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Marcello Gennari, Carole Duboc. Bio-inspired, Multifunctional Metal–Thiolate Motif: From Electron Transfer to Sulfur Reactivity and Small-Molecule Activation. *Accounts of Chemical Research*, 2020, 53 (11), pp.2753-2761. <10.1021/acs.accounts.0c00555>. <hal-03012179>

HAL Id: hal-03012179

<https://hal.science/hal-03012179v1>

Submitted on 19 Nov 2020

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The bio-inspired, multifunctional metal-thiolate motif: from electron transfer to sulfur reactivity and small molecule activation

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WORD COUNT OF THE ARTICLE = 4744+183+19 = 4946 words

Conspectus

Sulfur-rich metalloproteins and metalloenzymes, containing strongly covalent metal-thiolate (cysteinate) or metal-sulfide bonds in their active site, are ubiquitous in nature. The metal-sulfur motif is a highly versatile tool involved in various biological processes: (i) metal storage, transport and detoxification; (ii) electron transfer; (iii) activation of the sulfur atom to promote different types of S-based reactions including S-alkylation, S-oxygenation, S-nitrosylation, disulfide or thiyl radicals formation; (iv) activation of small earth-abundant molecules (such as water, dioxygen, superoxide radical anion, carbon oxides, nitrous oxide and dinitrogen).

This Account describes our investigations carried out during the last ten years on bio-inspired and biomimetic low-nuclearity complexes containing metal-thiolate bonds. The general objective of these structural, spectroscopic, electrochemical and catalytic studies was to determine structure - properties - function correlations useful to (i) understand the peculiar features or the mechanism of the mimicked natural systems and/or (ii) reproduce enzymatic reactivities for specific catalytic applications.

By employing a unique highly preorganized N₂S₂-donor ligand with two thiolate functions, in combination with different first-row transition metals (Mn, Fe, Co, Ni, Cu, Zn, V), we got access to a series of bio-inspired sulfur-rich complexes displaying a widespread spectrum of structures, properties and functions. We isolated a dicopper(I) complex that, for the first-time, mimicked concomitantly the key structural, spectroscopic and redox features of the biological Cu_A center, a highly efficient electron transfer agent involved in the respiratory enzyme cytochrome *c* oxidase. In the field of sulfur activation, we explored (i) sulfur methylation promoted by a Zn-dithiolate complex that mimics Zn-dependent thiolate alkylation proteins and shows different selectivity compared to the Ni and Co congeners, and (ii) a series of Co, Fe, Mn complexes as the first copper-free systems able to promote thiolate/disulfide interconversion mediated by (de)coordination of halides. Concerning metal-centered reactivity,

we investigated two families of metal-thiolate catalysts for small molecule activation, especially relevant in the fields of sustainable fuel production and energy conversion: (i) two isostructural Mn and Fe dinuclear complexes that activate and reduce dioxygen selectively, either to hydrogen peroxide or water as a function of the experimental conditions; (ii) a family of dinuclear MFe (M = Ni, Fe) hydrogenase mimics active for catalytic H₂ evolution both in organic solution and on modified electrodes in water.

This Account thus illustrates how the versatility of thiolate ligation can support selected functions for transition metal complexes, depending on the nature of the metal, the nuclearity of the complex, the presence and type of co-ligands, the second coordination sphere effects and the experimental conditions.

Key references

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Gennari, M.; Gerey, B.; Hall, N.; Pécaut, J.; Collomb, M.-N.; Rouzières, M.; Clérac, R.; Orio, M.; Duboc, C. A bio-inspired switch based on cobalt(II) disulfide/cobalt(III) thiolate interconversion. *Angew. Chem., Int. Ed.* **2014**, *53*, 5318-5321. *The first example of a copper-free disulfide/thiolate interconversion system is reported. This Co-based switch displays clean, fast and quantitative conversion mediated by chloride (de)coordination.*²

Brazzolotto, D.; Gennari, M.; Queyriaux, N.; Simmons, T.; Pécaut, J.; Demeshko, S.; Meyer, F.; Orio, M.; Artero, V.; Duboc, C. Nickel-centred proton reduction catalysis in a model of [NiFe] hydrogenase. *Nat. Chem.* **2016**, *8*, 1054-1060. *A [NiFe]-hydrogenase model complex reveals efficient electrocatalytic properties for H₂ production and redox chemistry localized at the Ni site as for the enzyme. Two catalytic intermediates, models of the Ni-L and Ni-R enzyme states, are also characterized.*³

Wang, L.; Gennari, M.; Cantú Reinhard, F. G.; Gutiérrez, J.; Morozan, A.; Philouze, C.; Demeshko, S.; Artero, V.; Meyer, F.; de Visser, S. P.; Duboc, C. A non-heme diiron complex for (electro)catalytic reduction of dioxygen: tuning the selectivity through electron delivery. *J. Am. Chem. Soc.* **2019**, *141*, 8244-8253. *The first non-heme iron molecular catalyst for dioxygen*

reduction exhibits an unprecedented change in selectivity under chemical (up to ~95 % of H₂O₂ formed) vs electrochemical (less than 10 % of H₂O₂) conditions.⁴

1. Introduction

Metal-thiolate/sulfide (M-S) bonds are widespread in nature, and provide a plethora of functions and reactivities to the metalloproteins and metalloenzymes.⁵ In metalloproteins, metal-sulfur centers can display a structural role, assisting folding and stabilizing the secondary structure (zinc fingers), can be involved in metal transport, storage and detoxification (metallothioneins) or can act as electron transfer mediators (iron-sulfur clusters, cupredoxins). In metalloenzymes, active sites with M-S bonds display a broad range of reactivities, which can be located either on the sulfur atom(s) (S-alkylation/oxygenation/nitrosylation, formation of disulfides or thiyl radicals), or on the S-bound metal center. Many of this last class of metalloenzymes are involved in the activation of small molecules, including the interconversion between H₂ and H⁺ and electrons (hydrogenases), the O₂ reduction (cytochrome P450), the O₂⁻ dismutation (Ni superoxide dismutase), the fixation of CO₂ and CO (CO-dehydrogenase and acetyl-coenzyme A synthase), the reduction of N₂O to N₂ (nitrous oxide reductase) and the fixation of N₂ to NH₃ (nitrogenase). The M-S bond, with respect to more common bio-relevant M-O and M-N bonds (typically carboxylates, phenols, imidazoles, ...) affects more strongly the properties of the metal center and/or the sulfur atom thanks to its higher covalent character.⁶ Besides, sulfur ligands display the propensity to act as proton relays, to lower the redox potential of the metal, to provide efficient electron transfer pathways, and to support cooperation between multiple metals. These are crucial properties to support efficient metal-centered reactivity.

The research of bio-inspired M-S complexes to reproduce the aforementioned biological structures and/or functions with the ultimate objective of better understanding the mimicked systems but also of developing efficient small molecule activation catalysts, is still an underdeveloped field despite its big potential.

In this context, we successfully employed the diprotic N₂S₂-donor 2,2'-(2,2'-bipyridine-6,6'-diyl)bis(1,1-diphenylethanethiol) ligand (H₂L, L²⁻ being the fully deprotonated form shown in Figure 1)⁷ as coordination platform to access a series of bio-inspired first-row transition metal thiolate-supported complexes. In addition to the two thiolate functions, L²⁻ displays other key features that have proven to be crucial to provide the desired activities to the corresponding complexes (vide infra): (i) a highly pre-organized structure enabling an easy control of complex

nuclearity, (ii) a redox non-innocent bipyridine unit stabilizing different metal oxidation states, and (iii) bulky phenyl substituents on the quaternary carbon adjacent to the sulfur atoms, which prevent uncontrolled thiolate bridging coordination and undesirable side reactions at sulfurs. Through this account, the reader will discover many L^{2-} -supported metal-thiolate complexes displaying a variety of structures and functions, ranging from electron transfer activity, to sulfur alkylation and thiolate/disulfide interconversion, to dioxygen reduction and dihydrogen production.

2. Electron transfer: a unique structural-functional model of the biological Cu_A site

Biological electron transfer (ET) mediators, including cytochromes, iron–sulfur clusters and copper redox centers, are essential components of proteins and enzymes involved in multi-electron redox conversions. The binuclear Cu_A site, the most efficient copper-based ET center, is found in cytochrome *c* oxidase (CcO) and nitrous oxide reductase (N_2OR), i.e. the terminal electron acceptors in aerobic and anaerobic respiration, respectively.⁸ Cu_A is an asymmetric bis(μ -cysteinate) dicopper complex, in which each Cu center is in a trigonal planar coordination, with one weakly bound additional ligand in axial position (Figure 1a). It cycles between a paramagnetic $Cu^{1.5+}Cu^{1.5+}$ mixed-valence (MV) state and a reduced diamagnetic $Cu^I Cu^I$ state. The MV form has been identified as a fully-delocalized (class III) MV state based on peculiar spectroscopic signatures. Its absorbance spectrum displays an intervalence charge transfer transition in the range 760-810 nm consistent with a direct Cu-Cu bond, and its EPR spectrum a seven-line pattern with hyperfine coupling constant supporting a high degree of delocalization of the electron onto the ligands. According to the semiclassical Marcus theory, the high ET rates achieved by Cu_A (up to 23000 s^{-1}) result from the low structural reorganization energy ($\lambda = 38.6\text{ kJ.mol}^{-1}$)⁹ accompanying the ET event as illustrated by the Cu...Cu distance that remains similar between the oxidized and reduced state. This is mostly a consequence of the high structural rigidity of Cu_A , brought from (i) the nearly planar $\{Cu_2S_2\}$ diamond core, (ii) a Cu-Cu bond in the MV state (Cu...Cu distance of $\sim 2.5\text{ \AA}$), and (iii) the site confinement inside the protein.

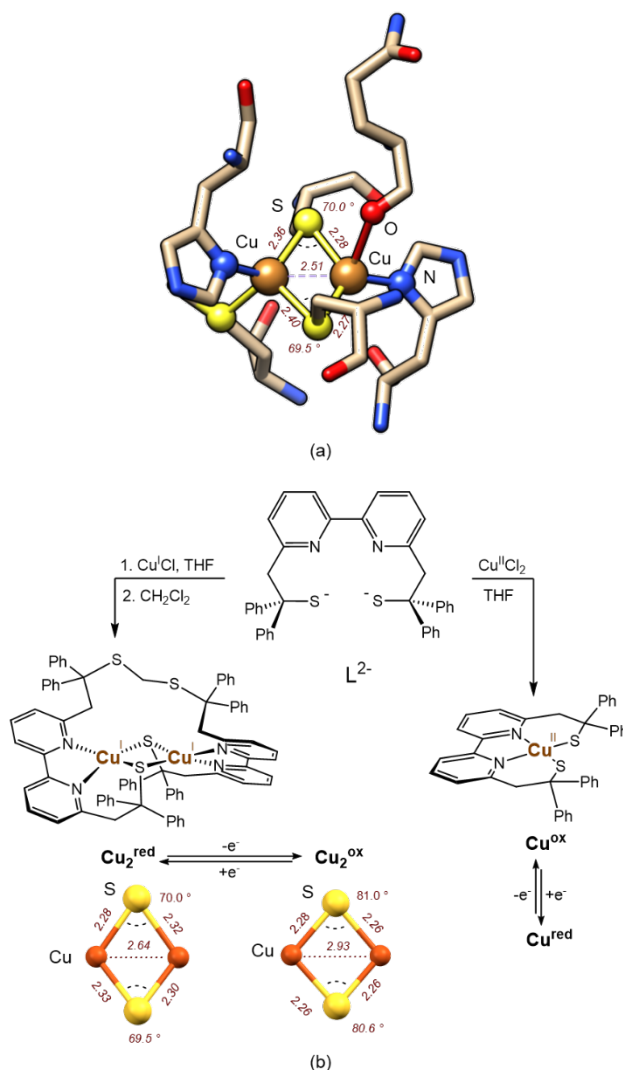


Figure 1. (a) Structure of the Cu_A center in the $\text{Cu}^{1.5+}\text{Cu}^{1.5+}$ state (PDB 2CUA, from CcO); (b) synthesis of the Cu_2^{red} and Cu^{ox} copper complexes; the structural changes of the $\{\text{Cu}_2\text{S}_2\}$ core induced by the electron transfer in $\text{Cu}_2^{\text{ox/red}}$ are displayed.

For many years, only one example of fully delocalized MV bis(μ -thiolato) dicopper complex was known.¹⁰ It well replicates the EPR and near-infrared features of Cu_A , but it lacks a Cu–Cu bond (Cu–Cu distance of ~ 2.9 Å) and it cannot be reduced to the $\text{Cu}^{\text{I}}\text{Cu}^{\text{I}}$ state. Through the use of a dinucleating ligand derived from L^{2-} (Figure 1b, see section 3), we succeeded in isolating the first, and still unique, bis(μ -thiolato) dicopper complex mimicking not only the main key structural and spectroscopic features of Cu_A but also its redox activity.¹ Both its $\text{Cu}^{1.5+}\text{Cu}^{1.5+}$ and $\text{Cu}^{\text{I}}\text{Cu}^{\text{I}}$ forms (Cu_2^{ox} and Cu_2^{red} in Figure 1b) were isolated and crystallographically characterized evidencing that, like in Cu_A , the rigid $\{\text{Cu}_2\text{S}_2\}$ diamond core is maintained in the two states. Accordingly, the $\text{Cu}^{1.5+}\text{Cu}^{1.5+}/\text{Cu}^{\text{I}}\text{Cu}^{\text{I}}$ redox system is perfectly reversible. The Cu_2^{ox}

complex is a class III MV species, as attested by an EPR spectrum displaying a seven-line pattern with a hyperfine coupling constant identical to that of Cu_A , and the presence of an intervalence bond at 1622 nm. This feature has been assigned to the mixed-valence $\psi \rightarrow \psi^*$ transition associated with spin delocalization between the two copper ions and is notably shifted to lower energy with respect to Cu_A consistently with the lack of direct copper orbital overlap. Additional DFT calculations have shown that the combined copper spin population amounts to 48%, while the sulfur ligands carry as much as 39% of the spin, as predicted for Cu_A (48 % on Cu vs. 44 % on S). The high preorganization of the dinucleating ligand is critical to stabilize the dinuclear structure in both redox states, even though this is not enough to prevent Cu...Cu elongation in the MV state (Cu–Cu distance of $\sim 2.9 \text{ \AA}$ vs $\sim 2.5 \text{ \AA}$ in Cu_2^{red}). This Cu-Cu oscillation results in a lower ET rate for $\text{Cu}_2^{\text{ox/red}}$ than for Cu_A ($1.4 \cdot 10^6 \text{ M}^{-1} \cdot \text{s}^{-1}$ and $2.2 \cdot 10^8 \text{ M}^{-1} \cdot \text{s}^{-1}$ are the respective rate constants estimated for the self-exchange electron transfer process i.e. the electron transfer between the $\text{Cu}^{\text{I}}\text{Cu}^{\text{I}}$ and $\text{Cu}^{1.5+}\text{Cu}^{1.5+}$ forms). Coherently, the corresponding inner-sphere contribution to reorganization energy (λ_i) was calculated to be higher for $\text{Cu}_2^{\text{ox/red}}$ than for $\text{Cu}_A^{\text{ox/red}}$ ($169.0 \text{ kJ} \cdot \text{mol}^{-1}$ vs $43.4 \text{ kJ} \cdot \text{mol}^{-1}$,¹¹ respectively). The predicted λ_i for the parent mononuclear Cu-dithiolate complex, $\text{Cu}^{\text{ox/red}}$ (Figure 1b) is also lower ($43.5 \text{ kJ} \cdot \text{mol}^{-1}$).¹² This result is unexpected, since larger λ_i values are calculated for mononuclear ET blue copper sites ($61.5 \text{ kJ} \cdot \text{mol}^{-1}$ for plastocyanin)¹¹ than for dinuclear Cu_A . However, it can be rationalized by considering the coordination properties imposed by the L^2 ligand, rigid enough to induce an intermediate geometry between tetrahedral and square planar, ideal to stabilize both Cu^{II} and Cu^{I} , with minimal structural changes, in the mononuclear complex.

Further efforts in ligand design are required to produce a Cu_A mimic that also displays (i) a Cu-Cu bond in the MV state,¹³ (ii) a trigonal planar coordination on each Cu center¹⁴ (tetracoordinated in $\text{Cu}_2^{\text{ox/red}}$), (iii) a different coordination for each copper center (the same N_2S_2 coordination in $\text{Cu}_2^{\text{ox/red}}$), (iv) higher ET rates, and (v) a higher reduction potential¹⁴ ($E_{1/2}$ for $\text{Cu}_2^{\text{ox/red}}$ is $\sim 350 \text{ mV}$ lower than for Cu_A).

3. Sulfur reactivity: metal-dependent thiolate/disulfide interconversion and S-alkylation

The intrinsic redox non-innocent character of thiolate ligands can result in a broad range of reactivity localized on the S atom, including disulfide formation, S-alkylation and S-oxygenation. These reactions are modulated by metal coordination, especially the degree of

covalency of the M-S bond, the Lewis acidity of the metal ion and its redox properties. We will not discuss S-oxygenation, since we never observed such reactivity with the L²⁻-supported complexes, even in the presence of reactive oxygen species such as O₂⁻ (with Ni)^{15,16} and H₂O₂ (with V).¹⁷

Disulfide/thiolate interconversion is relevant in biology to regulate many cellular functions. The process is typically mediated by copper to regulate either its transport in the cell (e.g. Cu delivery to the Cu_A site of CcO, see section 2) or the concentration of reactive oxygen species. With the aim of determining the factors that drive this metal-controlled (inter)conversion, chemists have developed Cu^I-disulfide/Cu^{II}-thiolate molecular switches that can be controlled by different stimuli, such as temperature, solvent polarity, acidic/basic conditions or (de)coordination of a halide.¹⁸⁻²¹

The L²⁻ ligand provided us a tool to extend these investigations to other transition metal ions than copper and thus to understand how the nature of the metal affects the process. We could isolate a series of isostructural L²⁻-complexes displaying M-driven thiolate/disulfide interconversion (M = Co, Mn and Fe). In the presence of halides, X⁻ (X = Cl, Br, or I), the dinuclear M^{II}-disulfide complexes [M₂^{SS}]²⁺ are converted into the corresponding mononuclear halide-bound M^{III}-thiolate species [M^{SX}] (Figure 2a).^{2,22-25} The reverse process occurs when the halide is removed. Halide binding to metal fosters an internal electron transfer from M^{II} to the disulfide leading to its reduction into thiolates with the concomitant metal oxidation to M^{III}. We observed that the properties of the three switches are strongly dependent on the nature of the metal. The Co system is the most efficient with fast (diffusion-limited), quantitative and reversible thiolate/disulfide conversion,² while the Mn one is much slower (hours vs minutes for the forward vs backward reaction, Figure 2) and the disulfide to thiolate conversion only partial.²² The behavior of the Fe switch is just in between, with diffusion-limited and quantitative disulfide to thiolate conversion, and quantitative but slow (few min) [Fe₂^{SS}]²⁺ regeneration from [Fe^{SX}].²³

The high structural similarity found in these series of dinuclear and mononuclear Co, Fe and Mn complexes implies that the differences in reactivity of the switches is essentially related to distinctive electronic and/or redox properties. When referring to redox chemistry, two conditions must be fulfilled for an efficient interconversion: (i) the M^{II} center must reduce the S-S bond upon halide coordination, and (ii) the thiolates must reduce the M^{III} ion, when removing the halide. In terms of redox potentials, these conditions translate in $E_{pc}(M^{III}-X \rightarrow M^{II}-X) < E_{pc}(RSSR \rightarrow 2RS^-)$ and $E_{pc}(RSSR \rightarrow 2RS^-) < E_{pc}(M^{III} \rightarrow M^{II}, X^- \text{ free})$ with E_{pc} = cathodic peak potentials. The case of Mn is representative: while the second requirement is satisfied (E_{pc}

(RSSR \rightarrow 2RS $^-$) = -1.17 V, E_{pc} (M^{III} \rightarrow M^{II}, X $^-$ free) = -0.47 V, vs Fc $^+$ /Fc) in agreement with the feasibility of the [Mn^SX] to [Mn₂^{SS}]²⁺ conversion, the first is not met (for X = I, E_{pc} (M^{III}-X \rightarrow M^{II}-X) = -0.68 V), consistently with the inefficient [Mn₂^{SS}]²⁺ to [Mn^SX] conversion. The properties of the Mn-based switch certainly arise from the particularly high stability of the Mn^{II}-bound disulfide to reduction compared to the Fe^{II} and Co^{II} homologues. The poor reductive activation of the S-S bond is most likely due to the low affinity of Mn^{II} for sulfur, leading to a weak coordination of the S-S unit. Even if the properties of these three switches can be qualitatively rationalized based on such analysis, the potential activity of such type of complexes to exhibit metal-driven disulfide/thiolate (inter)conversion properties remains difficult to generalize and anticipate. Additional studies involving other metals and sulfur ligands are thus required. In this vein, another Co system²⁶ and a Ni-based one displaying disulfide/thiolate (inter)conversion have been recently described,²⁷ demonstrating that such activity can be supported by a broad range of transition metal ions.

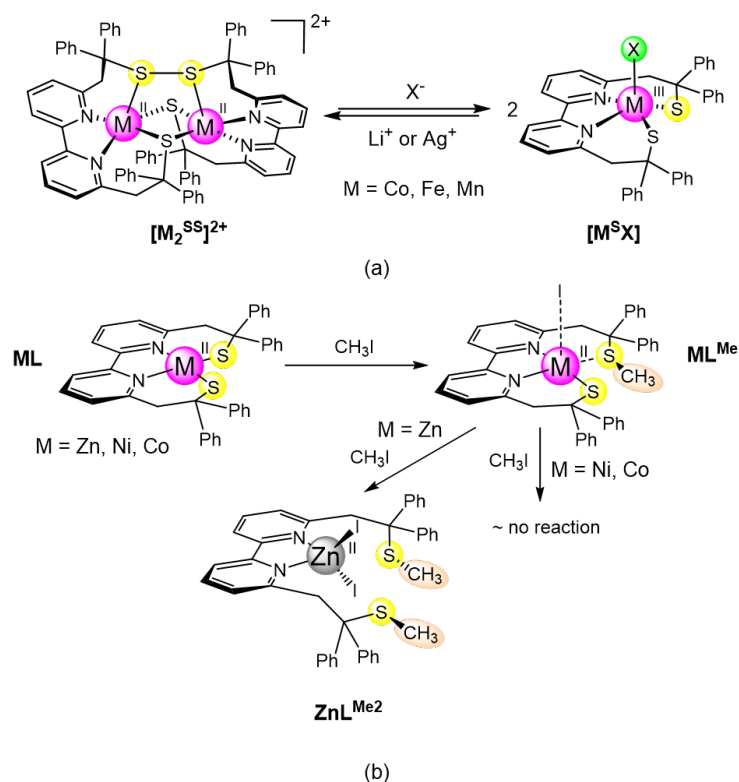


Figure 2. Examples of transition metal-controlled sulfur reactivity discussed in the text: (a) disulfide/thiolate interconversion mediated by halide (de)coordination (from)to the metal ion(s) (M= Co, Fe, Mn); (b) S-methylation of the ML complexes (M = Zn, Ni, Co) with CH₃I. The main atoms involved in the reactivity are highlighted with spheres of different colors.

S-alkylation reactivity is carried out by several Zn-containing enzymes including methionine synthase, farnesyl transferase, and the Ada protein involved in DNA repair.²⁸⁻³⁰ The nucleophilicity of metal-bound thiolate is thought to arise from a repulsive interaction between sulfur lone pairs and filled metal d-orbitals. The debate is still open to understand when the S-alkylation process occurs through a dissociative or associative pathway, i.e. implying the alkylation only after thiolate decoordination or directly on the metal-bound thiolate, respectively. Another central question is why the evolution has selected zinc to carry out such reactivity. While the first point has already been the subject of many investigations,³¹ the use of L²⁻-supported complexes allowed to gain insights on the second aspect. We isolated a series of three [M^{II}L] dithiolate complexes (**ML**, M = Co, Ni and Zn, Figure 2b) that display S-methylation reactivity with CH₃I as methyl donor.^{32,33} Based on kinetic data (Ni, Zn) and reported S-alkylation reactivity on neutral complexes, an associative mechanism can be proposed for the three systems, enabling their direct comparison. Most importantly, a different selectivity has been observed according to the nature of the thiolate-bound metal. In the presence of an excess of CH₃I, with Ni or Co a mono-S-methylated complex (**ML^{Me}**) was obtained, with the thioether remaining coordinated to the metal center, while with Zn a di-S-methylated complex was isolated (**ZnL^{Me2}**), with the two thioethers decoordinated from the metal. The difference in reactivity between the Ni/Co and Zn complexes is mostly related to the different nucleophilicity of the second thiolate group: while it is partially quenched with Ni/Co, it is fully conserved with Zn. Accordingly, the HOMO of **ZnL^{Me}** has a much higher thiolate-S character (68-70%) than the **NiL^{Me}** HOMO (18%) and **CoL^{Me}** SOMOs (<12.5%). The liberation of the product at the end of the reaction is an essential prerequisite for catalytic processes. Therefore, the fact that with these **ML** complexes the produced thioethers can be released from the metal coordination sphere, as found for Zn but not for Ni and Co, may explain why nature “has chosen” zinc to carry out S-alkylation reactions.

The ability of such systems to carry out metal-controlled S-alkylation was also evidenced in the preparation of the dinuclear Cu^I complex **Cu₂^{red}** (see Figure 1b), which involves the *in-situ* synthesis of a dinucleating ligand.¹ This ligand was obtained *via* S-based nucleophilic reactivity of two Cu^I-bound L²⁻ ligands with one CH₂Cl₂ molecule, a much weaker electrophile compared to CH₃I. The remarkable selectivity of this reaction is thought to result from a template effect induced by the formation of the {Cu₂S₂} core (see section 2).

4. Dioxygen activation: unprecedented non-heme Fe and Mn catalysts for O₂ reduction

Activation of triplet oxygen is a prerequisite for both O₂-promoted oxidation of organic substrates, and proton-assisted catalytic reduction of O₂ (Oxygen Reduction Reaction, ORR). While 4H⁺/4e⁻ ORR, producing H₂O, plays a key role in sustaining life (aerobic respiration) and in generating electrical energy (in fuel cells), 2H⁺/2e⁻ ORR yields H₂O₂, a versatile and clean oxidizing agent. Transition metal ions are known for their ability to promote the reductive activation of O₂.^{34,35} However, several aspects of metal-driven O₂ activation mechanisms remain to be elucidated, especially questions related to the selectivity, i.e. which factors regulate the competition between the O-O bond and the M-O bond(s) cleavage.³⁶ Among transition metals, manganese and iron exhibit extremely rich oxygen chemistry in both biological and synthetic systems. The donor abilities of the supporting ligand(s) are also crucial for O₂ chemistry. With respect to common N/O-donor ligands, coordination of thiolates is known to be even more suitable to promote O₂ activation at the metal center. Thiolates have actually been reported (i) to stabilize metal-(hydro/alkyl)peroxo, and -superoxo complexes, (ii) to decrease the activation barrier to O₂ binding, (iii) to foster metal oxidation by significantly lowering its redox potential, (iv) to stabilize coordinatively unsaturated M^{II} complexes suitable for O₂ coordination, (v) to increase the basicity of M-bound oxo ligands, and (vi) to generate a labile position *trans* to the thiolate, which facilitates product release.³⁷⁻³⁹

Despite these attractive properties, thiolates have been rarely used in the O₂ activation domain, certainly because of their propensity to be oxidized into sulfenic or sulfinic acid in the presence of O₂. Notably, coordination of the thiolate-rich H₂L ligand enabled us the access to the first non-heme manganese and iron ORR catalysts. More specifically, we isolate two isostructural dinuclear M^{II}-thiolate complexes, [L(HL)M^{II}₂]⁺ ({M₂^{SH}})⁺, M = Mn, Fe) containing a pendant metal-bound thiol suitable as potential proton relay (Figure 3a).^{4,40}

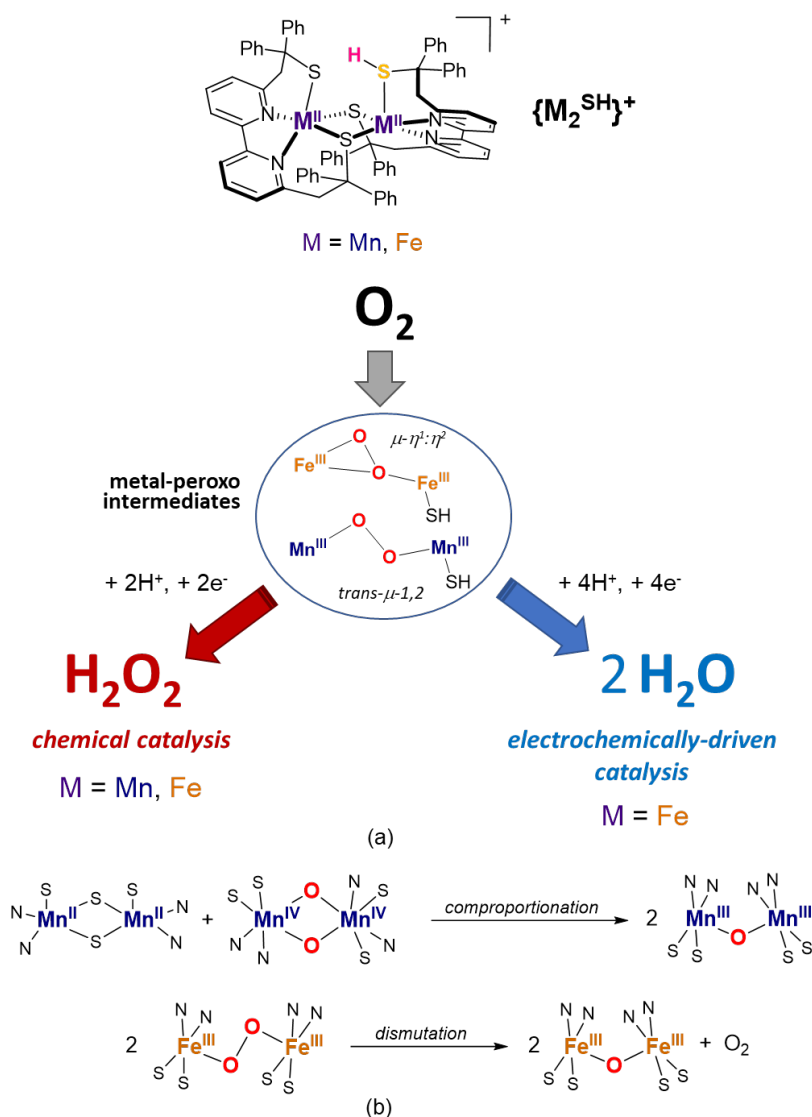


Figure 3. (a) ORR selectivity variation with the $\{M_2^{SH_3}\}^+$ catalysts ($M = Mn$ or Fe) depending on the electron delivery mode in MeCN solution (DFT-predicted geometries of the catalytic metal-peroxo intermediates are also shown); (b) reactions corresponding to the formation of the μ -(hydr)oxo M^{III} dimers as a function of the nature of the metal ion (only the case of μ -oxo M^{III} dimers is displayed, with the complexes shown in a simplified form).

The Mn and Fe complexes behave as efficient homogeneous ORR catalysts in MeCN solution in the presence of a proton source (2,6-lutidinium tetrafluoroborate) and a one-electron reducing agent (octamethylferrocene), generating H_2O_2 from O_2 with a selectivity of $82(\pm 2)\%$ and $94(\pm 4)\%$, respectively. Under similar experimental conditions, the Fe catalyst is one order of magnitude more reactive than the Mn counterpart ($TOF_i Fe = 8(\pm 1) \times 10^3 h^{-1}$, $TOF_i Mn = 4.0(\pm 0.4) \times 10^2 h^{-1}$), consistent with the fact that the Fe^{II} species is more easily oxidized than the Mn^{II} one ($E_{pa} M_2^{II} \rightarrow M_2^{III} = -0.19 V$ for Fe vs $-0.01 V$ for Mn , vs Fc^+/Fc). Most importantly,

the Fe^{II} catalyst can display a change in selectivity as a function of the experimental conditions. Indeed, water becomes the dominant product ($\geq 90\%$) when the process is driven electrochemically instead of using octamethylferrocene, while the other principal experimental parameters remain unchanged (solvent, catalyst/O₂/2,6-lutidinium concentrations). To date, this is the sole example of switch in selectivity observed for a same homogeneous ORR catalyst from chemical to electrochemical conditions.

The inner sphere reactivity of the {M₂^{SH}}⁺ catalysts with dioxygen was proven by the isolation of different metal-oxygen adducts under non-catalytic conditions. As final products, similar μ -(hydr)oxo M^{III} dimers have been characterized, demonstrating that under such conditions the reductive cleavage of the O–O bond occurs.^{40,41} However, the mechanism to access to these adducts is metal-dependent (Figure 3b): when considering only the oxo M^{III} dimers for the sake of simplicity, the Mn^{III} species is generated by comproportionation of the initial Mn^{II} complex with a high-valent oxo Mn^{IV} dimer,⁴² while the Fe^{III} derivate is proposed to result from dismutation of two μ -peroxo Fe^{III}₂ dimers (vide infra).⁴¹ The high-valent oxo Mn^{IV} dimer, characterized by X-ray diffraction as its protonated Mn^{IV}₂(μ -O)(μ -OH) form, was the first Mn^{IV}₂(μ -O)₂ species generated by direct reaction between Mn^{II} and O₂.⁴²

Under catalytic conditions (presence of an excess of protons and electrons), we propose the formation of M^{III}₂-peroxo intermediates, whose structures and reactivities have been theoretically calculated (Figure 3a). The peroxo ligand is predicted to bridge the two metal centers in a *trans* μ -1,2 (Mn) or μ - η^1 : η^2 (Fe) coordination modes resulting in rare examples of unsupported μ -peroxo dimers. The reactivity of these species is central to rationalize the process selectivity. They can either (i) react with protons to produce H₂O₂ via heterolytic M-O cleavage (in the case of Mn and Fe with Me₈Fc as reductant), or (ii) be reduced (and protonated) to generate H₂O through homolytic O-O cleavage (in the case of electro-assisted catalysis with Fe). Since with Fe both these pathways have been predicted to be thermodynamically feasible, the observed switch in selectivity can be interpreted in terms of a competition between acid-base and redox activity of the Fe^{III}-peroxo intermediate, with the electrochemical reaction-diffusion layer that drives more efficiently reductions with respect to a chemical reductant.

Globally, our work illustrates that (i) the use of thiolates as donor ligands is very promising for the development of non-heme ORR (electro)catalysts, (ii) on-demand ORR selectivity may become affordable if a perfect control on the reactivity of the metal-peroxo intermediates can be achieved, (iii) metal-bound thiols can act as proton relays to boost catalysis and/or to assist the control of ORR selectivity.

5. Dihydrogen production: a family of model complexes of hydrogenases

The [NiFe] and [FeFe] hydrogenases are great sources of inspiration to develop synthetic (electro)catalysts for efficient H₂ production and/or oxidation.⁴³ Their dinuclear active sites (Figure 4a) are distinct but have common features: two metal centers (Ni and Fe, or two Fe) working in synergy during the catalytic cycle, a sulfur rich environment including two bridging thiolates, and biologically uncommon CO and CN⁻ ligands. The remarkable catalytic efficiency of these enzymes is insured by controlled proton and electron transfers involving electron delivery to specific redox sites, and protonation steps to generate transient metal-hydrides and/or protonated ligands. During the catalytic cycle of the [NiFe]-hydrogenase, the Ni ion is solely responsible of the redox activity, switching between the I, II and III states, but also participates to substrate activation through the formation of bridged hydrides.^{44,45} In the case of the [FeFe]-hydrogenase, it is proposed that both Fe ions are redox active, switching between the I and II states, but only one of them is responsible for iron-hydride formation.⁴⁶ During the last two decades, numerous synthetic models of the active sites of these two hydrogenases have been described, leading to the development of efficient (electro)catalysts for the Hydrogen Evolution Reaction (HER).^{43,47,48} Despite this, the use of the L²⁻ supporting ligand provided us access to hydrogenase mimics with unique properties and reactivity.

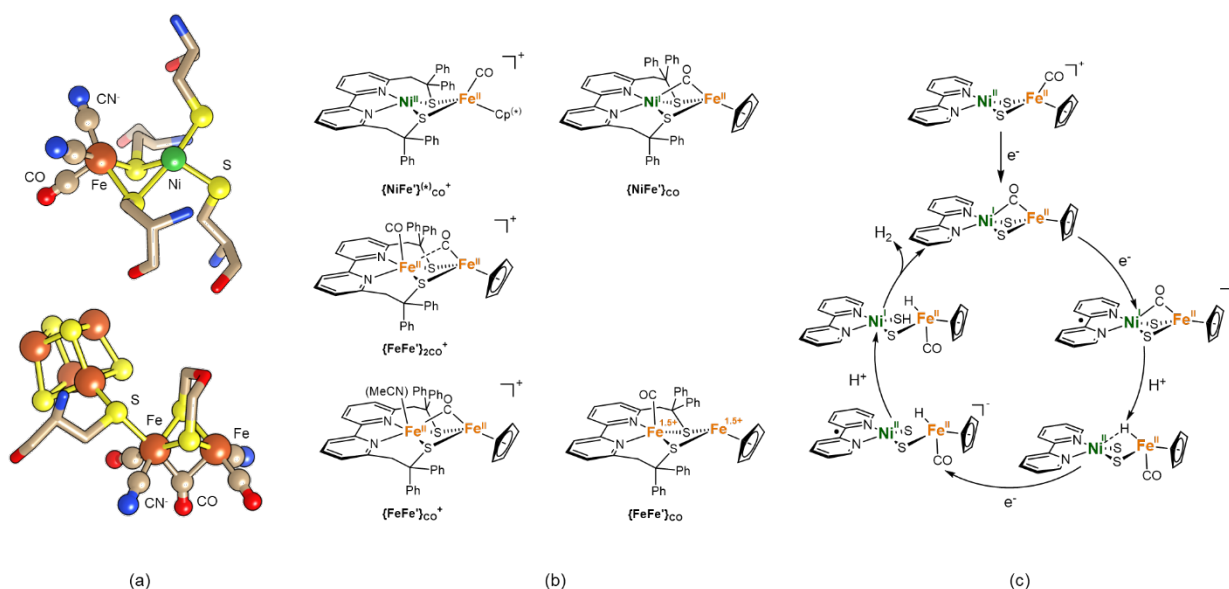


Figure 4. (a) Active sites of the [NiFe]- and [FeFe]-hydrogenases (above and below, PDBs 6EHQ and 3C8Y, respectively); (b) bio-inspired {MFe'}co⁺ (M = Ni, Fe) HER electrocatalysts and their reduced forms, as well as {FeFe'}₂co⁺; (c) proposed HER mechanism for the {NiFe'}co⁺ catalyst (E[ECEC]).

We have investigated the $[\text{LNi}^{\text{II}}\text{Fe}^{\text{II}}\text{Cp}(\text{CO})]$ complex ($\{\text{NiFe}'\}_{\text{CO}}$, Cp = cyclopentadienyl, Figure 4b), isolated from the reaction between $[\text{Ni}^{\text{II}}\text{L}]$ and $[\text{CpFe}(\text{CO})(\text{MeCN})_2]$ precursors, the Fe complex being successfully used as receivers to metal dithiolates synthon.⁴⁹⁻⁵¹ $\{\text{NiFe}'\}_{\text{CO}}$ reproduces some key structural features of the $[\text{NiFe}]$ -hydrogenase active site, including the structure of the $\{\text{NiS}_2\text{Fe}\}$ butterfly core (Ni \cdots Fe distance of 2.88(4) Å vs ~ 2.8 Å in the Ni-SI_a resting state).³ The originality of this active electrocatalyst towards H₂ production does not only reside on its remarkable intrinsic catalytic efficiency for H₂ production in MeCN solution (with Et₃NHBF₄, $k_{\text{cat}} = 2.5(\pm 0.3) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ and TOF = 250 s⁻¹ at $\eta = 690$ mV, as determined by cyclic voltammetry), but also on the fact that during catalysis the redox chemistry is centered at the Ni site as in the enzyme. The proposed catalytic cycle goes through an E[ECEC] mechanism (E = electron transfer, C = chemical reaction, the steps between brackets are catalytic) involving three reductions and two protonation steps (Figure 4c). This mechanistic proposal is based on both (i) the characterization of two active intermediates, i.e. a Ni^IFe^{II} ($\{\text{NiFe}'\}_{\text{CO}}$, Figure 4b) and a Ni^{II}(μ -H)Fe^{II} species mimicking the Ni-L and Ni-R states of the enzyme, respectively,⁴⁵ and (ii) theoretical calculations invoking the hemilability of thiol ligands.^{52,53} This catalytic cycle is similar to the [ECEC] mechanism proposed for the $[\text{NiFe}]$ -hydrogenase, apart from the fact that $\{\text{NiFe}'\}_{\text{CO}}$ needs to be first reduced before to enter in the cycle.

Another milestone was reached when this catalyst was physisorbed on a graphite electrode.⁵⁴ This followed a first attempt to heterogenize $\{\text{NiFe}'\}_{\text{CO}}$ through encapsulation in a MOF that was, however, less promising.⁵⁵ The $\{\text{NiFe}'\}_{\text{CO}}^+$ -modified graphite electrode displayed outstanding HER activity and robustness in acidic aqueous conditions (7.2 10⁶ TON in 10 hours at -1.10 V versus Ag/AgCl at pH = 3, TOF = 200 s⁻¹). At this potential the aforementioned Ni^IFe^{II} intermediate $\{\text{NiFe}'\}_{\text{CO}}$, model of Ni-L, directly reacts with protons as in $[\text{NiFe}]$ hydrogenase, instead of undergoing a second reduction as occurs in MeCN solution.

We also examined how modifications of the structural properties of the $\{\text{NiS}_2\text{Fe}\}$ core of $\{\text{NiFe}'\}_{\text{CO}}^+$ can affect its reactivity. To achieve this goal, we replaced the Cp ligand with the bulkier Cp* (pentamethylcyclopentadienyl), yielding the parent $[\text{LNi}^{\text{II}}\text{Fe}^{\text{II}}\text{Cp}^*(\text{CO})]^+$ ($\{\text{NiFe}'\}^*_{\text{CO}}^+$) complex (Figure 4b).⁵⁶ The $\{\text{NiS}_2\text{Fe}\}$ core is notably affected, with a remarkable increase of the Ni \cdots Fe distance (3.391(6) Å) leading to a quasi-planar $\{\text{NiS}_2\text{Fe}\}$ diamond core. Even if the substitution of Cp with Cp* does not affect significantly the catalytic HER efficiency with Et₃NHBF₄ in MeCN solution, the mechanism is notably impacted. With

$\{\text{NiFe}'\}^*\text{Co}^+$, the proposed pathway is E[CEEC] instead of E[ECEC], with the $\text{Ni}^{\text{I}}\text{Fe}^{\text{II}}$ intermediate that is protonated before further reduction.

With the aim of better understanding the role of iron and nickel in [NiFe]- and [FeFe]-hydrogenases, we synthesized another parent complex of $\{\text{NiFe}'\}\text{Co}^+$, $[\text{LFe}^{\text{II}}(\text{CO})\text{Fe}^{\text{II}}\text{Cp}(\text{CO})]^+$ ($\{\text{FeFe}'\}_2\text{Co}^+$, Figure 4b), in which Ni was replaced by Fe, for a comparative study.⁵⁷ Such comparison between NiFe and FeFe analogues was never reported before. While the $\{\text{NiFe}'\}^+$ structure includes one CO ligand terminally-bound to Fe, $\{\text{FeFe}'\}_2\text{Co}^+$ contains two CO ligands, one terminally bound to Fe in the $\{\text{LFe}\}$ site and the second in a semi-bridging position. In diluted MeCN solutions, one CO dissociates to afford the mono-CO adduct $\{\text{FeFe}'\}\text{Co}^+$, in which the remaining CO bridges the two metal ions (Figure 4b). Surprisingly, the electrocatalytic HER performances of $\{\text{FeFe}'\}\text{Co}^+$, determined by bulk electrolysis with Et_3NHBF_4 in MeCN solution, are comparable with those of $\{\text{NiFe}'\}\text{Co}^+$ (15 TON at -1.80 V vs 16 TON at -1.85 V, respectively, vs Fc^+/Fc). Regarding the mechanism, the main difference between the NiFe and FeFe systems is the catalytic entry point, i.e. the mono-reduced complex: while in the $\{\text{NiFe}'\}\text{Co}$ species the valence is localized on Ni with CO in a bridging coordination mode, the $\{\text{FeFe}'\}\text{Co}^+$ complex is a type II–III mixed-valence species with the CO terminally bound to the $\{\text{FeL}\}$ moiety (Figure 4b). However, the E[ECEC] pathway proposed for $\{\text{NiFe}'\}\text{Co}^+$ has been confirmed and directly probed, from cyclic voltammetry, for $\{\text{FeFe}'\}\text{Co}^+$. Interestingly, $\{\text{FeFe}'\}\text{Co}^+$ is a rare model of the [FeFe] hydrogenase that reproduces the iron oxidation states relevant to enzyme activity.⁴⁶

The fact that the catalytic performances and mechanism of $\{\text{NiFe}'\}\text{Co}^+$ and $\{\text{FeFe}'\}\text{Co}^+$ are comparable suggests that the nature of the metal is not so critical for the reactivity of such hydrogenase mimics. This is certainly the redox non-innocent character of the bipyridine moiety of the L^{2-} ligand acting as electron reservoir that is determinant. The second central property of H_2L that is relevant for HER catalysis resides in the hemilability of its thiol groups. Actually, transient decoordination of thiols, which can be formed under catalytic conditions by protonation of metal-bound thiolates of multidentate ligands, can create vacant sites that promote the formation of hydride intermediates.⁵⁸

6. Concluding remarks

In the last ten years, through the coordination of the N_2S_2 -donor, thiolate-rich L^{2-} ligand (Figure 1b) to a series of first-row transition metal ions, we have showed how the versatility of

thiolate ligation allowed to isolate metal complexes displaying a great variety of functions. The following general considerations can be extracted from our work:

- The ability of thiolates to bridge multiple metal centers, when it occurs in a controlled way, can induce structural rigidity and electronic communication in the generated complexes. In many of our studies, these properties arise from the formation of a $\{MS_2M'\}$ diamond core, which drives the synthesis of homodinuclear ($M = M' = \text{Cu, Co, Fe, Mn}$) or heterodinuclear ($M = \text{Ni, Fe, } M' = \text{Fe}$) complexes. The rigid $\{\text{Cu}_2\text{S}_2\}$ core in the Cu_A model $\text{Cu}_2^{\text{ox/red}}$ is responsible for the low reorganization energy between the two forms, resulting in optimized electron transfer properties. In small molecule activation catalysis (ORR and HER), the $\{MS_2M'\}$ core is essential to support the redox activity of the catalysts and/or to limit catalyst decomposition pathways.
- The nature, redox and electronic properties of the S-coordinated transition metal are critical to drive and control the reactivity of the sulfur atom(s). For example, in the specific case of the L^{2-} ligand, we found that cobalt is optimal to assist thiolate/disulfide switching, while zinc is the best choice for S-alkylation reactivity.
- Thiolates have strong donor abilities and thus induce a significant increase of the electron density of the S-bound metal centers (compared to common N/O-donors). For redox active metals, this facilitates the reductive activation of electron-deficient substrates like dioxygen and protons, allowing optimal ORR and HER catalytic performances.
- The potential protonation of metal-bound thiolates can boost small molecule activation catalysis, with the corresponding thiols acting as proton relays or hemilabile ligands.

Through this account we have illustrated the chemical richness of metal-thiolate complexes and their tremendous scope of application in bio-inspired chemistry. There can be no doubt that such a successful approach will contribute to the growth of the field in near future.

Acknowledgements

The authors gratefully acknowledge the French National Agency for Research in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02), ANR-JCJC (ANR-14-CE06_0002_01), ARCANE, CBH-EUR-GS (ANR-17-EURE-0003) and ANR-DFG (ANR-16-CE92_0012_01).

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