LETTRE SCIENTIFIQUE

iRTSV

Institut de Recherches en Technologies et Sciences pour le Vivant

Fonctions intégrées des protéines - Du vivant aux nanotechnologies

Direction des Sciences du Vivant

The Mössbauer facility for Biology at the iRTSV

Thematic n° 11 **November 2012**

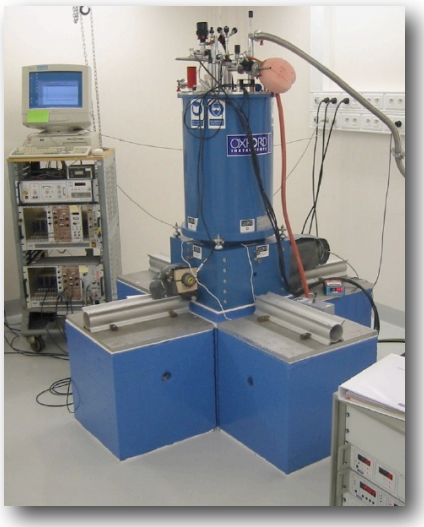
Editorial

Brief historical outline

The discovery of Mössbauer effect and spectroscopy had a profound and immediate impact on solid state physicists in the 1960s. At that time J. Chappert assembled a team working on hyperfine interactions in solids in the Physics Department of CEA-Grenoble [2]. Over thirty years their work encompassed the characterization of various kinds of solids [3], amorphous alloys and intermetallics, composed of iron of course but also rare earths and actinides. After JP Sanchez joined in the early 1990s these studies were pursued. The increasing use of a broadened set of physical techniques caused the decline of the use of Mössbauer spectroscopy and the final closing of the Mössbauer facility in the early 2000s.

In those last years, relinquishing to give up Mössbauer spectroscopy, two physicists Claude Jeandey and Jean-Louis Oddou decided to join the team of Jean-Marc Latour active in bioinorganic chemistry to start a Mössbauer laboratory devoted to the study of iron proteins and synthetic models.

This kind of biologically oriented Mössbauer studies had already been conducted in the past in the Physics Department. As early as 1965 Chappert and coworkers [4] had studied the magnetic properties of ferritin: this iron storage protein indeed fascinated physicists by its ability to store as many as 4000 Fe atoms in the cavity formed by the association of 24 protein chains. Several years later, in the early 1980s, Régnard, Marchon and



Oxford Instruments Cryomagnet Spectromag 4000 acquired in 2007

coworkers [5] used Mössbauer spectroscopy to characterize various iron porphyrins and porphyrin-cation radical complexes as models for oxidized states of hemoproteins. At about the same time, Auric and Meyer and coworkers [6] had published a series of articles characterizing the peculiar magnetic properties of bacterial ferredoxins iron clusters $[4Fe\text{-}4Se]^{2+/+}$ where the usual bridging sulfides had been replaced by selenides. This kind of study was initiated and developed through local collaborations to address biologists' and chemists' demand within the same institute. However, it did not expand to a larger community.

The facility: a few numbers

- four staff members: Martin Clémancey (IE UJF), Ricardo Garcia-Serres (MCF UJF), Geneviève Blondin (DR2 CNRS) and Jean-Marc Latour (DR CEA).

- four experimental set-ups

- two cryostats and a cryomagnet (*Figure*) allowing measurements from 1.4 to 300 K and with magnetic fields from 0.06 to 7 teslas, applied either parallel pr perpendicular to the γ-rays

- collaborations in France (Grenoble, Lyon, Gif-sur-Yvette, Paris, Brest, Strasbourg), in Europe (United-Kingdom, Portugal, Spain, Pays-Bas), in USA, India and Asia (Japan, South Korea)

- only six similar facilities exist worldwide, three in Germany, (Lübeck, Mülheim, Kaiserslautern) and three in the USA (Carnegie Mellon, Penn State, Texas A&M).

JLO *GB* *RGS* *MC* *JML*

Jean-Marc Latour,
responsable de l'équipe Physico-chimie des Métaux en Biologie du LCBM

Present Mössbauer activities

The initial setup, based on a 1960s vintage liquid helium cryostat, has now been replaced by two cryostats and a cryomagnet featuring "third millennium technology" and elevated to the rank of "Platform for Mössbauer in Biology" to adapt to current needs. It is engaged in collaborations with research groups from all over the world and its activities are focused on two main domains: iron-sulfur proteins and nonheme iron enzymes and model systems. The main focus of all studies is to provide an improved molecular understanding of the structure and function of the systems investigated.

Iron-sulfur proteins: biogenesis and enzymatic activities

Iron-sulfur clusters (ISC) were present in the most ancient organisms and have adapted to aerobic life. They constitute one of the most widespread and important class of proteins, being involved in numerous essential biological processes: electron transfer in respiratory chain, iron and superoxide sensing, and a large panel of enzymatic functions such as hydrolysis of substrates, bond formations (DNA synthesis, RNA modification, biotin synthesis, ...) to mention only a few [7-8]. They are constituted by assemblies of iron and sulfide ions anchored to protein cysteinate residues [9]. Although various nuclearities have been found, the [2Fe-2S] and [4Fe-4S] clusters are the most commonly encountered. They can exist in several oxidation states but again the $[2Fe\text{-}2S]^{+/2+}$ and $[4Fe\text{-}4S]^{+/2+}$ are the most common. In a simple (may be simplistic) view the $[2Fe\text{-}2S]^{+}$ cluster can be described as a pair of strongly antiferromagnetically coupled Fe^{2+}–Fe^{3+} ions bridged by two sulfide S^{2-} ions, that possesses an overall spin S = 1/2 and is EPR active. Its oxidized form $[2Fe\text{-}2S]^{2+}$ involves a strongly antiferromagnetically coupled pair of ferric ions Fe^{3+}–Fe^{3+} with a resulting overall spin S = 0. It is EPR silent as the cluster $[4Fe\text{-}4S]^{2+}$. Indeed in the latter, the four iron ions assembly can be viewed as an antiferromagnetically coupled dimer of the above Fe^{2+}–Fe^{3+} pairs, thus leading to an overall spin S = 0. One-electron reduction to the $[4Fe\text{-}4S]^{+}$ state that is composed of one ferric and three ferrous ions restores an overall spin S = 1/2 and the associated EPR spectrum. As a consequence of these diverse electronic states, every one of these clusters exhibits a distinct Mössbauer signature that is used to identify protein active sites and to monitor their functional changes [9].

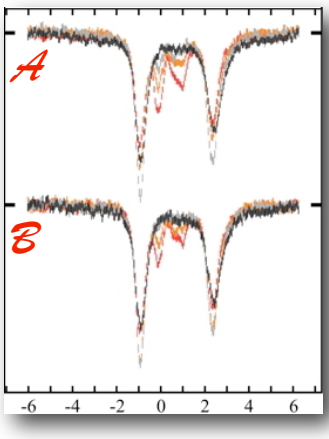


Figure 1: Time course of the formation of Fe-S clusters on IscU in the absence (A) and in the presence (B) of bacterial frataxin (CyaY). Mössbauer spectra were recorded at 4.2 K. Samples were frozen immediately after reaction initiation (black marks) or after an incubation time of 5 (grey), 15 (orange) or 30 min (red).

Biogenesis of iron-sulfur proteins and dysfunction

Iron-sulfur clusters (ISC) can be assembled *in vitro* from iron salts and sulfides [9], but *in vivo* their assembly requires a complex protein machinery. Several such machineries have been described over the past ten years but their functioning is not fully understood yet [10-11]. Of special interest is the Isc machinery that is conserved from bacteria to human. The Isc machinery involves a cysteine desulfurase (IscS or Nfs1 in eukaryotes) to generate sulfide anions and a scaffold protein (IscU or Isu in eukaryotes) where the cluster is assembled. The two proteins and an auxiliary protein (Isd11) form a complex with a particular protein, frataxin (FXN), the role of which is still hotly debated. Addition of iron ions, electrons provided by a ferredoxin, and cysteine to initiate sulfide production, to the complex induces the formation of $[2Fe\text{-}2S]^{2+}$ and $[4Fe\text{-}4S]^{2+}$ clusters within the scaffold protein. The strong interest of the community for frataxin comes from the fact that a defect in its gene has been identified as the cause for the neurodegenerative disease known as Friedreich ataxia [12-13]. It has now been evidenced that FXN deficiency results in the inability of assembling ISC, and later in the accumulation of Fe aggregates.

From biochemical and optical monitoring of ISC synthesis in a bacterial system (IscU) it was concluded that frataxin negatively regulates ISC synthesis, whereas an inverse effect was evidenced in a eukaryotic system [14]. In collaboration with A. Pastore (National Institute for Medical Research, London, United-Kingdom), we used Mössbauer spectroscopy to gain more molecular information on frataxin negative role in prokaryotes by following the respective formations of $[2Fe\text{-}2S]^{2+}$ and $[4Fe\text{-}4S]^{2+}$ clusters in IscU. ***Figure 1*** illustrates the time course of ISC formation over half an hour in the absence (A) and in the presence (B) of bacterial frataxin CyaY. It confirms the earlier observation on frataxin negative role in bacterial system, and reveals that this effect does not change the ratio of the individual clusters $[2Fe\text{-}2S]^{2+}$ and $[4Fe\text{-}4S]^{2+}$ nor the reductive transformation of the former into the latter [15].

The possibility that FXN is an iron storage protein was advanced in a number of papers and therefore it was of interest to investigate the nature of the Fe aggregates formed in various mutant strains impaired in their ability to synthesize or transfer ISC (collaboration with E. Lesuisse, Institut Jacques Monod, Paris, France). Traces A-C in ***Figure 2*** are the Mössbauer spectra recorded at 4.2 K on a mutant yeast mitochondria depleted in frataxin (Yfh1) or in proteins involved in ISC transfer (Ssq1, Ggc1). The signal is constituted of one slightly asymmetric quadrupole doublet with δ = 0.52(1) mm.s^{-1}, ΔE_Q = 0.63(2) mm.s^{-1} and Γ= 0.52/0.50(2) mm.s^{-1}, typical of a high-spin ferric iron bound to oxygen/nitrogen in an octahedral arrangement. Further experiments with applied magnetic fields confirmed the nature of the aggregate formed in all mutants as polydisperse nano-particles of iron phosphate [16]. Interestingly these aggregates differ strongly from those formed in the well-known iron storage protein ferritin (FTN) [17]. Moreover the observation that there is no difference of Fe aggregates in the two strains Δggc1 and Δggc1-YFH1 that over-expresses frataxin (***Figure 2C and 2D***) is not consistent with an Fe storage function [18]. This conclusion is further supported by the fact that the strain Δggc1-FTN that over-expresses ferritin exhibits a Mössbauer spectrum mostly identical to those of the other strains, the only difference being the presence of a signal (arrow in ***Figure 2E***) assigned to the high-energy line of a quadrupole doublet with $\delta \approx 1.23$ mm.s^{-1} and $\Delta E_Q \approx 2.98$ mm.s^{-1}, of a high spin Fe^{II} signal associated to the labile Fe pool [19].

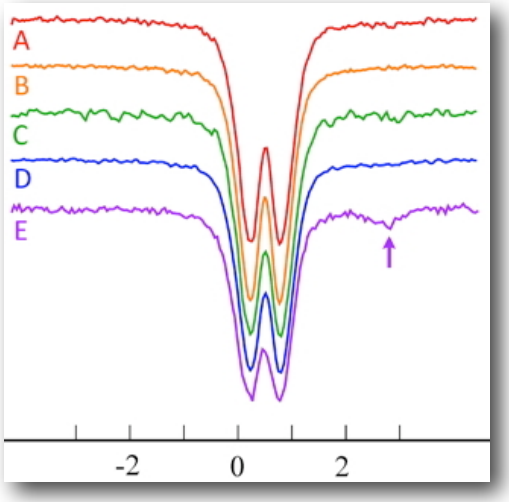


Figure 2: Mössbauer spectra recorded at 4.2 K of mutant mitochondria: A. Δyfh1, B. Δssq1, C. Δggc1, D. Δggc1-YFH1 and E. Δggc1-FTN.

Iron-sulfur enzymes

Two main classes of Fe-S enzymes have been described: hydrolytic enzymes (the paradigm for this class being aconitase) and enzymes involved in radical processes, among them the vast family of the so-called "Radical SAM" enzymes using the S-AdenosylMethionine cofactor [8]. Most enzymes of these classes have in common an active center constituted by a $[4Fe\text{-}4S]^{2+}$ center bound to the protein chain by three cysteine residues thus leaving a single Fe ion available for substrate interaction. Mössbauer spectroscopy has proven very efficient to detect this particular Fe ion and monitor its coordination.

Our very recent study of quinolinate synthase (NadA), a non radical-SAM enzyme, has provided a nice illustration of the potential of Mössbauer spectroscopy in this respect (collaboration with S. Ollagnier de Choudens, LCBM, Grenoble, France) [20]. NadA is a key enzyme in the synthesis of Nicotinamide Adenine Dinucleotide, an essen-

tial cofactor of many biological redox reactions. The Mössbauer spectrum of the enzyme is depicted in *Figure 3*. Biological studies have shown that the enzyme is strongly inhibited by 4,5-dithiohydroxyphthalic acid (DTHPA), but the molecular basis for this inhibition was unknown. The Mössbauer spectrum of the enzyme in the presence of DTHPA immediately shows that the inhibitor interacts with the $[4Fe\text{-}4S]^{2+}$ cluster through one single Fe ion. Indeed, in the absence of DTHPA (left part of *Figure 3*), the spectrum recorded is characteristic of classical $[4Fe\text{-}4S]^{2+}$ clusters and can be reproduced with the superposition of two slightly different quadrupole doublets (component 1: δ = 0.44 mm.s^{-1}, ΔE_Q = 1.25 mm.s^{-1}; component 2: δ = 0.45 mm.s^{-1}, ΔE_Q = 0.95 mm.s^{-1}) of equal intensities associated with the two delocalized antiferromagnetically coupled Fe^{2+}–Fe^{3+} pairs. Binding of a ligand to one ion of a pair induces a localization of the valences within this pair which can eventually leads to the pair (component 2, left part of *Figure 3*) appearing as two distinct quadrupole doublets (components 2 and 3, right part of *Figure 3*): component 1 (δ = 0.48 mm.s^{-1}, ΔE_Q = 1.20 mm.s^{-1}), component 2 (δ = 0.44 mm.s^{-1}, ΔE_Q = 1.04 mm.s^{-1}) and component 3 (δ = 0.63 mm.s^{-1}, ΔE_Q = 2.02 mm.s^{-1}). Comparison of the Mössbauer parameters with those of a model complex and to DFT calculated values suggests that the inhibitor chelates one unique Fe ion of the cluster.

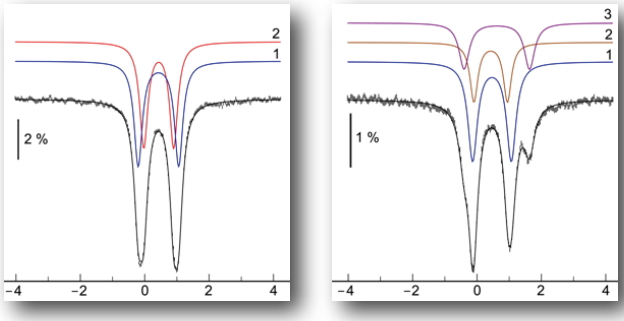


Figure 3. Mössbauer spectra of as-isolated NadA recorded at 4.2 K in the absence (left) and in the presence of the inhibitor DTHPA (right).

A number of radical-SAM enzymes have been discovered recently as key players in the modification of tRNA and ribosomal proteins in processes aimed at improving the accuracy of the genetic machinery. These enzymes commonly associate two $[4Fe4S]^{2+}$ clusters, one interacting with the SAM cofactor to initiate the generation of the adenosyl radical while the other interacts with the substrate [8]. We recently characterized by Mössbauer spectroscopy one such enzyme RimO that is able to perform the thiomethylation of an aspartate residue of a ribosomal protein S12 (collaboration with M. Atta, LCBM, Grenoble, France) [21]. Interestingly the Mössbauer spectrum of the protein depicted in *Figure 4* reveals the inequivalence of the two $[4Fe\text{-}4S]^{2+}$ clusters with the presence in one of them of a unique Fe site as found for NadA (see above). The first cluster can be taken into account with a single quadrupole doublet with usual parameters averaging the two pair components (δ = 0.45 mm.s^{-1}, ΔE_Q = 1.04 mm.s^{-1}). By contrast, the second cluster requires three components to be simulated as was the case for NadA in the presence of the inhibitor: component 1 (δ = 0.48 mm.s^{-1}, ΔE_Q = 1.15 mm.s^{-1}), component 2 (δ = 0.3 mm.s^{-1}, ΔE_Q = 0.9 mm.s^{-1}) and component 3 (δ = 0.60 mm.s^{-1}, ΔE_Q = 2.07 mm.s^{-1}). This observation raises the question of the nature of the peculiar ligand of the unique Fe ion of this cluster. As previously, the distinction of the coordination of this Fe ion constitutes a powerful tool to investigate the reactivity of the enzyme and to address the question of its mechanism.

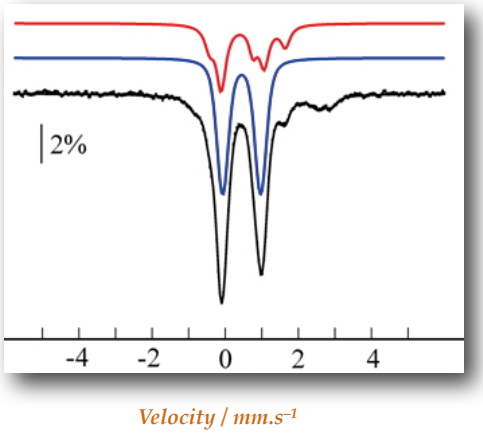


Figure 4. Mössbauer spectra of reconstituted RimO recorded at 4.2 K showing the contribution of the "classical cluster" (blue) and the differentiated cluster (red).

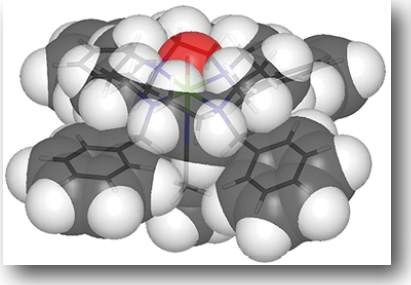
Nonheme iron enzymes and model systems

For the past three decades understanding how molecular oxygen is activated and transferred to inactive substrates and duplicating this reaction has constituted one of the main challenges posed to chemists with implications ranging from basic knowledge to far-reaching industrial applications. Oxygen atom transfer is the reaction catalyzed by enzymes called oxygenases, the paradigm of which are the cytochromes P450, a class of hemethiolate proteins. After more than thirty years of intense research, the active form of cytochromes P450 has been demonstrated recently to be an Fe^{IV}=O complex of a porphyrin radical cation [22]. In the nonheme world, the most fascinating enzyme is undoubtedly methane monooxygenase that uses an oxo-bridged diiron(IV) unit to oxidize methane into methanol. Trying to elaborate catalysts that can rival these enzymes in their oxidation power and selectivity is thus a very active research domain.

High-valent iron catalysts

The first non-heme Fe^{IV}=O complexes were characterized almost a decade ago in systems that were deactivated by the use of aromatic amine ligands [23]. Mössbauer spectroscopy revealed that these systems were characterized by an S = 1 spin state whereas all corresponding protein intermediates harbored a spin S = 2 state and a higher reactivity. Improving the reactivity of these model complexes and understanding the structure-reactivity relationships has become a major endeavor and Mössbauer spectroscopy has proved to be a tool of choice to characterize the electronic structures of trapped intermediates.

The influence of steric hindrance / distortion on the reactivity of the Fe^{IV}=O complex of tetranitrogen macrocylic ligands has been investigated by replacing four methyl groups 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane ligand (TMC) by four benzyl groups (TBC) (collaboration with W. Nam, Ewha Womans University, Seoul, South Korea; and E.I. Solomon,Stanford University, USA) [24]. *Figure 5* illustrates the Mössbauer spectra of the complex Fe^{IV}=O(TBC) recorded in different temperature (from 4.2 to 78 K) and applied field (from 60 mT to 7 T) conditions to investigate its electronic structure. Simultaneous fitting of all spectra allowed to conclude that the complex possesses a spin S = 1.



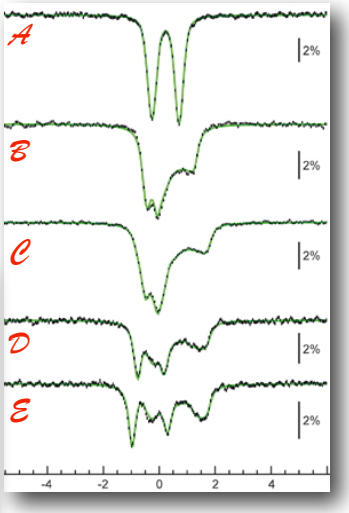


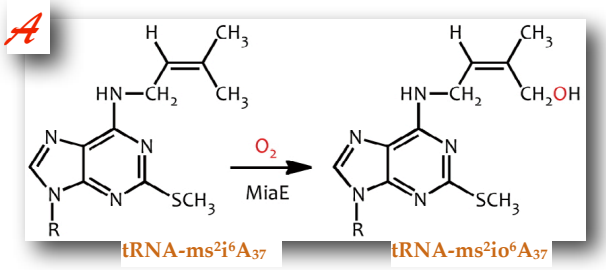
*Figure 5. Left: DFT calculated structure of Fe^{IV}=O(TBC). Right: Mössbauer spectra of Fe^{IV}=O(TBC) (vertical bars) measured at (A-C) 4.2 K, (D) 41 K and (E) 78 K in a magnetic field of (A) 60 mT, (B) 4 T and (C-E) 7 T. The solid (green) curve is a Spin Hamiltonian simulation with the following set of parameters: δ = 0.22 mm.s^{-1}, ΔE_Q = 0.97 mm.s^{-1}, D = 29.5 cm^{-1}, E/D = 0, $g_{x,y,z}$ = 2.3, 2.3, 2.0 and $A_{x,y,z}/g_N\beta_N$ = –18, –18, –2 T. Reprinted by permission from American Chemical Society: Journal of the American Chemical Society, 2012, **134**: 11791, copyright (2012).*

In a similar study, it was shown that the reaction of the Fe^{II} complex of the ligand Me_3NTB (Me_3NTB = tris((N-methylbenzimidazol-2-yl) methyl)amine) with m-chloroperbenzoic acid, a classical oxygen donor, produces the corresponding Fe^{IV}=O species, that has been characterized by Mössbauer spectroscopy as an intermediate spin system S = 1 (collaboration with W. Nam, Seoul, South Korea). Reactivity studies showed that this species is one of the most active catalysts reported so far for oxygen transfer reactions to inactivated aliphatic substrates [25].

Diiron systems

The dioxygenase MiaE

This enzyme belongs to a group of enzymes involved in improving the efficiency and fidelity in genome decoding through tRNA modifications. It catalyzes the post-transcriptional allylic hydroxylation of 2-methylthio-N-6-isopentenyl adenosine, a difficult oxygenation reaction of a methyl group (***Figure 6A***). Mössbauer spectroscopy proved invaluable to show that the enzyme active site comprises a diiron site similar to that of Methane MonoOxygenase (collaboration with M. Atta, LCBM, Grenoble, France) [26]. Traces a and b on ***Figure 6B*** reproduce Mössbauer spectra of the as-isolated enzyme. They revealed the presence of at least three components that were identified thanks to a temperature- and field-dependent study. The major component (54 %) which contributes the central quadrupole doublet is a diferric species that experiences a moderate antiferromagnetic coupling, revealed by the broadening of the doublet at 77 K (trace d on ***Figure 6B***), as found in μ-hydroxodiferric entities. The shoulders that flank both sides of the central doublets are assigned to a μ-oxodiferric species from its Mössbauer parameters and its strong antiferromagnetically coupling contributing 16 % of the total Fe content. The remaining 30 % of the iron correspond to a paramagnetic species that contributes at higher velocities (trace c on ***Figure 6B***) and behaves as a mixed-valent Fe^{II}-Fe^{III} pair. Its presence was confirmed by EPR spectroscopy.



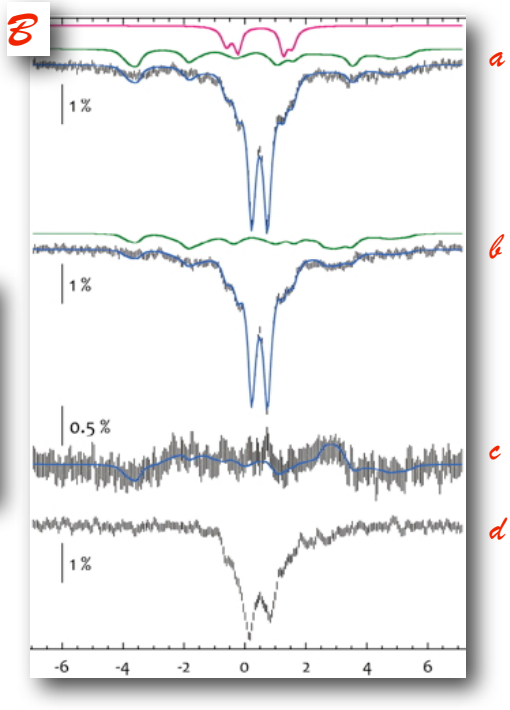


Figure 6. *A: Reaction catalyzed by MiaE. B: Mössbauer spectra of MiaE2H (vertical bars) measured at 4.2 K in a magnetic field of 60 mT applied parallel to the γ-beam (a) or 22 mT applied perpendicular to the -beam (b) or at 77 K and zero applied field (d). Spectrum c is obtained by subtraction (a-b). The solid blue lines are spin-Hamiltonian simulations. Contributions from the oxodiferric and mixed valence clusters are shown in pink and green, respectively.*

Mixed-valent $Fe^{II}Fe^{III}$ model complexes

Diiron complexes have been used for decades to try and model the structure and the reactivity of various enzymes with a diiron site. They are invaluable to investigate the potential cooperativity between the two sites involved in hydrolytic or redox reactions. The complex illustrated in ***Figure 7A*** is a model of the mixed valence state of hemerythrin that reproduces its pH behavior. It comprises a ferric (left) and a ferrous ion (right) bridged by a phenolate and two carboxylates. Their terminal ligation differs: the ferric site is bound to a bis(picolyl)amine group whereas an aniline ligand replaces a pyridine on the ferrous ion. The Mössbauer spectrum of ***Figure 7Ba*** shows the two quadrupole doublets of the two ions. Interestingly, when the complex is treated by triethylamine its spectroscopic properties change drastically as shown in ***Figure 7Bb***. The main change that occurs in the Mössbauer spectrum concerns the ferric site whose quadrupole splitting parameter increases dramatically from ΔE_Q = 0.39 mm.s^{-1} to ΔE_Q = 1.77 mm.s^{-1}. This change reveals that the ferric ion is bound to an anionic ligand in transposition with respect to the bridging phenolate. This in turn indicates that the aniline ligand has been deprotonated and that an internal electron transfer has occurred within the diiron pair [27]. In other words, the deprotonation of the aniline has induced a valence interchange, as illustrated in ***Figure 7C***. Further studies based on electrochemical techniques have shown that this proton-coupled intervalence transfer is a concerted process [28]. Apart from its bioinorganic interest this compound can be viewed as a proton induced redox switch.

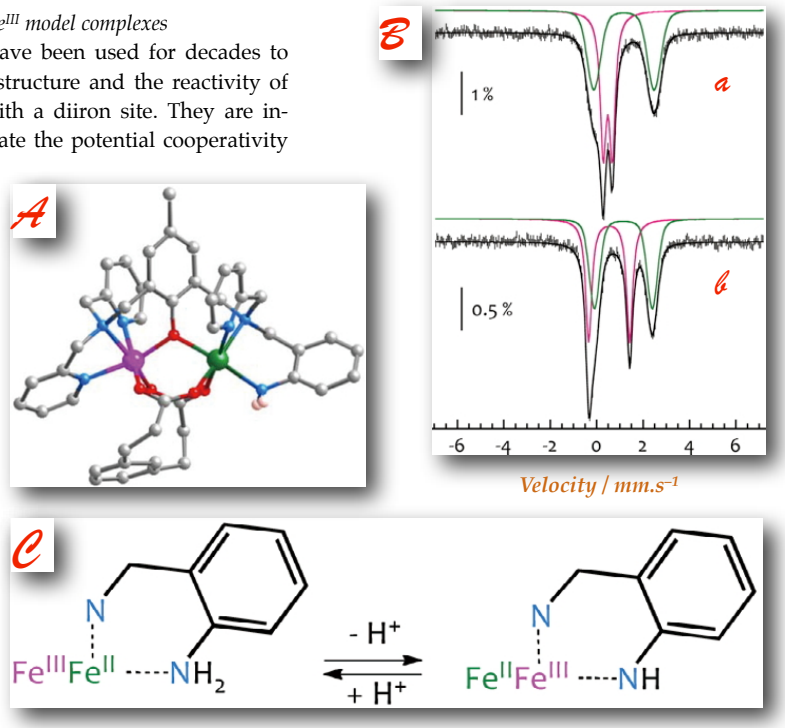


Figure 7. *A: X-ray structure of the mixed valence aniline complex where the Fe^{III} and Fe^{II} ions are shown in pink and green, respectively. The two hydrogen atoms of the coordinated aniline group are shown in light pink. B: Experimental (hatched marks) and simulated (solid lines) Mössbauer spectra of an acetonitrile solution of the aniline complex before (a) and after (b) the addition of 1.5 eq of NEt_3. The ferric and ferrous contributions are indicated as pink and green traces, respectively. C: Intervalence exchange induced by aniline (de)protonation. Reprinted by permission from American Chemical Society: Inorganic Chemistry, 2011, **50**: 6408, copyright (2011).*

High-nuclearity Fe complexes

High nuclearity Fe complexes are interesting in many respects among which understanding the interaction pathways occurring in small clusters that constitute basic elements of larger aggregates is of current interest for molecular and nanomaterials. The X-ray structure of the complex $[Fe_4(\mu_4\text{-}O)(\mu\text{-}OMe)_4(bisi)_4](ClO_4)_2 \bullet 4MeOH$ (Hbisi = N-(benzimidazol-2-yl)salicylaldimine) is depicted in *Figure 8A*. It reveals an original arrangement of four Fe^{III} ions in a slightly ruffled square where they are bridged by four μ2-methoxido anions and a central μ4-oxido anion that gives rise to two magnetic interaction pathways, J_1 and J_2, respectively (inset in *Figure 8B*). The temperature dependence of the magnetic susceptibility was successfully simulated within this coupling scheme with the following values of the exchange constants: $J_1 = -1.4$ cm^{-1}, and $J_2 = -19.2$ cm^{-1} (*Figure 8B*). *Figure 8C* illustrates the Mössbauer spectra recorded at various temperature and applied magnetic fields. They could be simultaneously simulated in the fast relaxation mode assuming a unique S = 0 system (traces a and b) or a symmetric dinuclear system with 5/2 local spins (traces a, b and c) with the following parameters $\delta = 0.515$ mm.s^{-1}, $\Delta E_Q = 1.011$ mm.s^{-1}, $\delta = 0.33$, $x_{fwhm} = 0.28$ mm.s^{-1}, $J_2 = -18.4$ cm^{-1} and $a_{iso} = -20.12$ T. As a consequence, at low temperatures, the tetranuclear cluster can be described as the sum of two identical and symmetric dinuclear high-spin Fe^{III} units that are moderately antiferromagnetically coupled through the μ4-oxido bridge. In addition, each Fe^{III} ion of a pair interacts weakly with the two sites of the second pair through the μ4-oxido-μ-methoxido bridging pattern (collaboration with J. Reedijk, Leiden University, The Netherlands) [29].

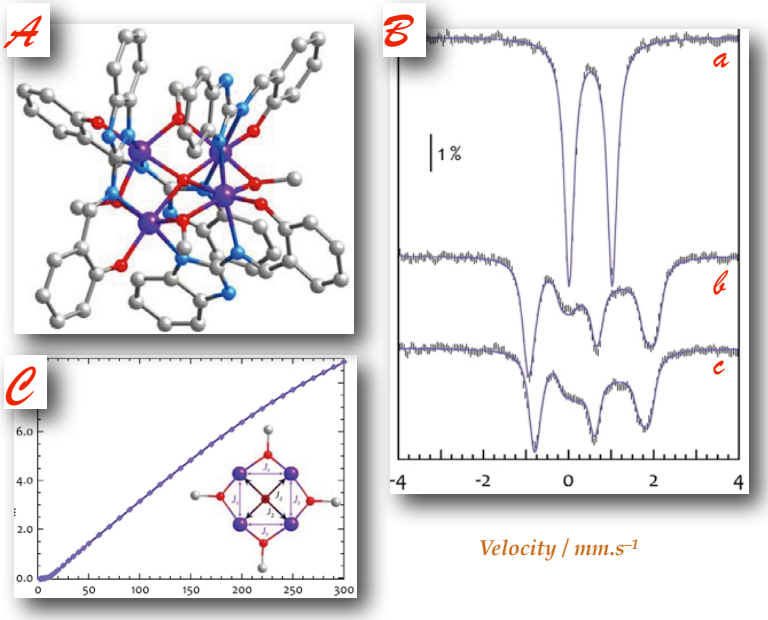


*Figure 8. A. Structural, magnetic (B) and Mössbauer (C) properties of $[Fe_4(\mu_4\text{-}O)(\mu\text{-}OMe)_4(bisi)_4](ClO_4)_2 \bullet 4MeOH$: X-ray structure (A), temperature dependence of the magnetic susceptibility (B) and Mössbauer spectra (C) recorded at zero field and 4.2 K (a), 7 T and 4.2 K (b) and 7 T and 50 K (c). Reprinted by permission from American Chemical Society: Inorganic Chemistry, 2010, **49**: 2427, copyright (2010).*

Conclusion and perspectives

Of course this short overview has not covered all of the activities, past or present, of the platform, and starting from this basis future work will engage deeper in reactivity studies of high-valent intermediates as well as the consideration of more complicated biological systems.

This brief survey has also illustrated how the transmission of expertise from physics to chemistry and biology has been successfully achieved in CEA-Grenoble, since it has allowed Mössbauer activity in Grenoble not only to survive but, after inputs of new people and investments, to progress steadily and engage in worldwide collaborations. Such inputs and investments were necessary to expand on the foundations led by Jean-Louis Oddou who transmitted his knowledge until he retired in 2010.

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Dr. Jérôme Garin

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Pascal Martinez - Pascal.Martinez@cea.fr

Comité de rédaction
Jean-Marc Latour.

Institut de Recherches en Technologies et Sciences pour le Vivant
http://www-dsv.cea.fr/irtsv
http://www-dsv.cea.fr/irtsv/lettres
CEA Grenoble
17 rue des Martyrs
38 054 Grenoble cedex 09
Responsable : Jérôme Garin
Tel. : 04 38 78 45 01
Fax : 04 38 78 51 55