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Review

Molybdenum and tungsten enzymes redox properties – A brief overview

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Dedicated to Professor Armando J.L. Pombeiro for his outstanding achievements in Coordination Chemistry and Catalysis.

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ABSTRACT

Metalloproteins and metal-containing enzymes are well known to be essential to life. Molybdenum and tungsten are the heaviest transition metals used by biology. The mononuclear molybdenum (and tungsten) containing enzymes have in common a particular conserved metal centre (Mo, W) coordinated by one or two pyranopterins. The metal coordination sphere is completed with oxygen and/or sulfur and/or selenium atoms in a diversity of arrangements. The enzymes organized in families (XO, SO and DMSOR) being diverse, can participate in a myriad of reactions involving atom insertion or abstraction and others, with different substrates and partners (physiological or not). The first and second coordination spheres tune the redox properties of the metal centres (and its catalytic features) for a wide range of reactions. In this review, a brief account is given on the main reactions catalysed by this class of enzymes, as well as a representative summary of the redox properties.

Contents

Abbreviations: 4-HBCR, 4-Hydroxybenzoyl-CoA reductase; *A. faecalis*, *Alcaligenes faecalis*; AOR, aldehyde oxidoreductase; Aro, arsenite oxidase; cSO, chicken liver sulfite oxidase; CV, cyclic voltammetry; *D. alaskensis*, *Desulfovibrio alaskensis*; *D. desulfuricans*, *Desulfovibrio desulfuricans*; *D. gigas*, *Desulfovibrio gigas*; DFT, density functional theory; DMSOR, dimethylsulfoxide reductase; DPV, differential pulse voltammetry; *E. coli*, *Escherichia coli*; EPR, Electron paramagnetic resonance; EXAFS, Extended X-Ray Absorption Fine Structure; FDH, formate dehydrogenase; FOR, formaldehyde oxidoreductase; GCE, glassy carbon electrode; HSO, human sulfite oxidase; *M. extorquens AM1*, *Methylobacterium extorquens AM1*; *M. formicium*, *Methanobacterium formicicum*; NaR, nitrate reductase enzymes in general (assimilatory and dissimilatory enzymes, from prokaryotic and eukaryotic organisms); NHE, normal hydrogen electrode reference; *P. pantotrophus*, *Paracoccus pantotrophus*; *P. putida*, *Pseudomonas putida*; *P. furiosus*, *Pyroccocus furiosus*; *R. capsulatus*, *Rhodobacter capsulatus*; *R. spharoids*, *Rhodobacter sphaeroides*; RT, room temperature; *Rs NT-26*, *Rhizobium species strain NT-26*; *S. novella*, *Starkeya novella*; *S. fumaroxidans*, *Syntrophobacter fumaroxidans*; SDH, sulfite dehydrogenase; SO, sulfite oxidase; *T.aromatica*, *Thauera aromatica T. litoralis*, *Thermococcus litoralis*; XO, xanthine oxidase.

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1. Introduction – Metalloenzymes

Bioinorganic Chemistry is a "non-sense name": an organic part, negated by the "in", which is counteracted by the introduction of "bio". It follows from the fact of having been realized that the chemistry of life (traditionally based on the processing of carbon compounds involved in life processes - such as citric acid, lactic acid, acetic acid, etc. - generally the areas of Organic Chemistry) needed inorganic elements. Bioinorganic Chemistry is a specialized field that integrates a wide range of chemicals elements into life, such as sodium, potassium, calcium, magnesium and many metals such as iron, cobalt, nickel and other less known, i.e., molybdenum, tungsten and vanadium, etc., without being exhaustive, the known "transition metal" of the Periodic Table, all having specific roles in metalloproteins/enzymes, modulating its properties and performing diverse functions [1,2].

Primordial biological processes (such as respiration, photosynthesis and nitrogen fixation) depend upon molecules containing inorganic elements. Bioinorganic chemistry associates and bridges inorganic chemistry with biological chemistry (biochemistry) with relevant implications of on electron-transfer proteins, substrate bindings and activation, atom and group transfer chemistry as well as metal properties in biological chemistry. Many fields are covered, namely catalysis, environment, medicine, pharmacology.

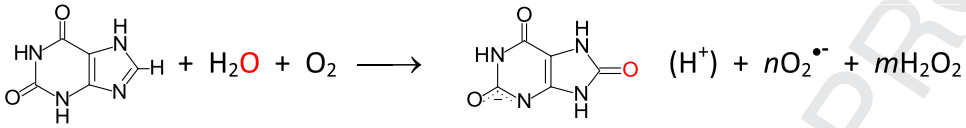
Metal concentration and regulation, transport and incorporation into the different macromolecules sites require highly complex homeostatic control systems that evolved with time, in parallel with the metal availability in the environment [3–8]. Metalloenzymes are highly efficient and selective catalysts that perform several highly puzzling chemical reactions, in mild physiological conditions, and many efforts have been made to mimic its abilities through the synthesis of chemical coordination compounds [9–13] or, more recently, via the synthesis of artificial (metallo)enzymes [14–17].

This review intends to highlight these similarities versus its different properties/functions in the specific case of Mo and W containing enzymes looking in particular to its redox properties.

2. An overview on mononuclear molybdenum (tungsten)-containing enzymes

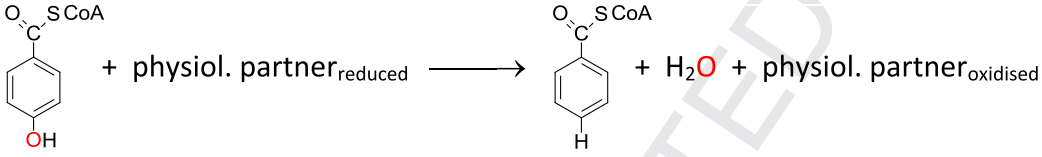
Molybdenum is abundant in seawater and bioavailable. Organisms use molybdenum in the active site of enzymes that catalyse (almost exclusively) oxidation/reduction reactions, where the molybdenum ion cycles between the Mo(VI) and Mo(IV) oxidation states [18–20]. Noteworthy, most of the molybdenum-dependent reactions (so far known) involve the transfer of one oxygen atom to/from a carbon, nitrogen or sulfur atom of key metabolites, as is exemplified by Eq. (1)–(5).

mammalian xanthine oxidase (xanthine hydroxylation to urate):



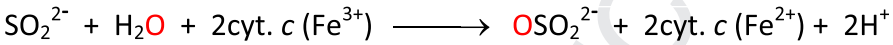
(1)

Bacterial hydroxybenzoyl-CoA reductase (hydroxybenzoyl-CoA dehydroxylation to benzoyl-CoA):



(2)

Vertebrate sulfite oxidase (sulfite oxidation to sulfate):



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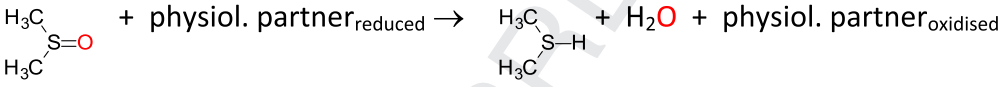
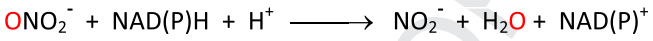
Bacterial dimethylsulfoxide reductase (dimethylsulfoxide reduction to dimethyl sulfide):



(4)

Plant nitrate reductase (nitrate reduction to nitrite):



(5)

With the exception of the iron/molybdenum cofactor of nitrogenase (the enzyme responsible for the fixation of the atmospheric dinitrogen into the "organic" ammonium) (Fig. 1a) [21–30], and a few other heteronuclear centres, whose physiological function is not yet fully understood (Fig. 1b) [11,31–34], molybdenum is found in a mononuclear form, hereafter designated as molybdenum centre (for simplicity). In these centres, molybdenum is coordinated by the *cis*-dithiolene group of one or two pyranopterin cofactor molecules (Fig. 1c) and by oxygen and/or sulfur and/or selenium atoms, in a diversity of dispositions that determines the classification of these molybdoenzymes into three families, denominated after one benchmark enzyme [35]: sulfite oxidase (SO) family (Fig. 1d), xanthine oxidase (XO) family (Fig. 1e) and dimethylsulfoxide reductase (DMSOR) family (Fig. 1f).

Our present knowledge about the mononuclear molybdenum-containing enzymes is impressive. During the last years, structural,

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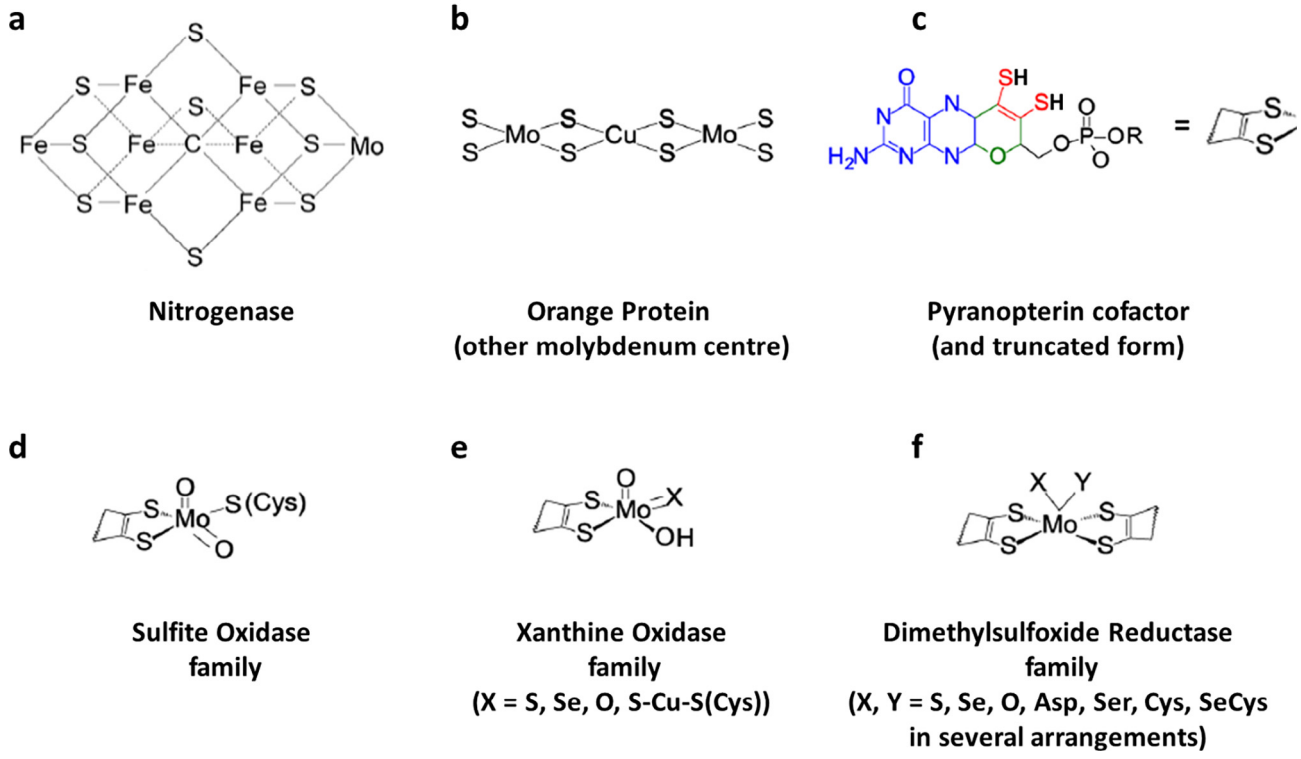

Fig. 1. Scheme with the structures of the active site of molybdenum-containing enzymes: a) nitrogenase, b) centre of the bacterial orange protein, c) pyranopterin cofactor (formed by the pyrano (green) – pterin (blue) – dithiolene (red) –methylphosphate (black) moieties, where the dithiolene (–S–C = C–S–) group (deprotonated) forms a five-membered ene-1,2-dithiolate chelate ring with the molybdenum or tungsten atom (and the truncated form used in the structures of the different families in d), e) and f)), d), e) and f) structures of the molybdenum centres of the three families of mononuclear molybdenum-containing enzymes in the oxidised form (for simplicity, only the *cis*-dithiolene group of the pyranopterin cofactor is represented); e) and f) the tungsten-containing enzymes present similar structures, where Mo is replaced by W. Adapted from [19].

spectroscopic, kinetic, mechanistic and theoretical data on enzymes (completed with the studies of model compounds) have provided an extraordinarily detailed picture of the molybdoenzymes. The key features of the three molybdenum-containing enzymes families are highlighted below. Readers interested in detailed information are referred to recent comprehensive reviews [18–20] or to the references cited for each case.

Although considered, for a while, as an antagonist and inhibitor of Mo-enzymes, tungsten was later recognized as a relevant constituent of different enzymes families.

The tungsten centre is coordinated by the *cis*-dithiolene group of two molecules of the same pyranopterin cofactor found in molybdoenzymes (Fig. 1c) [8,36,37]. The tungsten coordination sphere is also completed with oxygen and/or sulfur and/or selenium atoms in a diversity of arrangements, most often in the same geometry as found in members of the dimethylsulfoxide reductase family of molybdenum enzymes (Fig. 1f).

3. Redox properties of mononuclear Mo (W) containing enzymes

As discussed above, mononuclear molybdo (or tungsten)-containing enzymes harbour a metal site (Fig. 1d-f) coordinated by one or two pyranopterins with structural similarities, but with important differences that enable the catalysis of a wide range of reactions associated to a diversity of substrates. The reactions involve redox chemistry and atom transfer (O, H and S) but also non-redox reactions have been noticed [38]. The metal environment (see below) modulates in a subtle way the reduction potentials of Mo and W sites according to the substrate catalysed reaction. In general, the trigonal prismatic coordination geometry observed in the enzymes contrasts with the octahedral geometry found in model compounds, suggesting that the geometry in the enzymes is influenced not only by the pterin, in the first coordination sphere, but also by the polypeptide chain [39–42]. Small alterations introduced at the metal centre also modulate the reduction potential of the molybdenum (tungsten) site [43–48]. As an example, the highly covalent terminal sulfur atom (Mo = S) in xanthine oxidase or the presence of a thiolate (Mo-S(Cys)) in sulfite oxidase completely control the activity [19,49–54].

In the following, the description of the structural and redox properties (see note 1[1]) of an array of molybdenum (and tungsten) containing enzymes will illustrate how the organisms exploit the versatile redox chemistry of the metal sites.

3.1. Xanthine oxidase family

3.1.1. Xantine oxidases and aldehyde oxidoreductases

The active site of the XO family enzymes (in its oxidised form; Fig. 1e) has the distinctive feature of not having the molybdenum centre directly coordinated to the protein. In addition to the pyranopterin, these enzymes harbour one equatorial catalytically labile –OH group plus one terminal sulfido (Mo = S) or selenido (Mo = Se) group (in almost all enzymes; one remarkable exception is the carbon monoxide dehydrogenase, not discussed in this review) [55]. During the hydroxylation catalysis [19,56], the terminal sulfido (or selenido) group of the oxidised molybdenum centre, Mo^{VI} = S (equatorial), is key to activate the C–H bond to be cleaved, acting as a hydride acceptor, while the equatorial labile oxygen acts as

[1] All the redox potential values here presented are in the normal hydrogen reference (NHE) electrode scale.

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Table 1
Redox transitions and catalytic potentials of molybdenum (and tungsten) centre in mononuclear enzymes. A survey is presented for Mo(W) enzymes for different families and functions.

Family	Enzyme	Organism	Metal	Function	Centre Reduction Potentials/ V	Catalytic Potential/V	Methods	Refs.
XO	AOR	*P. furiosus*	W	Oxidation of aldehydes to carboxylic acids	W(V)/(IV) = +0.18 W(V)/(IV) < -0.500	– –	EPR redox titration, pH 7.5 EXAFS, pH 7	[77] [137]
	AOR	*D. alaskensis NCIMB 13,491*	Mo		Mo(V)/(IV) < −0.4	–	EPR redox titration, pH 7.6	[62]
	AOR	*D. gigas*			Mo(VI/V) = −0.415 Mo(V/IV) = −0.530	–	EPR redox titration, pH 8.5	[60]
					Mo(VI/IV) = −0.530 [not discriminated]	≈−0.5, pH 7.6	Direct CV, pH 7.6, RT	[61]
	FOR	*P. furiosus*	W		W(VI)/(V) < −0.4	−0.53, pH 8	EPR redox titration, pH 7.5	[78]
	FOR	*T. litoralis*			W(VI)/(V) = −0.280 W(V/IV) = −0.335	–	EPR redox titration, pH 8	[79]
	XO	Bovine milk	Mo	Oxidation of hypoxanthine to xanthine and subsequent oxidation to uric acid	Mo(VI/V), Mo(V/IV) = −0.355; Mo(VI/V) = −0.440 Mo(V/IV) = −0.480 (inactivated form)	–	Potentiometric titration, pH 8.2	[70]
					Mo(VI/V) = −0.342 Mo(V/IV) = −0.370	–	EPR and potentiometric titrations, pH 7.7, RT	[69]
					Mo(VI/V) = −0.353 Mo(V/IV) = −0.372	–	Direct DPV, pH 7.2 (immobilized XO)	[71]
					Mo(VI/V), Mo(V/IV) = −0.537 [not discriminated]	−0.119, pH 5, (reduction of nitrate)	Direct CV, pH 7 (immobilized XO)	[73]
	XDH	Bovine milk	Mo		Mo(VI/IV) = −0.395 [not discriminated]	–	Potentiometric titrations, pH 7.5, RT	[68]
	XDH	Chicken liver	Mo		Mo(VI/V) = −0.357 Mo(V/IV) = −0.337	–	Potentiometric titrations, pH 7.8, RT	[134]
	XDH	*R. capsulatus*	Mo	Oxidation of hypoxanthine to xanthine and subsequent oxidation to uric acid	Mo(VI/V) = −0.428 Mo(V/IV) = −0.485; Mo(VI/V) = −0.510 Mo(V/IV) = −0.540	+0.4, pH 8	EPR and potentiometric titrations, pH 8; CV; pH 8, RT (immobilized XDH)	[135]
	XDH	*P. putida*			Mo(VI/V) = −0.360 Mo(V/IV) = −0.300	–	Potentiometric titrations, pH 8, RT	[136]
	4-HBCR	*T. aromatica*	Mo	reductive removal of the hydroxyl group from the aromatic ring yielding benzoylCoA	Mo(VI/V) = −0.380 Mo(V/IV) = −0.500	–	Potentiometric titrations, pH 7, RT	[150]
SO	SDH	*S. novella*	Mo	sulfite oxidation to sulfate	Mo(VI/V) = +0.211 Mo(V/IV) = −0.118	≈+0.2	Redox titration; CV; adsorption on graphite, pH 8	[138;135]
	SDH				Mo(VI/V) = +0.172 Mo(V/IV) = +0.031	≈+0.3	EPR potentiometric titrations; CV; pH 8	[144]
	HSO	Human			Not reported	≈+0.1	CV; modified gold electrodes; RT; pH 8; (immobilized HSO)	[141]
					Mo(VI/V) = +0.042	–	Potentiometry, T = 300K; pH 7.5	[141]
	cSO	Chicken			Mo(VI/V) = +0.131 Mo(V/IV) =−0.086, pH 6 Mo(VI/V) = +0.038 Mo(V/IV) =-0.239, pH 7 Mo(VI/V) = −0.057 Mo(V/IV) =-0.233, pH 9	–	Microcoulometry, potentiometry, EPR; pH 6, 7, 9	[142]
	HSO	Human			Not discriminated	≈+0.150	CV; modified gold electrodes; RT; pH 8.4 (immobilized HSO)	[143]

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DMSOR	NarGHI	*E. coli*	Mo	Nitrate reduction to nitrite	Not observed	0; −0.3 (max)	CV; Adsorption on graphite; pH 7; RT	[105]
	NapA				Mo(V/IV) <−0.400	–	Potentiometric titrations; EPR; pH 8; T = 60K	[99]
	NapA	*D. desulfuricans*			Mo(VI/V), Mo(V/IV) <−0.500	–	Potentiometric titrations; EPR; pH 8; T = 60K	[86]
					–	−0.1	CV; immobilization on graphite; pH 7; RT	[107]
	NapAB	*R. sphaeroids*			Not observed	0; −0.2 (max)	CV; Adsorption on graphite, pH 7 to 9; RT	[145]
	NapA				Mo(VI/V) > +0.200 Mo(V/IV) < −0.200	–	Potentiometric and EPR titrations; pH 7.5; RT and T = 15K	[100]
	NapAB				Mo(VI/V) > +0.200 Mo(V/IV) < −0.200	–		
	NapA				Mo(V/IV) = −0.210	0; ≈−0.2 (max)	CV; Adsorption on graphite; Potentiometric titrations; pH 6; RT	[85]
	NapAB				Mo(V/IV) = −0.225	0; −0.15 (max)		
	NapAB	*P. pantotrophus*			Not observed	−0.09	CV; Adsorption on graphite; pH 6; RT	[106]
	NarB	*Synechococcus* sp. *PCC 7942*			Mo(VI/V) = −0.150 Mo(V/IV) < −0.500	−0.2	Potentiometric and EPR titrations; pH 8; T = 10K; CV; Adsorption on graphite; pH 8; RT	[101]
	FDH-H	*E. coli*	Mo	Formate oxidation to carbon dioxide (reversible reaction)	Not observed	−0.4	CV; protein immobilised on graphite, pH 6.8	[128]
	FDH	*D. desulfuricans*			Mo(V/IV) = −0.160	–	EPR potentiometric titrations; pH 7.6; CV; immobilized enzyme; graphite electrode, pH 7.6; RT	[87]; Cordas unpublished results
					Mo(V/IV) = −0.330 Mo(VI/V) = −0.161 Mo(V/IV) = −0.272	−0.2		
	FDH	*M. formicicum*			Mo(VI/V) = −0.319 Mo(V/IV) = −0.321 [inactivated] Mo(VI/V) = −0.330 Mo(V/IV) = −0.470	–	EPR potentiometric titrations; pH 7.7	[119;121]
	*FDH1	*S. fumaroxidans*	W		Not observed	−0.4	CV; immobilised on graphite, pH 7.8; RT	[113]
	*MeFDH1	*M. extorquens* AM1			Undefined	−0.4	CV; immobilized on modified GCE; pH 6.6; RT	[114]
	DMSOR	*R. sphaeriods*	Mo	Dimethylsulfoxide reduction to dimethylsulfide	Mo(VI/V) = +0.144 Mo(V/IV) = +0.160	–	Potentiometric titrations; pH 7.5; RT	[146]
					Mo(VI/V) = +0.037 Mo(V/IV) = +0.087		Potentiometric titrations; pH 8.5; RT	147
		R. capsulatus			Mo(VI/V) = +0.161 Mo(V/IV) = −0.102	−0.05	Spectroelectrochemistry; pH 8; RT	[160]
		R. sphaeriods	W		Mo(VI/V) = −0.194 Mo(V/IV) = −0.134	–	Potentiometric titrations; ERP; pH 7; T = 44K	[163]
	Aro	*Rs NT-26*	Mo	Arsenite oxidation to arsenate	Not observed	+0.3 to +0.6	CV; immobilized on modified graphite; pH 6; RT	[169]
					Not observed	≈+0.3, mediated by cyt c_{552}	CV; immobilized on modified gold; pH 6; RT	[148]
					Not observed	+0.370	CV; immobilized on graphite; pH 5.6	[149]
		A. faecalis			Mo(VI/IV) = +0.292 [not discriminated]	+0.2 to +0.6, pH 7	CV; immobilized on modified graphite; pH 6; T = 273K	[168]

Notes: Reduction potentials are related to the Normal Hydrogen Electrode.
*Recently the DMSOR W-containing enzymes have been recognised as a separated family (the W-enzymes family).

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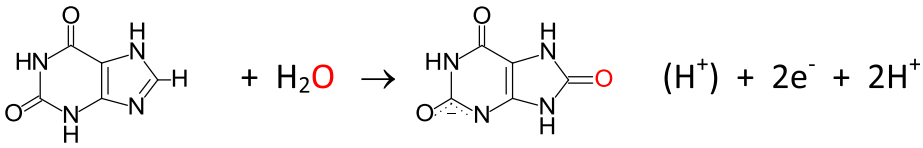
the direct oxygen donor. Water is the ultimate source of the oxygen atom incorporated into the hydroxylated product (Eq. (6)) and the molybdenum ion is re-oxidised via electron transfer from the physiological partner (i.e., the physiological partner acts only as the oxidising substrate and is not the oxygen source).



$$+ H_2O \rightarrow (H^+) + 2e^- + 2H^+ \quad (6)$$

The aldehyde oxidoreductase isolated from *Desulfovibrio gigas* (*D. gigas*) (*Dg*AOR-Mo) was the first protein member of the XO family whose crystal structure was solved [57]. This enzyme is involved in an electron transfer chain, together with flavodoxin, cytochrome c_3 and hydrogenase, allowing the oxidation of aldehydes (see note 2a[12]) and subsequent electron transfer towards hydrogenase, with concomitant reduction of protons and consequent hydrogen production. This chain has been reproduced *in vitro* [58] and, recently, used for the construction of an enzymatic multilayer fuel cell [59]. The Mo centre reduction potentials were first determined by EPR potentiometric titrations, with estimated values of −0.415 and −0.530 V for Mo(VI/V) and Mo(V/IV), respectively [60], and more recently, by direct electrochemistry (only observed on gold electrodes), a value of −0.530 V for Mo(VI/IV) was determined (without discriminating the two redox steps) [61]. The values for AOR-Mo isolated from *Desulfovibrio alaskensis* (*D. alaskensis*) could not be accurately determined (a range between −0.334 and −0.450 V was found for Mo(V) species), but using an approach by homology with *Dg*AOR-Mo, the redox couples transitions were considered to be comprise below −0.400 V [62], in agreement with the values found for *Dg*AOR-Mo [60].

*Dg*AOR-Mo crystal structure was used, for several years, as model for the xanthine oxidase enzyme with success, in particular for inferring the reaction mechanisms, until structures were solved for XDH and XO (see note 2b) forms of bovine milk, in 2000 [63] and later, in 2006 for the human enzymes [64,65]. Several crystal structures were since then been solved for enzymes from different sources (bacteria and mammals) [65,66].

The redox properties of XO (and XDH form) have been extensively studied (starting around the 1920 s and still ongoing) [68–72], including the redox properties of Mo (presented in Table 1) and Fe/S centres and flavin. The xanthine oxidase enzymes metal site present a similar range of reduction potentials for Mo(VI/V) and Mo(V/IV) as detected for the *Dg*AOR-Mo enzyme, between −0.342 and −0.537 V [69-71,73], for both Mo redox transitions.

The determination of the redox potentials has been key for establishing the intramolecular electron transfer within the four redox centres, the equilibrium between the redox species, and crucial for understand mode of function and kinetic models [69,74]. A similar model was also used by for the determination of the redox potentials of Mo-AOR from *D. alaskensis* [62].

Inhibition of the XO, AOR enzymes by cyanide (with the release of the S atom as thiocyanate) originates oxido coordinated species, desulfido inactive) that depict more negative potentials (the so-called EPR Mo(V) slow signals), in agreement with the lack of activity [70,75,76].

A similar enzyme containing W (AOR-W), isolated from *Pyrococcus furiosus* (*P. furiosus*), presents a higher formal potential of +0.180 V for the W(V/IV) couple upon oxidative redox titration [77]. The formal redox potentials for another AOR-W, isolated from *P. furiosus*, designated as formaldehyde oxidoreductase – FOR, since is highly specific towards the oxidation of formaldehyde to formic acid, could not be accurately determined by EPR redox titrations, but a low value of −0.400 V was suggested for both W redox couples [78]. For another enzyme with high sequence homology and similar structural features with this last one, *Tl*FOR-W, isolated from *Thermococcus litoralis* (*T. litoralis*), the reduction potential values obtained were −0.280 and −0.335 V, [W(VI/V) and W(V/IV) respectively] [79], as determined in the presence of formate. These studies highlights the fact that the redox potentials found are different when dithionite or the substrate (formaldehyde) are used, being the first a slow reducer and the second a very fast reducer [78].

Recently, the catalytic reduction of nitrate [73] and nitrite [80,81] by a wide range of mononuclear Mo-enzymes (including enzymes from XO family and others) has been studied revealing other roles of this enzyme, such as nitrate reductases [73] and "non" dedicated nitrite reductases [81–83]. Instead of the usual O insertion reaction, the site acquires the catalytic performance of O-atom abstraction, using the most reduced states of the Mo site. The redox chemistry is open to be explored in terms of these new reactions, but a catalytic current at −0.12 V was already found for the reduction of nitrate by bovine milk XO [73].

3.2. DMSO reductase family

DMSOR family includes a large diversity, of prokaryotic enzymes, such as the prototype DMSOR (Eq. (4)) [84], three different types of nitrate reductase (Nar) enzymes (dissimilatory membrane-bound enzymes, dissimilatory periplasmic enzymes and assimilatory cytoplasmic enzymes (see note 3[23]), Eq. (7) [85,86], formate dehydrogenase (FDH; Eq. (8)) [87,88], arsenite oxidase (Aro) (eq. (9)) [89,90], acetylene hydratase (eq. (10)) [38] and others [91]. Noteworthy, these enzymes catalyse remarkably different reactions, including oxygen atom transfer, hydrogen atom transfer, sulfur atom transfer and even hydration reactions (non redox).

$$ONO_2^- + \text{physiol. partner}_{reduced} \longrightarrow NO_2^- + H_2O + \text{physiol. partner}_{oxidised} \quad (7)$$

$$HCOO^- + \text{physiol. partner}_{oxidised} \longrightarrow CO_2 + \text{physiol. partner}_{reduced} \quad (8)$$

$$AsO_3^{3-} + H_2O + \text{physiol. partner}_{oxidised} \longrightarrow OAsO_3^{3-} + \text{physiol. partner}_{reduced} \quad (9)$$

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$$H\text{-}C{\equiv}C\text{-}H + H_2O \rightarrow H_3C\text{-}COH \quad (10)$$

The enzymes in this family are characterised by having molybdenum coordinated by two pyranopterin cofactors; the molybdenum coordination sphere is completed by an oxygen and/or sulfur and/or selenium atoms in a diversity of combinations, and including not only cysteine, but also selenidocysteine, aspartate and serine residues (in its oxidised form; Fig. 1f) [19]. In addition, and similar to the enzymes of the XO and SO families, the active site of these enzymes can also have terminal sulfido and oxido groups, whose presence is well correlated with the catalytic mechanism(s).

3.2.1. Nitrate reductases

The nitrate reduction proceeds at a quite positive redox potential: [92]

$$NO_3^- + 2e^- + 2H^+ \rightarrow NO_2^- + H_2O[E^o(NO_3^-/NO_2^-) = +0.420V] \quad (11)$$

There are three types of Nar enzymes (i) membrane-bound cytoplasm-faced respiratory Nar, involved in the generation of proton gradients across the cytoplasmic membrane, ii) periplasmic Nar (Nap) involved in generation of a proton motif-force or acting as electron sink to eliminate excess of reducing equivalents and iii) cytoplasmic assimilatory Nar involved in nitrogen assimilation) that catalyse the two-electron reduction of nitrate to nitrite (Eq. (7)). All contain a Mo centre coordinated by four sulfur atoms from two pyranopterin cofactor molecules (in the form of the guanine dinucleotide) and display significant differences in the other ligands that participate in the molybdenum coordination sphere. They are also different in subunit composition and cofactors content [19]. In the respiratory membrane-bound NaR, the molybdenum atom is further coordinated by an aspartate residue in bidentate or monodentate mode [93,94], in this case with one additional terminal oxido group. In the periplasmic Nar (also known as Nap) from *Desulfovibrio desulfuricans (D. desulfuricans)* (the first 3D structure determined for a Nar [95]) or *Cupriavidus necator (C. necator)*, the molybdenum atom is coordinated by a cysteine sulfur atom and one terminal sulfido group, establishing a partial disulfide bond [95–98]. The *E. coli* and *Rhodobacter sphaeroides (R. sphaeroides)* periplasmic Nar are yet different and molybdenum coordination contains a cysteine sulfur atom together with a terminal hydroxyl group [99,100]. Less is known about the cytoplasmic assimilatory Nar but a cysteine residue is suggested to be coordinated [101].

The periplasmic Nars (Naps) require an activation step, suggested to occur before catalysis can be initiated: it was proposed that the coordinating cysteine residue dissociates from the molybdenum atom to become bound to the terminal sulfido group, giving rise to a new, reduced, Mo-S-S(Cys) centre [102–104]. As a result of this "sulfur shift", the molybdenum centre has an available coordination site similar to the eukaryotic Nars and the nitrate reduction reaction can proceed and the substrate binds directly to the metal (Fig. 2b).

Although Nars have different global structures (subunit and metal clusters composition) they present similar active sites and catalytic reduction potentials/properties. For instance, NapAB isolated from *R. sphaeroids*, has two subunits, bearing the bis-pyranopterin coordinated to Mo and a [4Fe-4S] cluster in the larger subunit (NapA) and two heme *c* in the smaller subunit (NapB), starts to develop catalytic currents close to 0 V, while NarGHI from *Escherichia coli (E. coli)*, with three subunits, bearing similar Mo-coordinated bis-pyranopterin and a [4Fe-4S] cluster (NarG), a [3Fe-4S] and three [4Fe-4S] clusters (NarH) and two hemes b centres (NarI), also develops catalytic currents close to 0 V [85,105]. NapAB from *Paracoccus pantotrophus* (*P. pantotrophus*), holding a similar Mo catalytic site on its NapA subunit, present catalytic currents at −0.09 V [106]. Also, *D. desulfuricans* Nap (*Dd*Nap) catalysis occurs at −0.100 V [107]; all studies used similar methodologies (adsorbed protein on graphite electrodes and cyclic voltammetry measurements). In spite of the different Nars structures and roles, they maintain the catalytic Mo site conserved, and, as so, it is not strange that these enzymes present similar catalytic potential values, independently of the electronic pathway (with more or less metal clusters). Studies on *R. sphaeroides* NapA, NapAB and related mutants, using site-directed mutagenesis, EPR and protein film voltammetry, have shown that an "irreversible reductive activation" is necessary, in order to force these enzymes to be catalytically competent. This step was initially assigned to a catalytic centre reaction, necessary to overcome a dead-end inactive Mo (V) state [85]. This is in accordance with the mechanism previously discussed, which seem common to all nitrate reductases. Density functional theory (DFT) studies also supported the need of a reductive step for attaining a fully active catalytic centre seconding the hypothesis of ligand rearrangements in the second coordination sphere [108,109].

In spite of the catalytic overall potential values that are maintained, site-directed mutagenesis studies performed on *E. coli* NarGHI have pointed for the importance of the pyranopterin coordination and surroundings. Mutants with different pyranopterin-coordinating amino acid, and residues involved in bridging the proximal and distal pyranopterins, resulted in variations of the reduction potentials for the Mo(VI/V) and Mo(V/IV) couples. Results revealed that residues interacting with the oxygen of the distal pyranopterin have some modulation effect on the redox couples of the centre overall reduction reaction of Mo(VI/IV), diminishing the differences between the reduction values of Mo(VI/V) and Mo(V/IV) (in −0.088 and −0.036 V). Changes in residues neighbouring the pyranopterin and stabilizing the oxidation state of the proximal pyranopterin (changing His with Ala), have larger effects, with a more pronounced decrease in the overall potential difference between the centres (−0.143 and −0.101 V) and the stabilization of the non-active Mo(V) state. In this case, histidine residues in the vicinity of the pyran ring in its opening/-closed form and consequent oxygen protonation affect the charge density distribution, reinforcing the importance of the pyranopterin environment (again including the second coordination sphere) in the modulation of the Mo centre redox properties [110].

3.2.2. Formate dehydrogenases

Formate dehydrogenase (FDH), a member of the DMSOR family, catalyses the reversible transfer of a hydrogen atom (Eqs. (8) and (12)) and its active site harbours a terminal sulfido group (Mo = S), as the XO family enzymes, and one coordinating S atom from a cysteine (or selenidocysteine) side chain [19,111]. As is observed in XO catalysis the terminal sulfido group of the FDH oxidised molybdenum centre, Mo^{VI} = S, acts as hydride acceptor, while the reduced centre, Mo^{IV}-SH, acts as hydride donor (Fig. 2c), making possible the reversibility of the reaction [112–114 115].

$$CO_2 + 2\bar{e} + H^+ \leftrightharpoons HCOO^- [Eo(CO2/HCOO-) = -0.430V] \quad (12)$$

Formate dehydrogenases are also complex and show diverse subunit and cofactor composition [19,111]. The active site of FDH has a remarkable similarity with Nar. However, the operating mechanism is indicated to be quite different [19] (Fig. 2). The formate oxidation and carbon dioxide reduction were proposed to proceed through hydride transfer and the sulfido group of the oxidized and reduced molybdenum center, Mo^{VI}-S and Mo^{IV}-SH, are suggested to be the direct hydride acceptor and donor, respectively (Fig. 2c).

Tungsten has a relevant role in FDHs, but not exclusive. Formate dehydrogenase can be divided into two classes: metal-

independent or metal dependent (W or Mo, less frequent) [111,116,117]. As mentioned, these enzymes catalyse the formate oxidation to carbon dioxide, a reaction with standard reduction potential of −0.43 V (calculated from the free energy of formation in standard conditions) [115], and which is a physiologically important reaction since it is involved in C1 metabolism and in energy production (coupled with the reduction of electron acceptors) [81]. Although its structures present high diversity, metal-dependent FDHs possess the well-conserved bis-pyranopterin (either coordinated to W or Mo), with very similar behaviour but different potentials. Nowadays it is apparent that the known tungstoenzymes find homologous molybdoenzymes, either in the same or in different organisms [118]. The chemical similarities between tungsten and molybdenum make both metals coordinated by the same cofactor molecule, in the mononuclear enzymes.

Mo-containing FDH isolated from *D. desulfuricans* (*Dd*FDH-Mo) is composed by three subunits that contain the cofactors: α (Mo (bis-pyranoptein) and a [4Fe-4S] cluster), β (one [4Fe-4S]) and γ (four *c* type hemes). The redox potentials of the Mo couples (VI/V) and (V/IV) were obtained by EPR potentiometric titrations, with values of −0.160 and −0.330 V, respectively (pH 7.6, T = 4 K) [87]. *Dd*FDH-Mo reduction potentials were also obtained recently (our unpublished results, submitted), by direct electrochemistry (without the use of mediators) with the protein immobilised on graphite, pH 7.6, at room temperature, to be −0.171 V and −0.262 V for Mo(VI/V) and Mo(V/IV), respectively. Besides the formate oxidation, it was shown that this enzyme has high activity (k_{cat} = 46.6 s^{-1}) towards the reverse reaction, the CO_2 reduction to formate [112]. The catalysis both for formate oxidation (anodic currents) as for the CO_2 reduction (cathodic currents) is observed at the potential value −0.2 V (unpublished results, submitted).

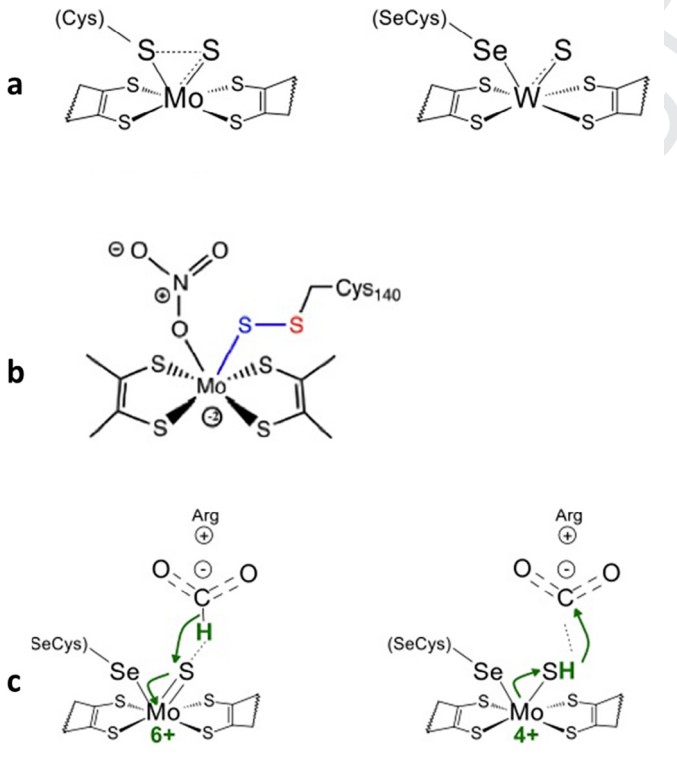

Fig. 2. Nitrate reductase and formate dehydrogenase – structures and mechanisms: a) comparison between nitrate reductase and formate dehydrogenase metal centres, b) reaction of nitrate with Mo centre in nitrate reductase (in evidence the "sulfur shift" and the direct binding of the substrate to the metal in the first coordination sphere), c) formate reduction and CO_2 oxidation at the metal site in FDH (in evidence the hydrogen transfer reaction and interaction of the substrate in the second coordination sphere). Adapted with permission from [19,102,111].

The redox potentials determined by EPR potentiometric titrations (at T = 15 and 100 K, pH 7.7) for the cytoplasmic Mo-containing FDH, isolated from *Methanobacterium formicicum* (*M. formicium*), *Mf*FDH-Mo were −0.319 V and −0.321 V (for Mo(VI)/Mo(V) and Mo(V)/Mo(IV) couples, see Table 1) [119–121]. Two more examples can be added to the discussion. W-containing FDH from *Syntrophobacter fumaroxidans* (*S. fumaroxidans*) is an interesting example. This organism possesses six FDHs (the most abundant are FDH1, cytoplasmic, and FDH2, periplasmic), which in addition of catalysing the formate oxidation reaction, is capable of CO_2 reduction. *Sf*FDH1-W is apparently a heterodimer (αβγ) with the W-centre located in the α subunit. The other subunits holds at least 2 [2Fe-2S] centres [122–124], maybe more [113]. Although there are no reports on the individual redox potentials of centres, including the W transitions, it was observed that both the catalytic formate oxidation, as well as the CO_2 reduction, starts at the same potential, namely −0.4 V (protein immobilised on graphite, pH 7.8), a lower value than the one found for the *Dd*FDH-Mo, in agreement with the lower potential values associated with W compared with Mo. The highest activity towards the CO_2 reduction, k_{cat} = 112 s^{-1}, was achieved upon a potential imposition of −0.8 V (pH 5.9) [113]. Both *Dd*FDH-Mo (data not published, submitted) and *Sf*FDH1-W present similar electrochemical behaviour in catalytic conditions, with a loss of activity after the first cycle. In addition, the cytoplasmic W-containing FDH isolated from *Methylobacterium extorquens* AM1 (*M. extorquens*) (*Me*FDH1-W), a NAD^+-dependent, is an heterodimer, holding the W-pyranopterin in the α subunit and a [4Fe4S] cluster in the β subunit [125], also shows the ability to perform the reverse catalytic reaction (CO_2 reduction). The direct electrochemistry of *Me*FDH1-W was achieved on a complex modified mesoporous Ketjen Black glassy carbon electrode (with pyridine terminated groups on gold nanoparticles). The potential values for the individual redox centres (including the W) were not discriminated but the direct potentials for the formate oxidation and CO_2 reduction were attained. As in the previous cases, the potential values where both catalytic processes start are coincident and are observed around −0.4 V (pH 6.6) [114]. The more negative reduction potentials and catalytic potentials associated to W-containing enzymes seem, however, to have some exceptions in the FDH enzymes, such as the *E. coli* formate dehydrogenase-H (*Ec*FDH-H). *Ec*FDH-H is a Mo-containing FDH with only one α unit, holding the Mo centre and a [4Fe-4S] cluster [126,127], that besides formate oxidation has activity towards CO_2 reduction, although much lower (k_{cat} < 1 s^{-1}) than the previous described. No redox potentials were reported for the Mo transitions, but the catalysis is observed, both for formate oxidation as for CO_2 reduction, at potential values of −0.4 V (protein immobilised on graphite, pH 6.8), similarly to the W-containing FDH [128], such as *Me*FDH1-W. These results, however, must be compared with some caution since experimental conditions may influence the observations made, namely, techniques and conditions such as, temperature, pH, amongst others. Some more examples and details are presented in Table 1.

The reduction potentials of the chemical reactions catalysed by the several tungstenoenzymes, such as W-benzoyl-CoA reductase, W-AOR/carboxylic acid reductase, W-*N*-formylmethanofuran dehydrogenase and W-FDHs have quite negative values of −0.622 V, −0.580 V, −0.500 V and −0.430 V, respectively [92,115,129]. The fact that W-Nar has not been isolated so far (the nitrate reduction occurs at +0.420 V) gave support to the hypothesis that W is better tuned to reactions that proceed at more negative potentials. So, molybdenum would be a good choice for reactions with higher reduction potentials, under either anaerobic or aerobic conditions, but not at extreme temperatures [36,118,130–133]. This is a general comment with some exceptions.

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4. Summary

As mentioned throughout the text, the pyranopterin moiety has a key role in the properties of the metal site in the group of mononuclear molybdenum (tungsten) enzymes with different roles: coordination; stabilization and modulation of the redox transitions of the centre, acting as a "redox buffer"; and for redox adjustment/match in a diversity of catalytic reactions. Table 1 select representative examples of the redox properties of the metal centres for each of the families XO [60–62,68–71,73,77-79,134–137], SO [135,138–144] and DMSOR [85–87,105,113,114,119,121,125,128,145–149] bearing the Mo- or W-pyranopterin moiety. The analysis of the data collected enables to extract some trends on the reduction and catalytic potentials observed for the enzymes of the different families. The XO family present, in general, redox potentials between −0.5 and −0.3 V for the couples Mo(V/IV) and Mo(VI/V) (or the correspondent W), respectively. Within this family, the catalysis is observed around potential values of −0.5 V, for AOR and FOR. Also, 4-Hydroxybenzoyl-CoA reductase (4-HBCR) isolated from *Thauera aromatic* (*T. aromatic*), presents values of −0.380 and −0.500 V for the same couples [150]. Related with 4-HBCR are the enzymes benzoyl-coenzyme A (benzoyl-CoA) reductases (BCRs) involved in the next step of the benzene ring reduction [151]. The class II BCR, discovered in *Geobacter metallireducens* (*G. metallireducens*), is part of a larger complex, containing an active tungstopterin cofactor (together with FeS clusters), and remarkably presents very low potential values for the catalytic reduction reaction of benzoyl-CoA/dienoyl-CoA) at −0.622 V [152,153]. Some exceptions were found, namely for *Pf*AOR-W, in a 1996 study [77], where only the redox potential of the W(V)/(IV) was determined with the value of +0.18 V, and in 2003 [154] when the catalytic activity of XDH, isolated from *R. capsulatus*, was observed at the potential value of +0.4 V, although the Mo couples redox potentials were assigned at values within the generally observed range (approximately from −0.4 to −0.5 V) [155–157]. The catalysis of the XO secondary function of nitrate reduction is observed around −0.12 V, but the redox centres (redox transitions not discriminated) were observed at −0.537 V [73] (Table 1).

The SO family present reduction potential values for the Mo transitions between +0.2 and −0.2 V and the catalytic activity (see note 4[4]) was observed between + 0.1 and + 0.3 V [142]).

Within the DMSOR family, FDH enzymes depict catalytic centre redox transitions between −0.47 and −0.16 V and catalysis between −0.4 and −0.2 V (more negative, in general for W-containing enzymes, as discussed earlier). In the case of Nar (and Nap) enzymes, the available data is scarce, although a few reports indicate redox transitions occurring around −0.2 V (still some dispersion on the results is found in the literature) and the catalytic activity is observed between 0 and −0.3 V (this last value corresponding to maximum catalytic activity) [85,105,106,145].

The dimethylsulfoxide reductase enzyme catalyses the reduction of dimethylsulfoxide to dimethylsulfide, according to Eqs. (4) and (13). [159]

$$(CH_3)_2SO + 2\bar{e} + 2H^+ \rightleftharpoons (CH_3)_2S + H_2O [E^o (CH_3)_2SO/(CH_3)_2S) = +0.160V] \quad (13)$$

The Mo redox transitions are reported in the range +0.161 and −0.102, for Mo(VI/V) and Mo(V/IV), and the catalytic activity was observed around −0.05 V [160]. Mo was successfully substituted by W with the redox transitions being found at more negative potential values, as expected (−0.194 V and −0.134 V for W(VI)/W and W(V/IV), respectively) [161–163].

So, in general terms, it is observed that enzymes of the DMSOR family present reduction potential values (for the metal redox transitions) between −0.4 and +0.2 V and catalytic potentials between −0.4 and 0 V, independently of the methodologies and even experimental conditions, such as T, media and pH. Also, the redox transitions of the metal centres are not associated with meaningful conformational changes (due to solvent exposition and reorganization energies, amongst other factors), as reported in the literature for hemic and non-hemic proteins, such as c-type cytochromes, myoglobin, superoxide reductase, among other examples [164–167].

An exception is observed for arsenite oxidase, where the Mo transitions were detected (not discriminated) at the potential value of +0.292 V [168] and the catalytic activity between +0.3 and +0.6 V [148,149,168,169], which is coherent with the standard reduction potential (pH 0, T = 21 °C) of +0.557 V for the reaction H_3AsO_4/H_3AsO_3 [170]. It should be noted, however, that outside standard conditions, the expected values for this redox couple are considerably lower, for instance for pH 6 the value is approximately +0.150 V [171].

Theoretical studies indicate that when the metal is in the bis-pyranopterin coordination environment, independently of the ligands, oxido or sulfido, all the catalytic reactions occur at negative (favourable) free energies, with negative reduction potentials; the enzymes from the DMSOR family, bearing two oxygen ligands, present higher oxidising power.

The calculated reduction potentials for model compounds of the Mo(VI)/Mo(IV) couple are negative for the SO and XO families and positive for the DMSOR family, which indicate that the oxidised state is more favourable for the first group, whereas in the second the reduced state is stabilized, in agreement with the proposed mechanisms, which is assumed as a strategy for the regeneration of the initial "ready-state" catalytic site [172]. Studies with model compounds revealed that oxido transfer processes from substrate to metal are faster with W sites and faster from substrate to the metal for Mo sites, showing that the metal has a direct effect on the catalytic kinetics [39].

The reaction mechanisms of XO, SO or DMSOR are presently well understood but the tungstoenzymes were less studied, although progressing. A vast majority of organisms use molybdenum and less tungsten, maybe due to bioavailability as well as metal specific properties. In particular, tungsten seems better adjusted for low reduction potential reactions carried out anaerobically at higher temperatures (not exclusive). Nowadays it is understood that the known tungstoenzymes find homologous molybdoenzymes, either in the same or in different organisms [118]. The chemical similarities between tungsten and molybdenum make both metals coordinated by the same cofactor molecule, in the mononuclear enzymes.

Pyrobaculum aerophilum (*P. aerophilum*) Nar can incorporate and be active with tungsten, when grown in the absence of molybdenum (although in the presence of both metals, the enzyme was reported to contain mostly molybdenum) [173,174]. A tungsten-containing form of the *E. coli* trimethylamine N-oxide reductase (that catalyses a reaction with a reduction potential of +0.130 V) is formed when this metal is more available in the medium [175]. Sulfate reducer bacterium *D. alaskensis* expresses both tungsten- and molybdenum-containing FDH and one molybdenum-containing AOR, and when grown in nitrate as respiratory substrate, also a Mo-Nar is expressed. As shown, molybdoenzymes are also able to catalyse reactions with low reduction potential values (namely the carboxylic acid/aldehyde reaction [176]). FDH enzymes from *D. vulgaris*, are active with either molybdenum or tungsten. W-substituted forms of Mo-containing *R. capsulatus* dimethylsulfoxide reductase (DMSOR) [162] and *E. coli* trimethylamine N-oxide (TMAOR) reductase are

[4] The couple (SO_4^{-2}/SO_3^{2-}) standard reduction potential is −0.220 V [158]

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also active [175]. While it has been observed that when W replaces Mo a decrease in activity is observed, such as in *E. coli* TMAOR or DMSOR isolated from *R. capsulatus* [163,177,178], the natural occurring W-containing enzymes present high activities for specific catalytic reactions, such as formate dehydrogenases [118] (see Table 1).

Computational studies (by density functional theory - DFT methods) on model complexes for dissimilatory and assimilatory Nar indicate that, besides the metal (Mo, W), the type and the number of ligands control the reaction steps along the nitrate reduction pathway. The differences between enzymes that contain mononuclear Mo versus a W in the catalytic centre were evidenced by DFT methods applied to prokaryote nitrate reductases (belonging to DMSOR family) models, showing that the reaction energies for the nitrate reduction were more favourable in compounds containing W than Mo. The same studies also show that oxido ligands stabilize high formal oxidation states and dithiolene ligands are not advantageous for oxygen and electron transfer reactions but, on the other way, they facilitate the regeneration of the "ready" Mo(IV) catalytic site [179].

These trends agree with studies performed by spectroscopic and computational methods on the role of dithiolene ligands in the stabilization of the metal centres in their different oxidation states – "redox buffer" effect [180].

Recent studies with model compounds also suggested that the pyranopterin–dithiolene assembly is responsible for small modulations in the Mo electronic density, via modifications in the second coordination sphere (based on experiments with compounds where pyranopterin has its "ring closed" or "open"), and conformational changes (planar or distorted angles) tuning the Mo redox properties and the enzyme catalytic potential, suggesting that specific conformations are associated with different enzyme families and function [181,182]. The "adaptability" of the molybdopterin also depends on the specificity of the enzyme versus the substrate, the overall protein structure and, in particular, the environment surrounding the catalytic centre, such as hydrogen bonds, salt bridges or possible protonation processes [183,184]. It is, indeed, a remarkable capability of the molybdopterin centres to maintain the right oxidising power and redox properties allowing that different global protein structures can catalyse the same reactions with very similar reduction potentials.

5. Conclusions and insights for future work

In this review we analysed a very specific active site composed by one Mo atom (or W) coordinated to one or two organic cofactors (pyranopterin) that yield a rich sulfur environment on the metal site. Although still under discussion, it has been accepted that pyranopterin(s) act as non-innocent ligands accepting and distributing/delocalizing charge density [110,180–182,185,186], promoting higher oxidation states of the molybdopterin and of the overall catalytic centre, acting as a "redox buffer".

The redox potentials at which electrons are given or received by a metal site in an enzyme is a complex issue that is modulated by multiple parameters: metal, coordinating atoms (first sphere), protein environment (second sphere), other distal atoms, hydrophobicity, accessibility and exposure to solvent, etc [19,187]. A lot of attention has been given to the role of the pyranopterin. Its influence has been detailed studied and model compounds for Mo and W-containing centres have been synthetized, although modelling mononuclear sites has been revealed not to be simple, due to propensity for the polymerization [187–189]. However, when the right experimental conditions are met, including the ligand choice, it is possible to achieve mononuclear centres [11], that can mimic the natural occurring centres and unveil trends for the redox potentials and reactivity [181,190–193]. Another interesting approach is the use of artificial enzymes, a close approach to the enzyme systems, leading to a better understanding of the protein properties, in terms of redox transitions and atom transfer capabilities [194]. Successful substitution by Mo of the native Fe in rubredoxin containing a rich sulfur environment given by four cysteines provides a matrix for centre rearrangement with increase of the coordination number by addition of oxygenated species, water and thiols. Several of the attained models can replicate redox properties and even atoms transfer (like oxygen) partially mimicking the catalytic properties of mononuclear enzymes [17,189,192,195,196]. This is a wide-open route to expand our knowledge of the metal containing enzymes and simultaneously find novel and more efficient applications.

The −0.4 to 0 V catalytic potentials found in general (DMSOR family) indicate a fine tuning of the molybdopterin containing enzymes adapted to the specific reaction and substrate, functioning like a "redox buffer".

In Fig. 3, a graphical representation was made for the span of the redox potentials of the several families of mononuclear Mo (W) enzymes. Also, in the same figure the substrate reduction potentials are indicated, as well as, the average value of the catalytic potentials for the different substrates.

This has some analogy with the electrochemical behaviour of other type of metalloproteins, namely iron-sulfur (FeS) proteins, such as ferredoxins and high-potential iron-sulfur proteins (HiPIPs), where the FeS moiety (and the environment of the residues' hydrophobic pocket in case of HiPIPs) confers high chemical and electrochemical stability maintaining these proteins' redox properties within a specific range of potential values [197–199]. The different Fe-S clusters can modulate and maintain its reduction potential values between approximately −0.7 to −0.1 V and the HiPIPs around +0.1 to +0.4 V [60,200–202].

A similar reasoning can be made for heme proteins and modulation of their redox potentials by the type of heme (*c*, *b*, *d* types,

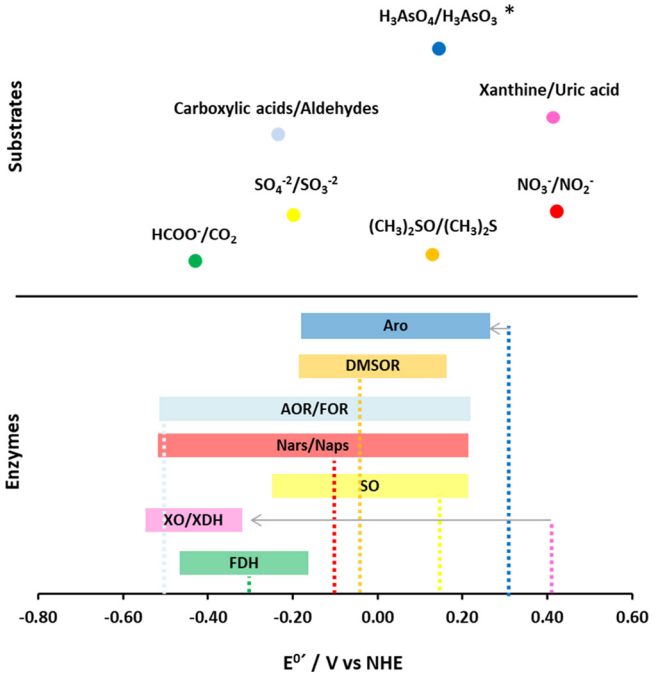

Fig. 3. Graphical representation of Mo(W) centres redox potentials of the different mononuclear Mo(W) enzyme families, together with the reduction potential of the substrates (*represents the experimental value found for the arsenate/arsenite couple, pH ≈ 6). The dashed lines represent the corresponding average value of the observed catalytic potentials.

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etc. [202]), its covalent or non covalent binding to the protein chain as well as heme axial ligation (His, Met, Cys, OH^-, OH_2).

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccr.2019.05.005.

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