [(μ-S_2R)$Fe_2(CO)_6$] and (B) [(μ-S_2R)$Fe_2(CO)_4(PMe_3)_2$] in weak acid solution (From [50]).

Independently of the work reported by Darensbourg and coworkers, we also investigated the electrochemical behavior of hexacarbonyl di-iron complexes [(μ-S_2R)$Fe_2(CO)_6$] (R = C_3H_6, C_6H_4 or $CH_2C_6H_4CH_2$) but in our case in the presence of strong acid (i.e., HBF_4 in Et_2O) [52]. Our purpose was to determine whether the primary reduction of these complexes could increase the basicity of the di-iron site and thereby facilitate protonation at this position. As electrochemical reduction of thiolate-bridged hexacarbonyl di-iron complexes further induces replacement of CO ligands by solvent molecules [51], the experiments were carried out in CH_2Cl_2, a poorly coordinating solvent as compared with MeCN, for example. The primary reduction of [(μ-$S_2C_6H_4$)$Fe_2(CO)_6$] takes place at −1.44 V versus $Fc^{+/0}$ (Table 1), a potential about 0.22 V less negative than for the propanedithiolate derivative [(μ-$S_2C_3H_6$)$Fe_2(CO)_6$]. This makes the toluenedithiolate di-iron complex a potentially more attractive catalyst than the propanedithiolate compound. In acid-free solution, the reduction of the toluenedithiolate complex appears chemically reversible ($I_P^a/I_P^c \sim 1$ at $v < 20\,\mathrm{V\,s^{-1}}$) [52], contrary to that of the propanedithiolate analogue ($I_P^a/I_P^c \sim 0.45$ at $v = 0.5\,\mathrm{V\,s^{-1}}$) [51] (As discussed below, reversible reduction is mandatory for a clean catalytic proton reduction to occur). Fast scan voltammetry and the rotating disk electrode technique further suggest that the primary reduction of [(μ-$S_2C_4H_6$)$Fe_2(CO)_6$] is a two-electron process with the second electron transfer slightly more favorable than the first one [52] (Fig. 1).

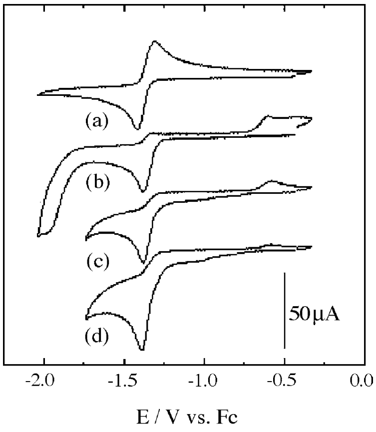
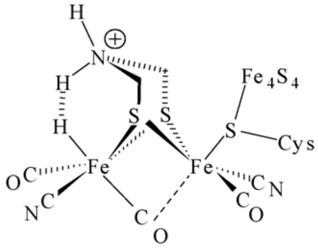


Fig. 1. Voltammograms (first scan, $v = 0.2\,V\,s^{-1}$) at a glassy carbon electrode of a solution of $Fe_2(\mu\text{-}SC_6H_4S)(CO)_6$ in Bu_4NPF_6–CH_2Cl_2, before (a) and after addition of 0.7 (b), 2.1 (c) and 4.4 equiv. HBF_4 (d), respectively.

A possible explanation is that in the case of the toluenedithiolate one of the two Fe–S bond is broken upon reduction (Scheme 13) [53].

Besides, using the toluenedithiolate as an internal standard, we were able to conclude that the primary reduction of the $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$ is a one-electron process (unpublished results), which was to date not clearly established.

Upon addition of strong acid (i.e., HBF_4 in Et_2O), the primary reduction of the $[(\mu\text{-}S_2R)Fe_2(CO)_6]$ ($R = C_3H_6$, C_6H_4 and $C_2H_4C_6H_4$) becomes chemically irreversible indicating that the reduced form of these complexes reacts with protons on the voltammetric time scale. In addition, the reduction wave increases with increasing acid concentration, suggesting a catalytic proton reduction (e.g., Figs. 5 and 6 in [52]). The reduction wave for the propanedithiolate and the *o*-xylenedithiolate complexes appears more responsive to acid concentration than that of the toluenedithiolate derivative [52]. Since protonation of electron-rich Fe site has already been reported [39], we postulate that the catalytic site is the Fe–Fe bond which is protonated to an iron-hydride species. In the presence of excess acid, proton/hydride coupling leads to hydrogen evolution by regenerating the starting complex. Although the primary reduction of the propanedithiolate complex involves only one electron on the cyclic voltammetry timescale, this process affords, as for the toluenedithiolate derivative, intermediate species able to activate proton reduction. It appears hence that the complete cleavage of the Fe–Fe bond (corresponding to a two-electron reduction process) is not a prerequisite for catalysis of proton reduction by $[(\mu\text{-}S_2R)Fe_2(CO)_6]$ complexes. The presence of CO π-acceptor ligands in the coordination sphere of the metal allowed us to generate Fe^0 center at potentials about 500 mV less negative than in the case of iron porphyrins [39]. However, a drawback of the toluenedithiolate-bridged hexacarbonyl di-iron complex as catalyst is that the reaction of its reduced form with protons seems to be slow. Although $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_4(L)(PMe_3)]$ ($L = PMe_3$ or CN^-) compounds activate the electrochemical proton reduction at potentials slightly more negative (about −1.7 V compared to −1.4 V versus $Fc^{+/0}$ in the case of the hexacarbonyl derivative), they appear as more efficient and robust catalysts because they afford stable $Fe^{II}(\mu\text{-}H)Fe^{II}$ complexes in the presence of strong acid and/or are less easily decomposed upon reduction.

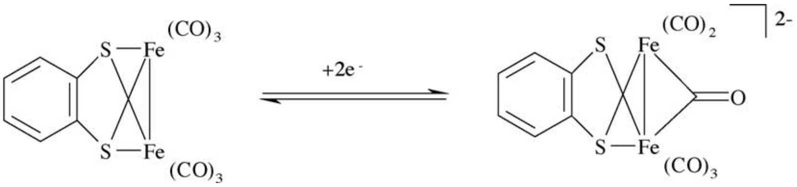


Scheme 14. Possible intermediate in proton reduction and hydrogen oxidation catalyzed by Fe-only H_2ases (from [4,12,13]).

3.3. Effects of the bridging ligand

The identity of the three light atoms that link the sulfur atoms in the $[2Fe]_H$ sub-site of the Fe-only H_2ases cannot be precisely determined from the crystallographic data. They were initially modeled as carbon atoms but it was later postulated that the central atom might be an hetero-atom such as nitrogen. This internal base would be well positioned to deliver proton to the iron center working as the hydrogen producing site (Scheme 14).

Among the di-iron complexes with an azadithiolate bridge [22,23,32,54–56], only $[(\mu\text{-}S_2C_2H_4NR)Fe_2(CO)_6]$ ($R = CH_2C_6H_4Br$ [54], CH_2CH_2OMe [55]) and $[\{\mu\text{-}S_2C_2H_4N(CH_2CH_2OMe)\}Fe_2(CO)_5({}^tBuNC)]$ [55] have been investigated with regard to catalysis of proton reduction. Importantly, the introduction of a basic site in the bridge does not cause a negative shift of the reduction potential. On the contrary, the azadithiolate bridged hexacarbonyl species are even slightly easier to reduce than the propanedithiolate



Scheme 13. Proposed structure of $[(\mu\text{-}S_2C_4H_6)Fe_2(CO)_6]^{2-}$ [53].

analogue (Table 1), which suggests that the LUMO of the dithiolate hexacarbonyls has little $\{-CH_2XCH_2-\}$ character, and is principally a metal–metal and metal-CO antibonding molecular orbital. This is consistent with the fact that the electrochemical reduction of $[(\mu\text{-}S_2C_2H_4NR)Fe_2(CO)_6]$ ($R = CH_2CH_2OMe$) leads to reversible CO loss [55] (see Section 4.2).

Crystal structure analysis of $[(\mu\text{-}S_2C_2H_4NR)Fe_2(CO)_6]$ (R = *p*-bromobenzyl) reveals that the nitrogen lone-pair is actually pointing toward one of the iron atom [54]. Protonation of the hexacarbonyl complex by strong acids at the N bridgehead atom was observed in acetonitrile for R = Me [32], $CH_2C_6H_4Br$ [54] and CH_2CH_2OMe [55], but not for R = Ph [54]; the pK_a of the tertiary amine (R = Me) was estimated to be $7.6 \leq pK_a \leq 10.6$ [32], while $[(\mu\text{-}S_2C_2H_4NH_2)Fe_2(CO)_4(CN)_2]^-$ is deprotonated by water in MeCN [23]. Despite the low basicity of the tertiary amine, and contrary to what was observed for the propanedithiolate hexacarbonyl complex (see above), the first step of proton reduction by the azadithiolate bridged hexacarbonyl derivatives consists in protonation at N. This protonation step facilitates the following electron transfer by 0.4 V [54,55] (to be compared with the shift of ca. 1 V toward more positive potentials when the protonation takes place at the iron–iron bond). Cyclic voltammetry in the presence of excess acid further shows that the reduction peak of $[\{\mu\text{-}S_2C_2H_4N(H)R\}Fe_2(CO)_6]^+$ at −1.2 V is followed by a second reduction process at ca −1.4 V versus $Fc^{+/0}$. An increase in height of this second reduction step along with a shift of the reduction potential towards more negative values with increasing acid concentration are clearly indicative of a catalytic proton reduction. However, the nature of the catalytically active species is unsettled [54,55]. Ott et al. [54] propose that the reduction of $[\{\mu\text{-}S_2C_2H_4N(H)R\}Fe_2(CO)_6]^+$ generates a Fe^0Fe^I species which protonates at the Fe–Fe bond to afford an hydride complex. The reduction of the latter at about −1.4 V versus $Fc^{+/0}$ could trigger the release of H_2 and regenerate the starting material, available for another catalytic cycle. However, we obtained preliminary evidence that controlled-potential electrolysis of $[\{\mu\text{-}S_2C_2H_4NR\}Fe_2(CO)_6]$ ($R = CH_2CH_2OMe$) at −1.2 V in the presence of acid (1 and 2 equiv. HBF_4/Et_2O) regenerates the starting material after transfer of ca. 1 and 2 F mol^{-1}, respectively, which indicates that the twice protonated complex reduces at −1.2 V (ECE process). Since the protonated complex $[\{\mu\text{-}S_2C_2H_4NH(CH_2CH_2OMe)\}Fe_2(CO)_6]^+$ undergoes a reversible CO loss upon reduction [55], thus generating a vacant site at a metal center in the vicinity of the protonated N atom, there is a possibility that the proton reduction process might involve an intermediate as shown in Scheme 14. The problem here is that CO decoordination is reversible, which means that CO and H^+ (or H_2) compete for the vacant site. Although the reversibility of the reaction does not prevent a catalytic reduction of protons, it is likely to introduce at least a kinetic limitation. On the other hand, azadithiolate di-iron derivative seems to be more efficient catalyst in terms of stability and activation overpotential compared the propanedithiolate hexacarbonyl di-iron complex and in terms of turnover number compare to toluenedithiolate derivative.

As indicated above, two different mechanisms for proton reduction may be encountered, depending on the properties of the complex, particularly on its basicity. The first step of the proton reduction mechanism catalyzed by chemical complexes is either an electron transfer (Scheme 10, step E_1) which increases the electron density at the metal core so that a subsequent proton transfer can occur, or a protonation step (Scheme 10, step C_1) which causes a positive shift of the redox potential of the compound thus facilitating a subsequent electron transfer. In order to protonate (usually at the Fe–Fe bond), the di-iron complexes must be sufficiently electron-rich, which is achieved by the substitution of donor ligands (CN^-, PMe_3, CNR) for carbonyls in the coordination sphere. The inevitable consequence of this is that the complexes become difficult to reduce, so that the positive potential shift resulting from protonation is (partly or totally) consumed to compensate for the negative potential shift due to the presence of the electron-releasing ligands (Table 1).

In order to reconcile the above contradictory conditions, a basic site is needed in the metal coordination sphere, which would have little effect on the redox potential of the compound. This might happen if the LUMO of the complex receives no contribution from the basic site, which seems to be the case of the azadithiolate bridged compounds.

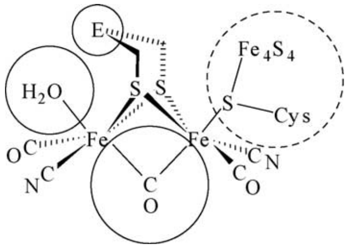
4. Targets for a biomimetic approach of the [2Fe]H sub-site

Although the biomimetic complexes synthesized so far present some of the structural and spectroscopic properties of the enzymes active site, they lack their reactivity. This is the consequence of the fact that what is modeled, with more or less accuracy, by the synthetic catalysts is the CO-inhibited form of the Fe-only H_2ases. Consequently, even the most active of these models is either too unstable, or operates at too negative potentials, to be of practical interest.

For the biomimetic approach to proton reduction (or hydrogen oxidation) catalysis to become of practical significance, several problems must still be solved (see Scheme 15), and the key-features of the enzyme active center with regard to the catalyzed reaction must be clearly identified in order to define a synthetic strategy for efficient catalysts.

4.1. Does the E bridgehead atom provide a site for protonation?

The question about the nature of the bridgehead atom was raised on the basis of crystallographic studies of the DdH H_2ase. Although this remains a pending question, the proposition that the sulfur bridge is made of a di(thiomethyl)amine



Scheme 15. A representation of the enzymes active site [3–5] pointing out some of the questions or major difficulties as far as modeling is concerned.

[5,12] is very attractive, since it would provide some of the desired properties for both the reduction of protons, as a basic site (protonation at this site would shift the redox potential of the H-cluster to less negative potentials, see above), and the oxidation of dihydrogen, as an internal base capable to assist the heterolytic cleavage of H_2 (see Scheme 14). DFT calculations confirm that the presence of a nitrogen atom in the sulfur bridge provides lower energy routes for hydrogen oxidation or evolution than in the absence of such an internal base [44,58,59].

As indicated above (Section 3.3), the complexes with an azadithiolate bridge are protonated at the N bridgehead atom, which is the first step of the proton reduction by these compounds. Therefore, the catalytic process occurs at a potential where the starting (unprotonated) compound is not reducible itself; as a consequence, there is no need for the reduction of the complex to be reversible, whereas this is required when the first step of the catalysis is a reduction. The only condition is that the reduced N-protonated complex is sufficiently long lived to undergo further protonation (which is generally fast) and reduction steps; release of H_2 then regenerates the parent compound. However, these azadithiolate compounds are still hexa- or pentacarbonyl species where the metal centers are in a wrong redox state, that is [Fe^I–Fe^I] in the starting material. As a consequence, proton reduction catalysis still takes place at a too negative potential (−1.2 to −1.4 V against $Fc^{+/0}$, that is ca. −1.0 to −1.2 V against NHE) [55,56]. We believe that syntheses of azadithiolate di-iron complexes with Fe^{II} center(s) should rapidly become a major objective, since Fe^{II} complexes would reduce at a less negative potential than Fe^I derivatives. Provided the change in the redox state of the metal center(s) from Fe^I to Fe^{II} does not prevent protonation at the N atom, a substantial gain in potential might be obtained.

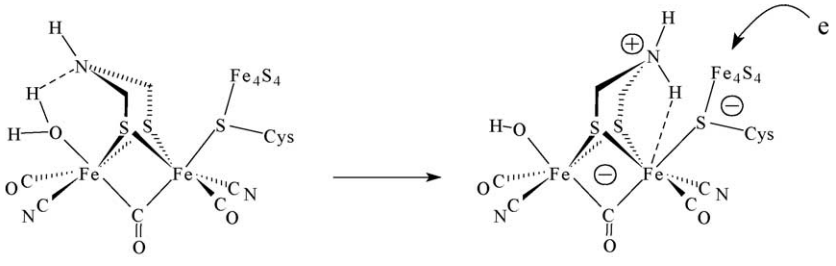
4.2. *A vacant site at a metal center: a labile aqua ligand?*

The crystallographic data reported for the CpI H_2ase show the presence of an aqua or hydroxo ligand at the distal iron center [3,60] which is not present in the crystals of DdH H_2ase [4,5,12]. The requirement of a vacant coordination site for the chemical compounds to show an activity analogue to that of the enzyme (Scheme 14) is emphasized by the fact that the coordination site, either vacant in DdH or occupied by a water molecule in CpI, is occupied by the exogenous CO in the CO-inhibited form of the enzyme [11].

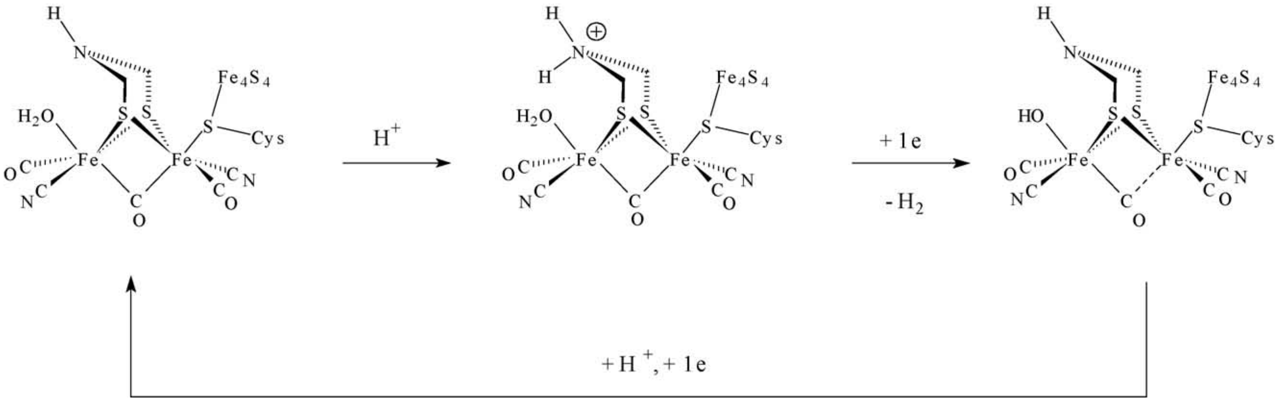
A different role of the aqua ligand, which would act as a proton source, has been suggested [63], Scheme 16. The electron-withdrawing bridging CO would lower the pK_a of the water molecule bound in a *trans* position in such a way that the latter could protonate the neighboring N bridgehead atom. A subsequent conformational rearrangement of the azadithiolate bridge would bring the proton close to the proximal iron center.

It should be reminded that the absence of the bound H_2O molecule in the crystals of DdH was assigned to the different redox states of the as-isolated enzymes, the DdH being in a more reduced state than the CpI H_2ase. However, there is no information to date on the crystal structure of reduced CpI, so that the release of the aqua ligand upon reduction remains speculative, even though it is supported by DFT calculations [44,58]. It is known that the reactivity of aqua ligands is highly sensitive to the redox state of the metal center(s) [61,62,64–66]. While oxidation of a M–OH_2 complex can induce deprotonation of the bound water molecule [62,66], electrochemical reduction may also generate a hydroxo complex, formally by loss of a hydrogen atom [62]. This suggests that in CpI, reduction of the $[2Fe]_H$ sub-site could induce the release of H_2 and generate a hydroxo ligand [60], Scheme 17.

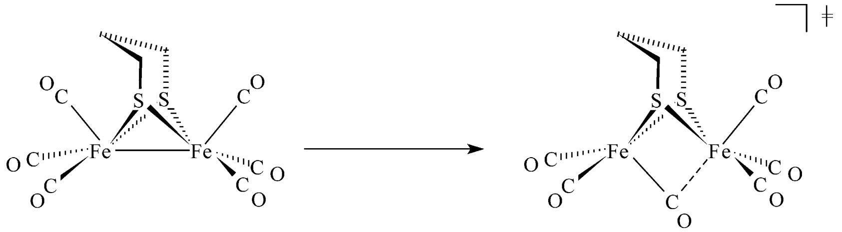
Further studies on the electrochemical behavior of aqua- and hydroxo complexes, as well as crystallographic studies on the reduced form of CpI would be interesting in order to check whether or not the aqua ligand could be directly involved in the proton reduction process catalyzed by CpI H_2ase (Scheme 17).



Scheme 16. Possible roles of the bridging CO and aqua ligands at the $[2Fe]_H$ sub-site (from [63]).



Scheme 17. Possible implication of the aqua ligand in proton reduction catalyzed by CpI H_2ase (the net charge of the H-cluster is not indicated).



Scheme 18. Ground state and transition-state upon rotation of a $Fe(CO)_3$ unit in $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$ (from [7,8]).

4.3. Shift of a CO ligand from a bridging to a terminal coordination mode upon reduction

The effects of the redox state of the H-cluster of DdH H_2ase on the stretching frequencies of the CO and CN ligands have been monitored by FTIR spectroscopy [5]. This showed that the carbonyl which bridges the two iron centers in the oxidized $[2Fe]_H$ sub-site shifts to a terminal coordination upon reduction. This was confirmed by crystallographic results on the reduced DdH H_2ase, where the CO ligand was found terminally bound to Fe_d [5]. One role of this particular CO is probably to relieve the electronic strain resulting from the reduction, in order to stabilize the low oxidation state of the $[2Fe]_H$ sub-site [5,44].

On the other hand, the presence of the bridging/terminal CO ligand underneath the metal–metal bond prevents protonation of the $[2Fe]_H$ sub-site at this position, in contrast to most of the synthetic compounds.

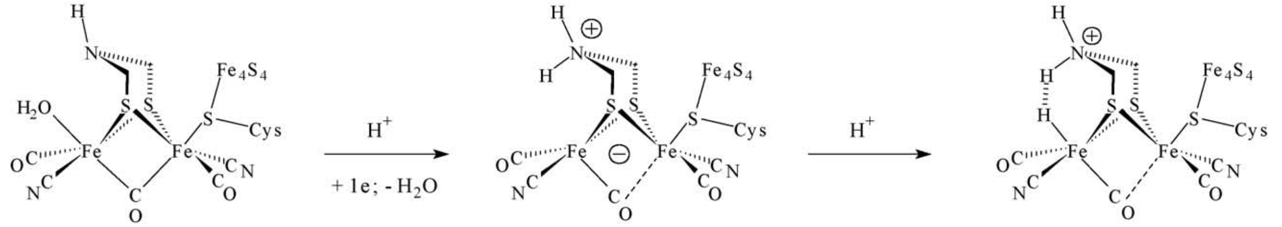
DFT calculations on the rotation of a $Fe(CO)_3$ unit in $[(\mu\text{-}S_2C_3H_6)Fe_2(CO)_6]$ revealed that the optimized transition-state geometry is characterized by a CO ligand beneath the Fe–Fe vector making one square pyramid inverted relative to the other (instead of two edge-bridged square pyramids in the ground state, Scheme 18) [7,8].

The similarity of the transition-state geometry to that of the $[2Fe]_H$ sub-site of DdH H_2ase suggests an entatic state in the latter. The bridging CO as well as hydrogen bonding of protein residues to the cyanide ligands stabilize the $[2Fe]_H$ site in a conformation such that the site liberated by the decoordination of the aqua ligand is maintained in the vicinity of the (putative) N bridgehead atom (Sections 4.1 and 4.2).

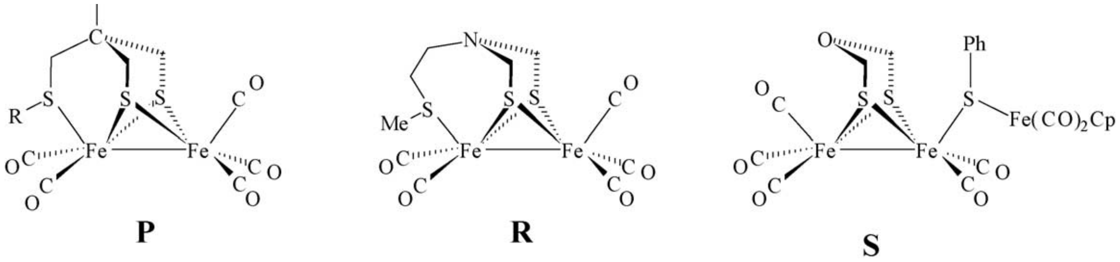
The collected data suggest a reaction path for the reduction of protons catalyzed by the H-cluster of Fe-only H_2ases in which the bound water molecule may (Schemes 16 and 17) or may not (Scheme 19) be directly involved.

4.4. A {2Fe3S} core in the Fe^{II}–Fe^{II}/Fe^{II}–Fe^{I}/Fe^{I}–Fe^{I} redox states

It is generally thought that the role of the proximal $[Fe_4S_4]$ in the H-cluster is to shuttle electrons in and out the $[2Fe]_H$ sub-site. In an electrochemical proton reduction



Scheme 19. Possible reaction sequence in proton reduction catalyzed by Fe-only H_2ases (the charge of the $[2Fe]_H$ sub-site is not indicated).



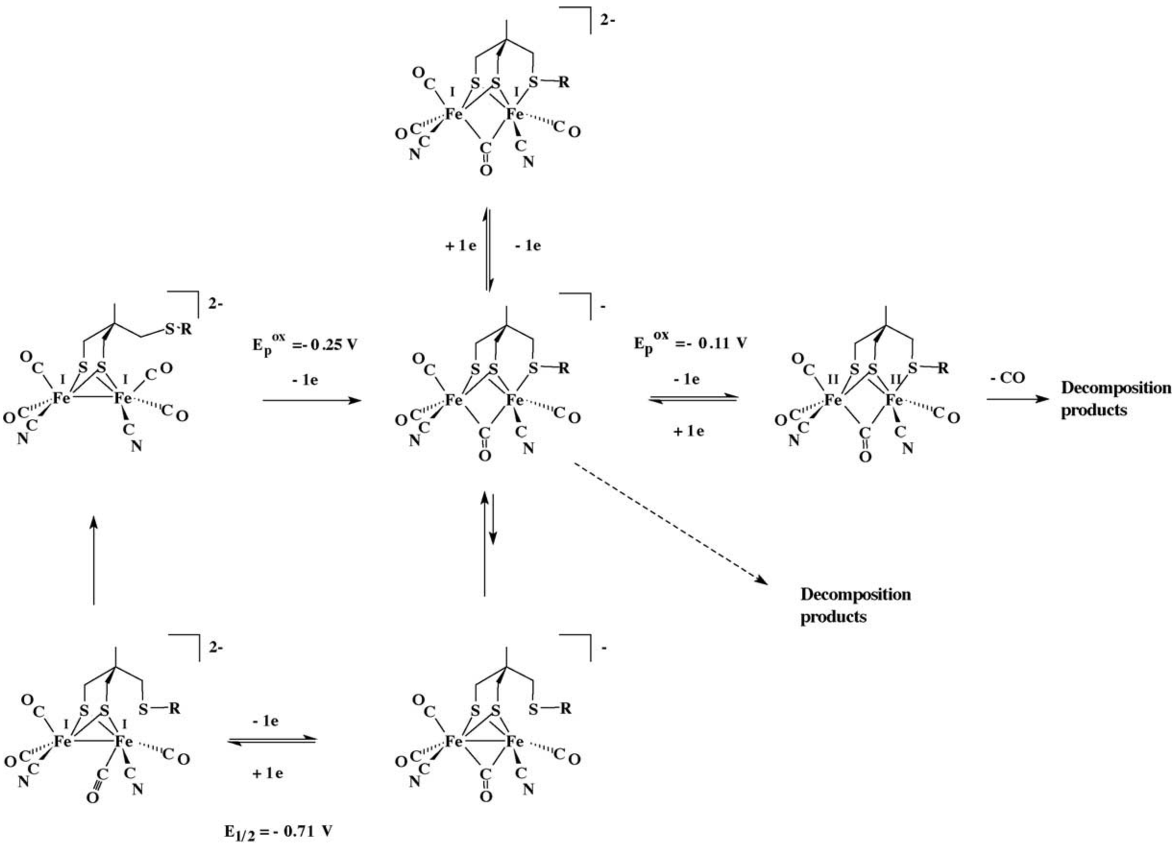
Scheme 20. Three different types of complexes with a {2Fe3S} core.

process, this function is devoted to the cathode, so that modeling the -S(Cys)-[Fe_4S_4] ligand may not be considered as a priority. However, there is little doubt that a comparison of electrochemical and reactivity studies of models with {2Fe2S} and {2Fe3S} assemblies could provide new insights in the chemistry occurring at the $[2Fe]_H$ sub-site.

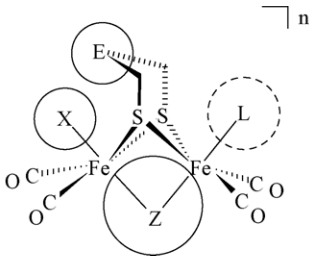
Three different types of complexes with {2Fe3S} cores have been synthesized so far by Pickett (Schemes 20 and 21) [19,31,57,63], Rauchfuss and coworkers [22] and Song et al. [67] (Scheme 20).

Whereas the thioether ligand constitutes the third leg of the sulfur bridge in Pickett (**P**) and Rauchfuss (**R**) complexes, Song compound (**S**) is a trinuclear species where the third SR ligand is bound to two iron centers, modeling more closely the thiolate bridge between the $[2Fe]_H$ subsite and the proximal [Fe_4S_4] of the H-cluster of Fe-only H_2ases.

Among these species, only the reactivity of **P** type compounds has been investigated in detail [19,31,57,63]. Particularly, complexes in the Fe^{II}–Fe^{I} and Fe^{II}–Fe^{II} redox states have been generated by electrochemical oxidation of a Fe^{I}–Fe^{I} precursor, Scheme 21. Even though the {Fe^{II}(μ-CO)Fe^{I}} state is only short-lived [57,63], its one-electron reduction produces a {Fe^{I}(μ-CO)Fe^{I}} derivative which is stable in solution at low temperature [57,63]. The mixed-valence {Fe^{II}(μ-CO)Fe^{I}} species rearranges at room temperature via de-coordination of the thioether arm and reduction regenerates the starting compound with a shift of the bridging CO to a terminally bound mode (Scheme 21).



Scheme 21. Electrochemistry of electrogenerated Fe^{II}–Fe^{I} and Fe^{II}–Fe^{II} complexes with a {2Fe3S} assembly (C.J. Pickett, private communication).



Scheme 22. Proposed targets for biomimetic models of the $[2Fe]_H$ sub-site (E = O, NR; X = anionic ligand, OH (or H_2O); L: 2e-donor ligand; Z = CR_2, PR_2).

It is remarkable that the Fe^{II}–Fe^{I} complex with a {2Fe3S} core possesses a bridging carbonyl associated with terminal CO and CN ligands, the stretching frequencies of which largely match those of the oxidized enzyme [57]. These characteristics make this model one of the closest analogues of the CO-inhibited form of the H-cluster.

4.5. *Towards a biomimetic catalyst*

From the preceding sections, it seems reasonable to assume that a biomimetic catalyst should combine at least a protonable bridgehead atom and a vacant site at a metal center. Several complexes with aza- or oxadithiolate bridge are now known, and a binding site can be generated by electrochemical reduction of the hexacarbonyl parent [55]. Although catalytic proton reduction is observed, reversible loss of CO and too negative reduction potentials severely restrict the practical interest of these model compounds.

Further synthetic work and studies of the reactivity, including electrochemically-induced reactivity, of new compounds are clearly needed. Scheme 22 summarizes what we believe could be the starting point of a new generation of biomimetic complexes.

- The complexes should both protonate at the bridgehead atom E (NR or O) and not reduce at a too negative potential. Therefore, compounds with terminal carbonyl ligands (including L, Scheme 22) look as an acceptable compromise. Complexes where the metal centers are in the Fe^{II}–Fe^{I} or Fe^{II}–Fe^{II} state (instead of Fe^{I}–Fe^{I} for most of the models known so far) should also contribute to satisfy the second condition. This could be achieved by the introduction of the terminally bound X and of the bridging Z ligands.
- It is known that the electrochemical reduction of complexes containing M–X bonds (X = anionic ligand) can lead to the irreversible cleavage of this bond, and thus to the generation of a substrate-binding site at a metal center [68–74]. The electrochemical cleavage of the Fe–X bond (Scheme 22) may thus provide a situation similar to that depicted in Scheme 14.
- The bridging ligand Z should have different functions. First, it would serve to protect the Fe–Fe bond from protonation. Secondly, it should confer some rigidity to the structure and prevent (/limit) the apical/basal CO site exchanges, so as to maintain the site generated by Fe–X bond cleavage in the apical position. Thirdly, depending on its electronic properties, it might contribute to accommodate the increased electron density arising from the reduction steps. Finally, it may affect the reactivity of the ligand in the *trans* positions. It has been demonstrated that the bridging thiolate in $[Fe_2(\mu\text{-}S_2C_3H_6)(\mu\text{-}SMe)(CO)_6]^+$ has a labilizing effect on the carbonyl *trans* to it, under photolytic conditions [75].

5. Conclusion

This review summarizes recent advances in the catalysis of electrochemical production of H_2 by di-iron sub-site models. The first generations of chemical models which have been developed are analogues of the CO-inhibited form of the Fe-only H_2ase and none of them show the same efficiency as the enzyme in proton reduction catalysis. The elaboration of efficient and economically viable catalysts remains a realistic goal for inorganic chemists but it is obvious that mechanisms of H_2 production and uptake are still insufficiently well understood. Information derived from biological studies on the enzyme, and from theoretical calculations performed on realistic models of the H-cluster, must be analyzed and exploited to develop new synthetic compounds. Electrochemistry should also contribute to a better understanding of this chemical problem. A concerted chemical–electrochemical approach of the design of biomimetic models is needed. Introduction of ‘sacrificial’ ligands which could be eliminated by electron-transfer step(s), or of electrochemically-controlled device, could give access to isolable metal complexes, precursors of efficient electrogenerated biomimetic catalysts. In this context, it is worth noting that, up to now, very few detailed electrochemical studies of di-iron dithiolate systems have been developed. Such statements suggest that one of the most important challenges which would allow new insights into mechanisms of production of H_2 by H_2ase is now to elaborate and study new generations of molecules in which the key features of sub-site of all-iron H_2ase have to be retained.

Acknowledgments

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