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Review

Bioinorganic chemistry of molybdenum and tungsten enzymes: A structural–functional modeling approach

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Contents

Abbreviations: dithiolene, dithiolene in its dithiolate form unless otherwise noted; mnt, maleonitrile dithiolate; bdt, 1,2-benzene dithiolate; OAT, oxygen atom transfer; EXAFS, extended X-ray absorption fine structure; FMO, frontier molecular orbital; SO, sulfite oxidase; Psr, polysulfide reductase; NAP, periplasmic nitrate reductase; FDH, formate dehydrogenase; AOR, aldehyde oxidoreductase; AH, acetylene hydratase; CODH, carbon monoxide dehydrogenase; Moco, molybdenum cofactor; MGD, molybdopterin guanine dinucleotide; S_2Pd, pyranopterindithiolate; TMNO, trimethylamine-N-oxide; E, enzyme; S, substrate; I, inhibitor; ES, enzyme–substrate; EI, enzyme–inhibitor.

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ABSTRACT

Chemical approaches toward the bioinorganic chemistry of molybdenum and tungsten enzymes had been either biomimetic (structural modeling) or bioinspired (functional modeling). Among the dithiolene type of ligands, bdt (1,2-benzene dithiolate) and related aromatic molecules as model ene–dithiolene ligands were used to react with pre-designed molybdenum complexes in organic solvents. Whereas in the alternative approach mnt (maleonitrile dithiolate) is used to mimic the ligand backbone of the central atom in the active sites of these enzymes using molybdate or tungstate as the metal source in water. Structural–functional models are known for some selected enzymes, namely, sulfite oxidase, aldehyde ferredoxin oxidoreductase, tungsten formate dehydrogenase, acetylene hydratase, polysulfide reductase and dissimilatory nitrate reductase. The protocols and methodologies adopted to achieve these model systems compared with various other model systems described in this review give testimony to chemist's ability, through chemical manipulations, to achieve the model systems which may potentially serve as structural–functional mimics of natural enzyme systems.

1. Introduction

The element, molybdenum is unique among metals in the periodic table due to its varied roles and probably the most prominent use of this element is in the form of bio-catalysts as found in the enzymatic reactions in several molybdoproteins in nature. Much of the higher valent chemistry of molybdenum and tungsten is reminiscent of the chemistry of nonmetals such as they readily undergo polymerization to form anionic polymolybdates and polytungstates similar to the reactions of silicate and phosphate but unlike them, both molybdenum and tungsten can mediate oxygen atom transfer (OAT) reactions [1] at low potential (<0 V). To complete the catalytic cycle in the regenerating stages, proton coupled sequential single electron transfer reaction is equally accessible. Depending on its various oxidation states, molybdenum shows approximately equal affinity for hard donor oxo and soft donor sulfido ligands. The ready availability of different oxidation states with the possibility of a variety of different coordination numbers from 4 to 8 is another important aspect of this metal. All these properties taken together thus show the uniqueness of this particular metal, which is reflected in its biological endeavor [2].

The current interest in molybdenum is due to the importance of this special metal ion as an essential trace element which participates in a number of important enzymatic reactions [3–5]. The higher congener of molybdenum, tungsten also participates in enzymatic reactions. The bioinorganic chemistry of tungsten with a biological perspective has recently been reviewed [6] and therefore will not be addressed here. Some selected examples of the types of reactions involving molybdenum and tungsten are shown in Fig. 1.

Molybdenum is found as an important component of the multinuclear center of nitrogenases and as the mononuclear active sites of a much diverse group of molybdenum oxotransferases [7–10]. There are some enzymes like polysulfide reductase and formate dehydrogenase which do not catalyze oxygen atom transfer and some other do not possess any {Mo = O} moiety. According to Hille's classification [11], the mononuclear molybdenum enzymes have been most reasonably categorized into three main families which contain one (xanthine oxidase and sulfite oxidase family) or two (DMSO reductase family) pterin dithiolate cofactors along with variable axial ligations.

Chemical approaches to achieve the model active sites of molybdenum and tungsten containing native enzyme systems had been either biomimetic (structural modeling) or bioinspired (functional modeling). Bioinorganic model chemistry of molybdenum and tungsten enzymes was elegantly described [12] and some selected topics are reviewed recently [13]. Several model systems have been reported for different families of molybdenum and tungsten enzymes, some of which have met the criterion of structural mimicry while some are able to react with the biological substrate (functional) or in some cases with some proxy substrates. However, most of these could not demonstrate the reaction with biological substrates obeying Michaelis–Menten saturation kinetics, a kinetics followed by most of the simplest forms of the native enzymes. An approach toward structural–functional mimicry was thus essential.

Among all the ene–dithiolate ligands used to model mononuclear molybdo or tungsto enzymes, the maleonitriledithiolato (mnt) ligand [14–17] is the best behaved ligand so far allowing the maximum use of aqueous media in synthesis. This ligand readily duplicates the reactivity and/or with structural similarity with some selected enzymes, namely, sulfite oxidase, aldehyde oxidoreductase, acetylene hydratase, formate dehydrogenase, polysulfide reductase and dissimilatory nitrate reductase.

In order to avoid repetition, this review does not intend to cover each and every model system of molybdenum and

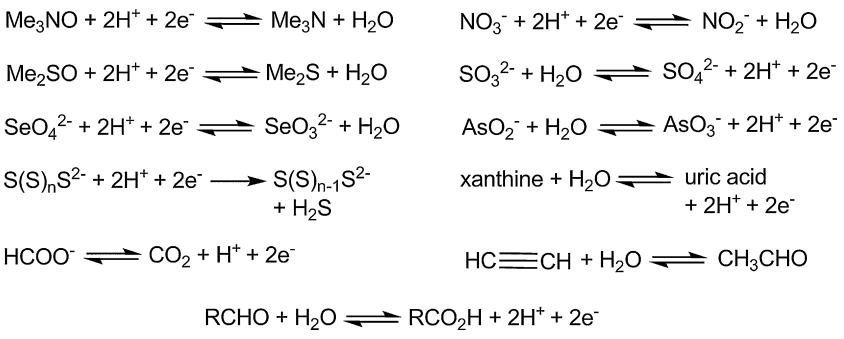

Fig. 1. Important chemical transformations mediated by molybdenum/tungsten in biology.

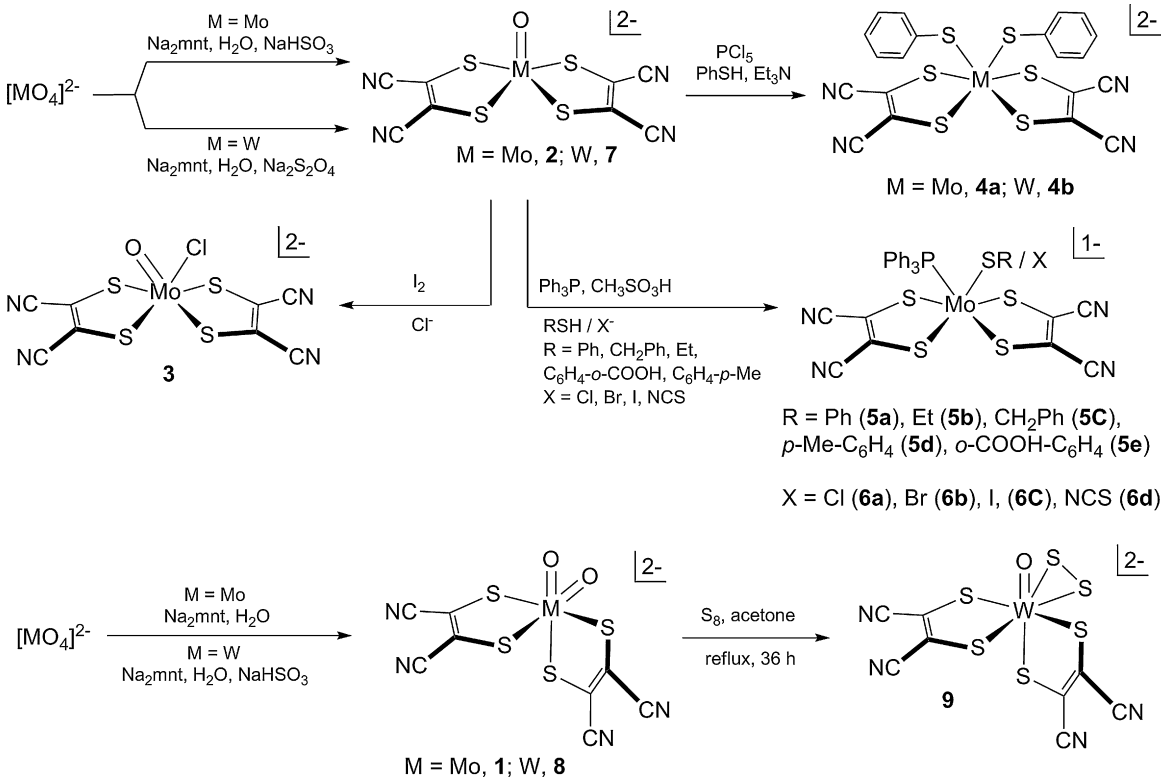

Fig. 2. Schematic diagram with compound designations for the synthesis of bis(dithiolene) Mo/W complexes.

tungsten enzymes. Earlier modeling chemistry involving various non-dithiolene ligand systems can be found elsewhere [18]. Modeling for the DMSO reductase and TMNO reductase systems are previously described in detail [12]. Arsenite oxidase activity has been only recently described for a model system [19]. Another important enzyme, xanthine oxidase has not been perfectly modeled yet [12,20] and it is only recently that a model tungsten compound of relevance to the xanthine oxidase active site has been reported [21,22]. Synthetic strategy and reactivities of model systems described here (shown in Fig. 2 with compound designations) for some selected enzyme systems may well be treated as structural–functional model systems. The protocols and methodologies undertaken give a brief overview about the successful structural–functional modeling of the molybdenum and tungsten enzymes and thus extend the prospect of bioinorganic modeling to be in parallel with biological transformations themselves.

2. Molybdenum enzymes: a biological perspective

2.1. Importance of molybdenum containing enzymes

The enzymes that contain molybdenum and the molybdenum cofactor (Moco) include oxidases, reductases and dehydrogenases and are found in bacteria, plants and animals including humans. Not only these molybdenum enzymes are important to their host organisms for metabolism and energy generation but also the products from the catalytic cycles in which these enzymes participate have major impact in the nitrogen, sulfur, carbon and arsenic cycles.

The assimilation of nitrogen by plants, algae, fungi and bacteria, is catalyzed by molybdenum enzymes in part by facilitating the reduction of nitrate to nitrite and the reduction of amine oxides to amines [23–25]. The molybdenum enzymes sulfite oxidase [26–28] and DMSO reductase [29–34] are important to the global sulfur cycle. The reduction of DMSO yields dimethyl sulfide, which is photooxidized to methane sulfonic acid ($MeSO_3H$), a compound important in droplet formation in clouds [35]. $MeSO_3H$ is eventually metabolized to sulfite by soil bacteria and then oxidized to sulfate by the molybdenum enzyme sulfite oxidase. In the methanogenic bacteria, which ultimately produce methane, an early step in the reduction of CO_2 is catalyzed by the molybdenum enzyme methanofuran dehydrogenase [36,37]. In the carboxydobacteria, Moco enzymes catalyze the oxidation of carbon monoxide (CODH) [38,39] and in a variety of organisms, the oxidation of formate (formate dehydrogenase) [40,41], both reactions produce CO_2. As a component of the arsenic cycle, the molybdenum enzyme arsenite oxidase catalyzes the oxidation of arsenite (As(III)) to arsenate (As(V)) [42]. In higher organisms the production of bioantioxidants such as uric acid, the proposed reduction of biotin sulfoxide to biotin (Vitamin H) [43], the oxidation of toxins such as hydrogensulfite [44,45], and the metabolism of purines [46] are all catalyzed by molybdoenzymes.

2.2. Molybdenum cofactor (Moco)

Other than the enzyme nitrogenases, all known molybdoenzymes possess a pterin cofactor [47,48]. Tungsten containing enzymes also contain a similar if not identical pterin [49–51]. In general, this pterin framework is found in a number of biological settings, including the active sites of enzymes and the pigments of eyes and insect wings. Pateman et al. first postulated the existence of a molybdenum cofactor common to several molybdenum enzymes [52] in early 1960s. This cofactor was later shown to contain a pterin [53] but whether this pterin shares a common biosynthetic pathway with other pterins (such as tetrahydrobiopterin) [54] is unknown [55,56]. All molybdenum enzymes contain some variant of this pterin, called molybdopterin (pyranopterin), except for nitrogenases, which possesses a homocitrate-containing iron–molybdenum sulfide cluster designated as FeMoco [57]. Reconstitution of the apoprotein from *Nit-1*

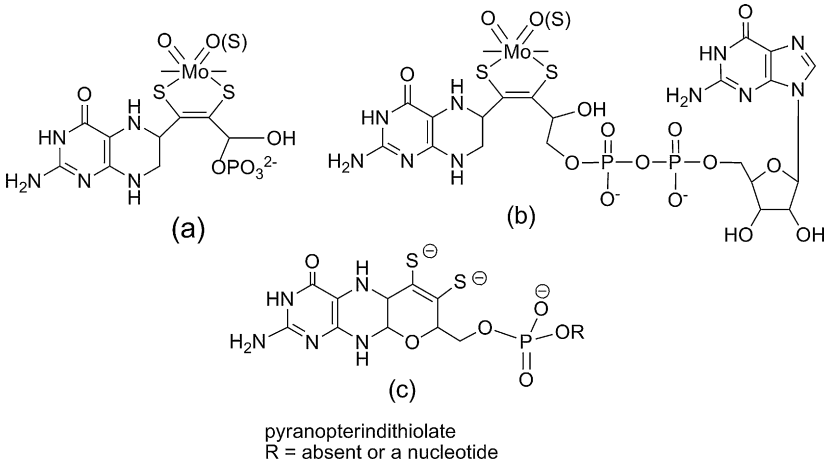

Fig. 3. Structure of Moco with molybdenum in the Mo^{VI} oxidation state (a), proposed structure of molybdenum cofactor of molybdopterin guanine dinucleotide form (b) and pyranopterindithiolate (c).

with Moco from a variety of sources demonstrates the idea of a universal molybdenum cofactor.

Unlike most of the known cofactors in biology, the molybdenum cofactor is not isolable using normal procedures due to its labile nature in the presence of air. For the structural characterization of the molybdenum cofactor, elegant synthesis and spectroscopic studies done by Rajagopalan and coworkers [53,58–60] led to the discovery of the structure of the molybdenum cofactor (Fig. 3(a)). The important features of this cofactor are: (a) the presence of a pterin moiety, (b) the side chain of the pterin contains a dithiolene group, (c) the presence of a phosphoester group and (d) the coordination to molybdenum via dithiol moiety to give dithiolene coordination. The dithiolene is a part of guanidine metabolism and assists both one and two electron transfer reactions. The entire ligand without molybdenum is known as molybdopterin (MPT) which as well as the molybdenum cofactor is anionic in nature. Complementary work by Taylor et al. confirmed the structure of several of the pterin decomposition products [61,62] formed in the oxidative decomposition of Moco. Kruger and Meyer proposed the possibility of having a different form of molybdenum cofactor from carbon monoxide dehydrogenase of *Pseudomonas carboxydoflacea* [63,64]. A new pterin derivative of molybdopterin guanine dinucleotide (MGD) was isolated from dimethyl sulfoxide reductase from *Rhodobacter sphaeroides* [29–34] which has been shown in Fig. 3(b). The actual structure was subsequently known to be a pyranopterindithiolate as shown in Fig. 3(c). Molybdopterin moieties like molybdopterin guanine dinucleotide, molybdopterin adenine dinucleotide and molybdopterin hypoxanthine dinucleotide have been identified in formyl methanofuran dehydrogenase from *Methanobacterium thermoautotrophicum* [65]. The diverse nature of this class of enzymes in relation to their availability from different species and their diverse role in light of broad and specific substrate selectivity could be the reason for these variations.

2.3. Oxygen atom transfer (OAT)

The ability of molybdenum and tungsten sites in their higher oxidation states to undergo oxygen atom transfer is well known [1,3,18]. Mechanistically, this process can be viewed as the transfer of two electrons and an oxide ion in opposite directions. Oxygen atom transfer is the two-electron counterpart of classical inner sphere electron (oxo) transfer involving for example, a bridged precursor complex by the reaction of hypochlorite and nitrite. The oxide ligand bridges the redox partners, allowing the two-electron transfer to occur, and ends up bound to the oxidized reaction partner like nitrate. Clearly, in chemical systems, the reaction of small molecules such as phosphines, sulfides and tertiary amine oxides appear to proceed by simple 'oxo' transfer. The catalyzed reactions of most of the molybdoenzymes can be loosely classified into two types: (1) insertion of an oxygen atom into a C–H bond (e.g., xanthine and purine oxidation), and (2) "simple" oxygen atom transfer reactions (e.g., DMSO and nitrate reduction). Murray et al. [66] demonstrated by ^{18}O isotopic experiment that the oxidation of reducing substrate takes place by oxygen atom transfer from the solvent, i.e. water. Using broad substrate specificity they also showed that xanthine oxidase and xanthine dehydrogenase can catalyze direct transfer of ^{18}O from ^{18}O-N-oxide to xanthine for uric acid formation. Stohrer and Brown [67] have substantiated this view and generalized that heterocyclic N-oxides are biological oxygenating agents. Hille and Sprecher [68] demonstrated that it is the oxo transfer reaction between Mo=O moiety and xanthine which is taking place. The participation of water as a source of oxygen takes place in the regeneration stages of the enzyme. Thus for the second and subsequent catalytic cycles, the oxygen from water is incorporated into the reduced molybdenum center to generate oxidized oxomolybdenum species which in turn transfers oxygen into the reduced substrate. A general description of OAT reactions in model systems is presented in Fig. 4.

3. Criteria and types of model active sites

Molybdenum and tungsten have always fascinated the bioinorganic chemists because of the presence of these two metals in almost 50 enzymes, of which many are directly related to the health and ecological concerns. Chemical approaches have been either biomimetic where the constructions of ligand systems around the metal atom are as close as possible to the coordinating environment and active site structures found in nature, or bioinspired, where the goal is to achieve the enzymatic function under ambient conditions, irrespective of the ligand. These two approaches have lead to the formation of two new terminologies in the context of modeling bioinorganic chemistry, namely, "structural modeling" and "functional modeling".

"Structural modeling" is a biomimetic approach where the synthesized complexes should have very similar donor atom environment around molybdenum to the active site of the native enzyme. In contrast, "functional modeling" is a bioinspired approach where the synthesized model complex should be able to function in a fashion similar to the native enzyme. The functional model may not demonstrate exactly identical activity of the

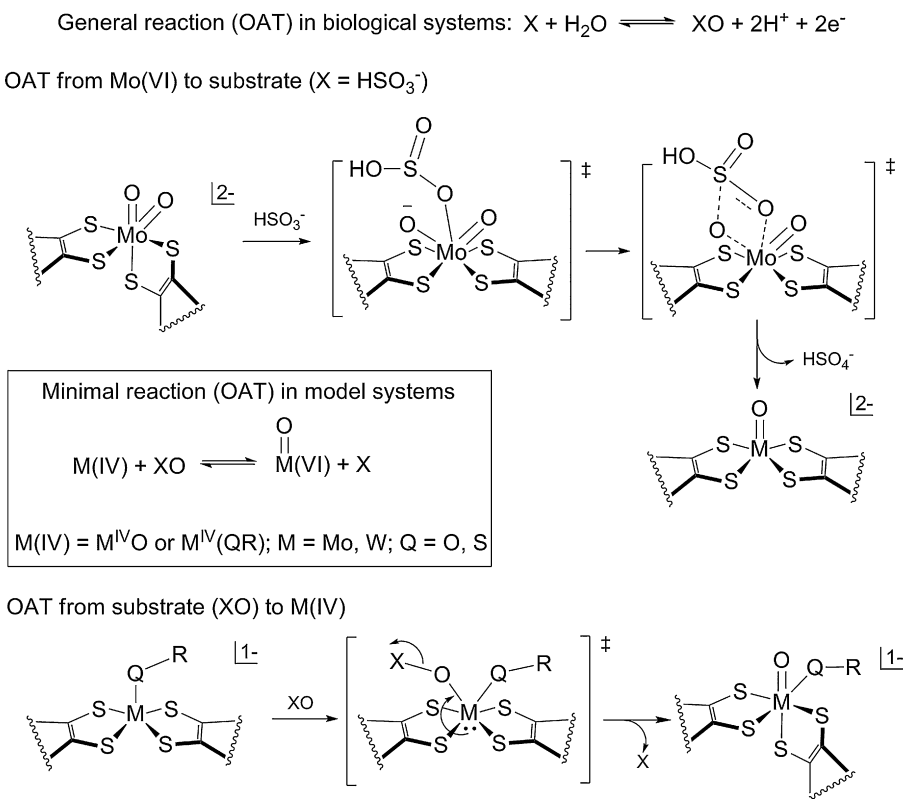

Fig. 4. General description of OAT reaction (see Fig. 1 for catalyzed reactions) showing reductase and oxidase activities (particular dithiolene systems are not shown).

molybdenum center present in the enzyme simply because of the fact that the activity of these enzymes generally follows ping-pong kinetic mechanism [69] of a hybrid nature. Direct electron (oxo) transfer in the catalytic cycle is only half way via molybdenum and the other complementary half utilizes another redox center attached to the molybdenum. Therefore a full catalytic cycle resembling enzymatic reaction is not viable with a simple molybdenum model compound. It is to be noted that functional model or enzymatic reactions are essentially solution chemistry. The paramount role of water as an essential chemical reactant in enzymatic function is to be borne in mind because a functional model reaction in nonaqueous media definitely will be far away from functional mimicry of the real enzyme.

4. Ligand systems used in model study

Based on the above stated limitations and essential qualifications of a model compound ligand systems have been utilized to mimic the pterin part in the native active site. These ligands can be classified into two groups, nondithiolene and dithiolene systems. Among these two classes the dithiolenes (Fig. 5) are obviously the better one to mimic the dithiolene bite exhibited by the native pyranopterindithiolate ligand (Fig. 3(c)). An account of early developments of metal–dithiolene systems can be found elsewhere [70]. Synthesis, structural trends, electronic structure-spectroscopic properties, solid state properties and biological relevance of various transition metal dithiolene systems have been systematically and extensively discussed [71]. Most commonly used dithiolene systems (Fig. 5) [1,18,72,73] belong to two fundamental types which in their classical, fully reduced forms can be represented as ene–1,2-dithiolate ($R_2C_2S_2$; R = H, Me, Ph, CF_3, CN, COOMe, etc.) type and benzene-1,2-dithiolate (bdt) type (with one or more substituents such as Me, Cl, $SiPh_3$, $NHCOCH_3$, $NHCOCPh_3$, etc.).

5. Selected molybdenum/tungsten enzymes and relevant modeling chemistry

5.1. Sulfite oxidase (SO)

5.1.1. Native SO

Sulfite oxidase catalyzes the physiologically vital oxidation of sulfite to sulfate [9,27], which is the terminal reaction in the oxidative degradation of the sulfur-containing amino acids cysteine and methionine. The enzyme also plays an important role in detoxifying exogenously supplied sulfite and sulfur dioxide. Oxidation of sulfite by the enzyme is efficient even at very low concentration of substrate, occurs in the presence of electron acceptors other than oxygen and is unaffected by the presence of free radical scaveng-

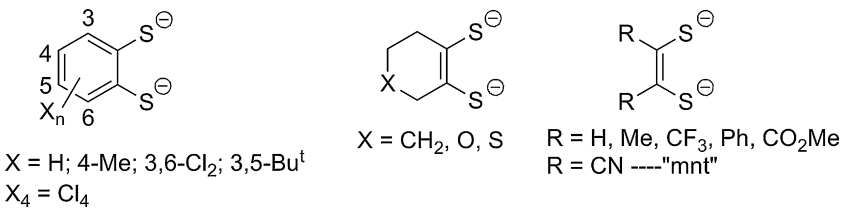

Fig. 5. Selected dithiolene ligands.

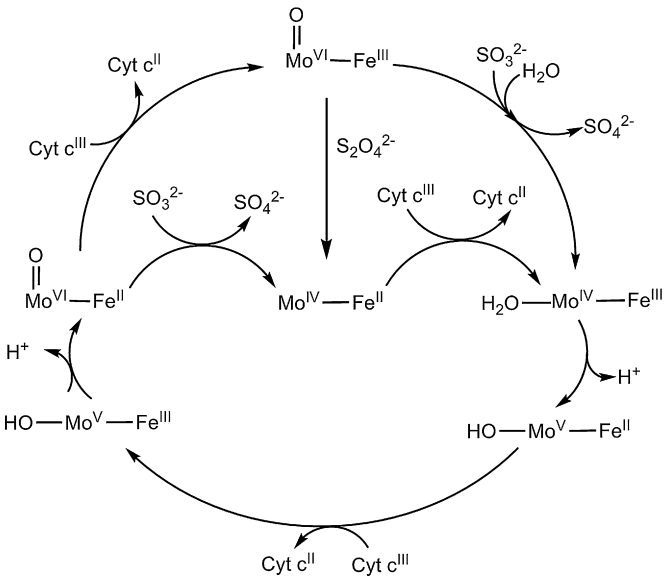

Fig. 6. Overall mechanism of animal SO.

ing agents [74]. These criteria distinguish the enzyme-catalyzed reaction from non-enzymatic aerobic sulfite oxidation which proceeds by a metal-catalyzed free-radical mechanism, requires high concentration of sulfite and oxygen and is inhibited by free radical scavengers [75]. The conversion of sulfite to sulfate is a two-electron oxidation, whereas cytochrome c, the physiological electron acceptor for sulfite oxidase, is a one electron acceptor. Sulfite oxidation occurs at the molybdenum center and cytochrome c reduction at the heme site. According to the overall mechanism of animal SO (Fig. 6), originally proposed by Hille [76–78], SO catalyzes the oxidation of sulfite to sulfate in the forward reductive half reaction via oxygen atom transfer (OAT) with subsequent reduction of two equivalents of cytochrome c in the process wherein the oxygen atom incorporated into substrate is ultimately derived from water. The enzyme sulfite oxidase as a part of sulfite oxidizing enzymes has recently been reviewed [79] in light of recent developments in the understanding of sulfite oxidizing enzyme mechanisms.

Hepatic sulfite oxidase (SO) is a dimeric enzyme with each monomer containing a single Mo cofactor and a cyt b_5-type heme [80]. All the three oxidation states of the molybdenum atom of SO have been studied by EXAFS [81] and EPR techniques [82–85]. Two terminal oxo groups are present in the fully oxidized enzymes, which were expected to be *cis* to one another with an O–Mo–O angle near about 106° [86]. One terminal oxo group appeared to be present in the Mo(V) and Mo(IV) states of the enzyme [82,83]. The hydroxo ligand attached to the Mo(V) center appeared to be *cis* to the terminal oxo group as suggested by ^{1}H super hyperfine splitting [82–85]. The active site structure of sulfite oxidase was determined in 1997 by X-ray crystal structure [87] which provided the first complete model for any member of this family. Moco consists of a single molybdopterin as expected from earlier experiments and is deeply buried in the second domain of SO. As in the other structures of Moco containing enzymes [88,89], the pterin forms a tricyclic ring system with a pyran ring fused to the pyrazine ring of the pterin. The molybdenum atom is coordinated by five ligands with approximate square pyramidal geometry. The terminal oxo group at a Mo–O distance of 1.7 Å occupies the axial position of the pyramid, and the equatorial positions are occupied by three sulfur atoms and one water/hydroxo ligand. As evident from earlier experiments [80–88] two sulfur ligands arise from the dithiolene sulfur of one molybdopterin with Mo–S distance of 2.4 Å and the third by the sulfur atom of Cys-185 at a distance of 2.3 Å. Recently a crystal structure of plant sulfite oxidase has also been reported [90].

5.1.2. Model chemistry of SO

Dithiolene type ligands are noninnocent and higher valent metal centers are usually reduced during the incorporation of dithiolene ligand. Of particular note is the case of Mo(VI) where pentavalent Mo–dithiolene complexes are usually formed. Very few of dithiolene coordinated Mo(VI) complexes have been synthesized using different synthetic protocols to overcome this problem. Another requirement for the model active site of sulfite oxidase is the monodithiolene ligation, which is an uncommon type of complex (excluding the examples of organometallic compounds). The coordination chemistry of Mo(VI) demands the hexacoordination for its stability, having two positions occupied by two terminal oxo groups and the remaining four positions are occupied by two dithiolene ligands. These problems were successfully tackled by Holm and coworkers [91] following the reaction sequences shown in Fig. 7. The structural parameters of this complex were in good agreement with that obtained from EXAFS and X-ray crystal structure of oxidized chicken liver sulfite oxidase [87] and the collective evidence supports this complex $[Mo^{VI}O_2(2,3,5\text{-}Pr^i{}_3\text{-}C_6H_2S)(bdt)]^{1-}$ as an accurate structural model of sulfite oxidase. Unfortunately, this complex does not show any oxygen atom transfer reaction either with the biological substrate ($SO_3{}^{2-}$/$HSO_3{}^-$) or with the well known proxy substrate, PPh_3. There are also reports [92,93] of other two monodithiolene complexes, but they are in the reduced form of Mo(IV) and the other site is ligated by nitrogen containing bidentate ligand. These complexes reacted with strong oxo donor agent like N-oxides to form the oxidized $Mo^{VI}O_2$ moiety, but oxidized states were very unstable and immediately underwent a comproportionation reaction to form dimeric species. Other reported monodithiolene systems contain Mo(V) and are not discussed here.

All other dithiolene ligated oxo–molybdenum complexes [12,18,94–108] contain the ligation of two dithiolene ligands around the molybdenum center. Several methods have been applied to synthesize bis(dithiolene) oxo–molybdenum complexes [12] and were isolated either in their monooxo Mo(IV) state or Mo(VI) dioxo state. The Mo(IV) monooxo bis(dithiolene) complexes could get oxidized by strong oxo-donor reagents like TMNO thereby leading to the formation of bis(dithiolene) Mo(VI) complexes [101–108], which constitutes another route to synthesize the oxidized forms. However, most of these Mo(VI) dithiolene complexes do not react with the biological substrate sulfite (or bisulfite). Some of those complexes could react with the proxy substrate phosphine and the reaction follows a second order kinetics [109,110].

5.1.3. Structural–functional model chemistry of SO

Prior to the crystallographic definition of the SO site, the complexes, $[Mo^{VI}O_2(mnt)_2]^{2-}$ (**1**), $[Mo^{IV}O(mnt)_2]^{2-}$ (**2**) and

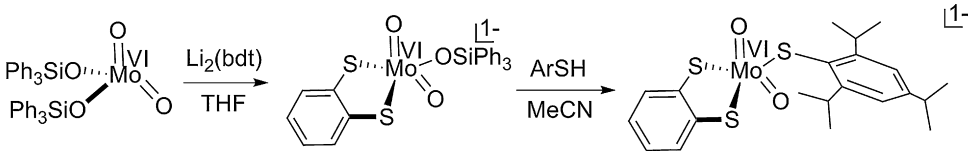

Fig. 7. Synthesis of the model system for the oxidized active site of sulfite oxidase.

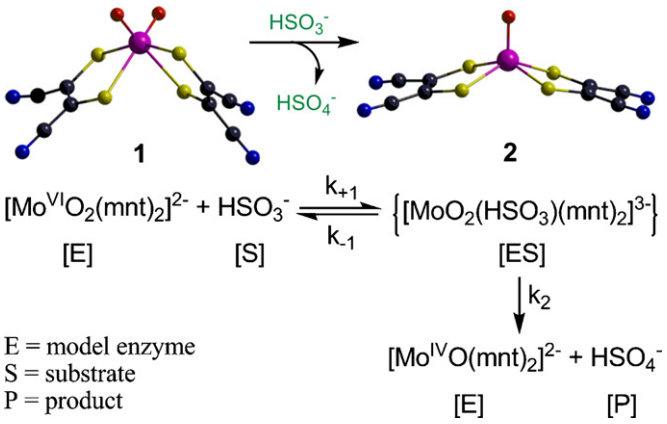

Fig. 8. Sulfite oxidase activity exhibited by the model complex **1** containing a cis–dioxo feature. Color code: pink, Mo; yellow, S; red, O; blue, N; black, C.

$[Mo^{V}OCl(mnt)_2]^{2-}$ (**3**) (Fig. 2) were synthesized [111–113] which are relevant to the active site of SO. Complex **1** was directly synthesized from Na_2MoO_4 and Na_2mnt in the presence of citric acid–phosphate buffer (pH 6) in water, whereas **2** was synthesized from the same source materials in the presence of $NaHSO_3$ in water. Complex **2** upon treating with iodine yielded **3** [112].

Na_2SO_3 when dissolved in water raises the pH of the solution because of the formation of $NaHSO_3$. Moreover, at physiological pH, sulfite remains in equilibrium with bisulfite. The close association of the activity of SO with mitochondrial electron sequence reaction and the low pH available in mitochondrial reaction strongly suggests that the reactive substrate should preferably be bisulfite (HSO_3^-). Complex **1** was cleanly reduced by bisulfite [112] in acetonitrile–water medium (Fig. 8) and the reaction follows Michaelis–Menten saturation kinetics with $K_M = 0.010$ M and $k_2 = 0.87\ s^{-1}$ at 20 °C. The same kinetics scheme was reported with similar parameters ($K_M = 0.039$ M, and $k_2 = 1.02\ s^{-1}$) in a subsequent re-investigation in 1:1 acetonitrile/water (v/v) [110]. Complex **2** was oxidized back to **1** which confirmed the oxidation of reduced $\{Mo^{IV}O\}$ species to the oxidized $\{Mo^{VI}O_2\}$ species with the incorporation of the additional oxo group from water. Moreover the complex anion, $[Mo^{V}OCl(mnt)_2]^{2-}$ (**3**) partially mimics the low pH form of the molybdenum(V) state of SO in the presence of excess of Cl^-. The EPR parameters for **3** are similar to those of sulfite oxidase at low pH form [81]. Different inhibition types of the saturation kinetics involving the model complex, **1** and HSO_3^- as the substrate by structurally similar anions SO_4^{2-}, $H_2PO_4^-$ and $H_2PO_3^-$ have been described [114] which is of relevance to the reductive half reaction of SO. SO_4^{2-} acts as a competitive inhibitor whereas the mixed-type non-competitive inhibition by $H_2PO_4^-$ and the sigmoidal type inhibition by $H_2PO_3^-$ have been explained by a diamond-configuration random-order model. This model involves a random binding sequence of the substrate and the inhibitor, and forms, in addition to two binary complexes (ES and EI), one enzyme–substrate–inhibitor type ternary complex (ESI) by the participation of at least one more binding site in addition to the catalytic site. This is possible in this model study only by coordination enhancement of molybdenum in E, brought about by nucleophilic attack of the S or the inhibitor I at the molybdenum, forming a hepta-coordinated binary complex with the generation of an oxoanionic functional site, called the allosteric site [115].

The fundamental question in the oxidation of sulfite (or bisulfite) to sulfate by native SO and also in model complexes had been the mode of sulfite (or bisulfite) attack to the molybdenum center. It may be either oxoanionic or sulfur lone pair attack. The initial proposal [111] of oxoanionic attack of HSO_3^- on the Mo(VI) center of **1** was questioned [110] based on the unique experimental results [116] reported by Hille and Brody involving neutral dimethylsulfite as an alternate substrate of the native SO. It has also been shown [116,117] that the methylation of two oxoanions of sulfite reduces the affinity of dimethylsulfite for the active site of the native SO. Formation of a Michaelis complex was implied from the exhibition of saturation kinetics by dimethylsulfite, which was interpreted [116,117] in terms of possible electrostatic interaction between the active site and modified substrate. Direct oxoanionic coordination of sulfite to the Mo center has been suggested by Rajagopalan and coworkers [118]. To address this problem the reactivity of oxo-acceptors such as dimethylsulfite, PPh_3 and HSO_3^- has been examined with **1** [119]. In the pH range 5–7 dimethylsulfite did not show any reactivity toward **1** whereas after standing at pH 8 for a few minutes it became capable of reducing **1**. Checking the difference in reactivity of dimethylsulfite in the pH range 5–7 and 8 toward **1**, the inability of neutral dimethylsulfite to react with **1** has been clearly demonstrated, suggesting the inability of sulfur lone pair to initiate any redox reaction. Once the neutral dimethylsulfite is base hydrolyzed (pH 8) yielding HSO_3^-, the reaction progresses smoothly. Interestingly, PPh_3 also reduces **1**. The basic difference between the reactivity of HSO_3^- and PPh_3 is that the phosphines invariably respond to oxo abstraction by following second order kinetics (without the involvement of a Michaelis complex) whereas HSO_3^- reacts with **1** following enzymatic kinetics (with the involvement of a Michaelis complex). Thus the reactivity of anionic HSO_3^- toward **1** is clearly dependent on the direct coordination of HSO_3^- to the Mo site which also explains the observed competitive inhibition by sulfate [114], otherwise the lone pair attack of sulfur on the coordinated terminal oxo group and the direct binding of SO_4^{2-} to Mo would have resulted in mixed non-competitive inhibition. On the basis of these experimental observation and understanding of the detailed substrate oxidation and inhibition pattern in model study of the active site of SO it has been shown that the fulfillment of the criteria to exhibit enzymatic rate law as well as the enzymatic inhibition phenomena are dictated by symphoria [120]. However, the mechanistic inference drawn from such studies may not be the same as in the case of native enzyme. In view of this ambiguity it has been pointed out that the fulfillment of this criterion is not a definitive conclusion toward our understanding of the structure–function relationship of an enzyme and, therefore, the criterion of a "structural model" and a "functional model" have been revised to include substrate analogues. On the basis of kinetic studies it has also been shown [120] that the effect of medium can lead to substrate–inhibitor type dualism and hence the effect of medium can play a key role for the success of modeling the active site function of an enzyme. Based on the typical second order kinetics found in case of PPh_3 and DMSO as substrates in contrast to the Michaelis–Menten kinetics found in case of any enzymatic reaction of the simplest type, it has been proposed that the reactivity of PPh_3 or DMSO, at most, can be a mimic of the catalytic step of an enzymatic reaction. But this cannot be a mimic of the important step which involves the formation of a Michaelis complex. In case of **1**, it is the substrate (HSO_3^-) oxoanionic binding to Mo(VI) that fulfills the symphoric criterion and forms the Michaelis type complex.

A detailed theoretical calculation [121] shows that the initial step in the oxygen atom transfer reaction of $[Mo^{VI}O_2(S_2C_2Me_2)SMe]^{1-}$ and **1** with HSO_3^- takes place by oxoanionic binding of the substrate to the Mo(VI) with the formation of a stable Michaelis complex. Although **1** contains four sulfur coordination in contrast to three sulfur coordination in native active site, the trans (to axial oxo) –Mo–S bond is elongated to 2.984 Å in the transition state, thereby involving similar transition state as like the native system in terms of coordination environment. This intermediate complex participates in product

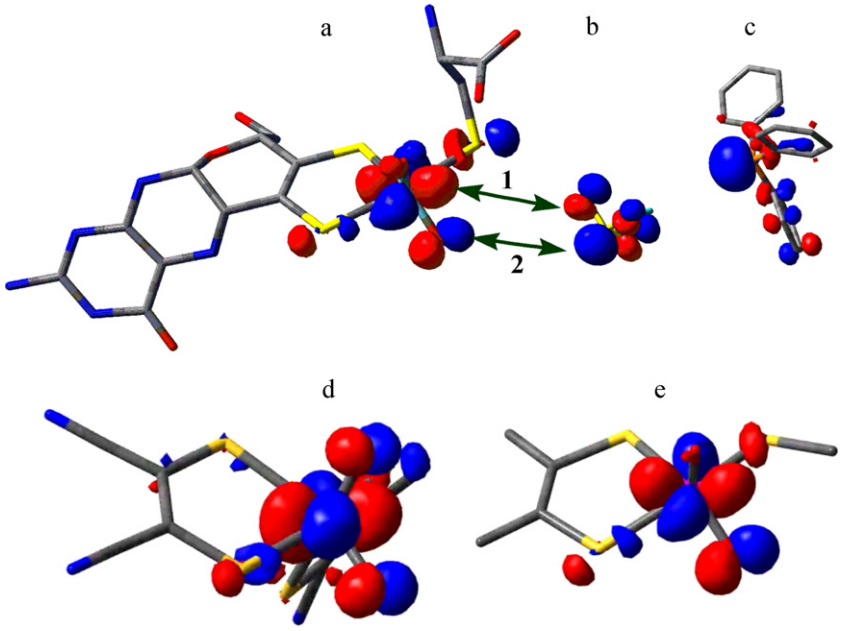

Fig. 9. MO isosurface: (a) LUMO of Moco; (b) HOMO of HSO_3^-, arrows indicate the FMO interaction of the same phase; 1, interaction between d_{xy}(Mo) and p(O) of HSO_3^-, 2, interaction between O_{eq} and S atom of HSO_3^-; (c) HOMO of PPh_3 showing only one possible interaction; (d) LUMO of $[Mo^{VI}O_2(mnt)_2]^{2-}$; (e) LUMO of $[Mo^{VI}O_2(S_2C_2Me_2)(SMe)]^{1-}$ showing close analogy with the LUMO of Moco. H atoms omitted for clarity. Color code: pink, Mo; yellow, S; red, O; blue, N; grey, C. Reproduced with permission from Ref. [121]. Copyright Wiley–VCH Verlag GmbH & Co. KGaA.

formation through a six-membered $\{MoO_2HOS\}$ transition state involving breaking of the Mo–O_{eq} bond and formation of the $S_{sulfite}$–O_{eq} bond. The LUMO of Moco (Fig. 9) was predominately populated by the d_{xy} orbital of the central Mo atom (from the antibonding interaction between 60% d_{xy}(Mo), 11% p(O_{eq}), and 4% p(O_{ax}) orbitals) while the HOMO of HSO_3^- comprised 40% s(S), 23% p(O anionic), and 20% p(O). The HOMO of PPh_3 was predominantly viewed as the lone-pair orbital of the P atom. Considering FMO interaction between the HOMO of HSO_3^- and the LUMO of Moco, two interactions, one between d_{xy}(Mo) of the LUMO and p(O) of the HOMO and the other between p(O_{eq}) of the LUMO and S of the HOMO seems to be possible. However, similar FMO interaction is not possible with phosphine (Fig. 9). The so-called phosphine lone pair of electrons can interact with the Mo=O_{eq} antibonding MO to facilitate the cleavage of the Mo–O_{eq} bond by a one-step process leading to a different mechanism which may follow typical second-order kinetics. These theoretical results [121] regarding the formation of Michaelis complex is in agreement with kinetic studies reported earlier [114,120], thereby once again establishing the oxo-anionic attack of HSO_3 with which more agreements are coming up recently [122].

5.2. Polysulfide reductase (Psr)

5.2.1. Native Psr

ATP formation from ADP and inorganic phosphate is coupled to electron transport in many anaerobic prokaryotes [123,124]. Electron transport in many anaerobic prokaryotes is catalyzed by electron transport chains within the membrane and is coupled to the generation of an electrochemical proton potential across the membrane that drives ATP synthesis. These processes are termed anaerobic respiration wherein O_2 is replaced by other terminal electron acceptors such as nitrate, fumarate or polysulfide. Anaerobic respiration with polysulfide is termed polysulfide respiration (Eqs. (1) and (2)) and has been most thoroughly studied in *Wolinella succinogenes* [125–128]. The electron transport chain catalyzing these reactions consists of polysulfide reductase (Psr) and either hydrogenase or FDH integrated into the bacterial membrane.

$$HCO_2^- + S(S)_nS^{2-} + H^+ \rightarrow CO_2 + S(S)_{n-1}S^{2-} + H_2S \quad (1)$$

$$H_2 + S(S)_nS^{2-} \rightarrow S(S)_{n-1}S^{2-} + H_2S \quad (2)$$

Isolated Psr catalyzes the reduction of polysulfide to sulfide with borohydride and the oxidation of sulfide to polysulfide with 2,3-dimethyl-1,4-napthoquinone [123–128]. The enzyme is made up of three different subunits, Psr A, Psr B and Psr C. The catalytic subunit Psr A contains a molybdenum atom bound to two MGD, where the reduction of polysulfide takes place and an FeS center. Psr B mediates electron transfer from Psr C to Psr A via its four FeS centers. On the basis of the EPR parameters obtained and by comparison with other molybdoenzymes of the DMSO reductase family like nitrate reductase, formate dehydrogenase and DMSO reductase itself, the structure for the observed Mo(V) states of polysulfide reductase is proposed [129] as shown in Fig. 10.

5.2.2. Structural–functional model chemistry of Psr

To synthesize a model complex structurally similar to the active site of Psr, an oxo–desoxo conversion process was employed in basic medium. Complex **2** was treated with PCl_5 in presence of an excess of thiophenol followed by the addition of Et_3N in chloroform to yield the model complex for Psr A, $[Mo^{IV}(SPh)_2(mnt)_2]^{2-}$ (**4a**) [130]. This complex has been shown to reduce polysulfide with the evolution of H_2S. A mechanism proposed for this polysulfide reduction can be found elsewhere [130].

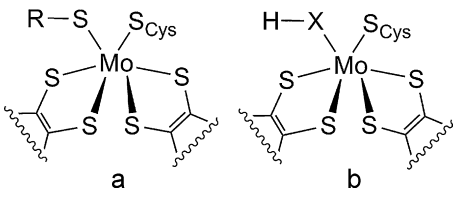

Fig. 10. (a) Polysulfide bound Mo(V) and (b) X = OH/SH bound Mo(V).

This clearly demonstrated the ability of **4a** to mimic the reactivity of the enzyme Psr A, and supported a structure–function relationship with the enzyme active site. The capability of the desoxo complex, **4a**, to revert back to the starting material, $[Mo^{IV}O(mnt)_2]^{2-}$ in moist dichloromethane [130] demonstrated the interchangeability of the oxo and desoxo Mo(IV) forms depending upon the local environment along with the lability of the Mo–SPh bond in **4a**. Tungsten analogue of **4a**, $[W^{IV}(SPh)_2(mnt)_2]^{2-}$ (**4b**) also catalyzes the same reaction, albeit slowly.

5.3. Nitrate reductase

5.3.1. Native periplasmic nitrate reductase (NAP)

Periplasmic/dissimilatory nitrate reductases couple the reduction of nitrate to nitrite at the expense of menaquinol to generate a transmembrane proton gradient and like the DMSO reductase from *E. coli* is comprised of three subunits. *E. coli* expresses three different nitrate reductases: the predominant nitrate reductase A form, inducible under anaerobic conditions, a minor nitrate reductase Z form, expressed under aerobic growth, and a third periplasmic form. These have been systematically discussed by Hille [11].

The periplasmic/respiratory/dissimilatory nitrate reductase (NAP) from the sulfate reducing bacterium *Desulfovibrio desulfuricans* is induced by growth on nitrate. The oxidized active site has been structurally characterized as $[Mo^{VI}(OH_x)(S_{Cys})(S_2Pd)_2]$ ($x = 1$ or 2) and the reduced desoxo site $[Mo^{IV}(S_{Cys})(S_2Pd)_2]$ has been proposed to mediate the reduction of nitrate to nitrite [131]. Molybdenum atom is located at the bottom of a 15 Å deep crevice, and is positioned 12 Å from the [4Fe–4S] cluster. Mo^{VI} is coordinated by six ligands in a distorted trigonal prismatic geometry. Four ligands are provided by the two dithiolene sulfur atoms of MGD 811 and MGD 812 (Mo–S = 2.2–2.4 Å). A fifth ligand is the side chain of Cys140 (Mo–S = 2.5 Å) and a hydroxo/water ligand (Mo–OH_2 ∼ 2.2 Å) completes the sixfold coordination around the molybdenum. The metal atom deviates ∼0.7 Å from the mean plane defined by the four dithiolene sulfur atoms. Nitrate has been proposed [131] to bind at the molybdenum center of the reduced cofactor with the formation of an ES complex followed by the essential oxotransfer and the elimination of nitrite ion with the formation of oxidized molybdenum cofactor, $[Mo^{VI}(O)(S_{Cys})(S_2Pd)_2]$. This oxo form being very protophilic readily converts to the protonated oxidized species $[Mo^{VI}(OH_x)(S_{Cys})(S_2Pd)_2]$ ($x = 1$ or 2).

A second dissimilatory nitrate reductase from *Escherichia coli* has been crystallographically characterized [132] to contain a $[Mo^{IV}(O_2C_{Asp})(S_2Pd)_2]$ site with an unsymmetrically coordinated carboxylate group. Molybdenum is coordinated by six ligands in a distorted trigonal prismatic geometry including four cis-dithiolene sulfur atoms of the Mo-bisMGD (Mo–S distance ∼2.4 Å) and a bidentate interaction from both side chain oxygen atoms in the carboxylate group of Asp222 (Mo–Oδ1 ∼ 1.9 Å and Mo–Oδ2 ∼ 2.4 Å).

Very recently, the NAP [131] has been revisited and the sixth molybdenum ligand has been assigned as a sulfur atom [133] instead of OH/OH_2 ligand [131]. An essential aspect has been proposed to be the redox interplay of molybdenum and sulfur, whereby the (partial) formation of a disulfide bond can influence the interconversion of Mo(VI) to Mo(IV). This would involve both molybdenum and ligand-based redox chemistry instead of the currently accepted solely molybdenum based redox chemistry in the redox cycle of the enzyme. There are, however, several points against the mechanism proposed in this study [133] and several structural data needs further explanation. It is hard to believe that the terminal Mo=S double bond length is similar to Mo–S (thiol) single bond or most of the times it is longer as reported. Such a long bond may be from a species like –SH and these bonds if present at all, would be very susceptible to hydrolysis. A more plausible explanation could be a chloride ion from the crystallization or purification artifact. In support of the X-ray data, EPR of the reduced Mo(V) species have been reported which does not show any hyperfine structure due to the absence of chloride ion. The nuclear magnetic moment of chloride is small enough and the super hyperfine splitting may not be observed readily. Furthermore, the intermediate trigonal prismatic geometry of the coordination sphere of central molybdenum may specially position the d orbital containing unpaired electron in such a way which may not overlap with the chloride orbital. Therefore absence of such interaction is not a proof that chlorine may not be there. Some more points are worth reporting like cyanolysis. If the moiety like Mo^{VI}=S reacts with CN^- to produce NCS^- then such reaction liberates two electrons and it is Mo(VI) that accept these two electrons to form Mo(IV). This happened in case of xanthine oxidase and is a common chemistry of Mo^{VI}=S in inorganic reactions. Further, the reduced species, nitrite under physiological pH liberates the corresponding free acid which is unstable. Native nitrate reductase does liberate nitric oxide and the adjoining Fe–S clusters get nitrosylated [134]. A Mo=S terminal bond will be immediately attacked by nitrogen oxides and sulfur will be abstracted. Based on these chemical reasons, it becomes obvious that this new proposal should undergo further experiments along with proper explanations and hence is not further considered during the discussions regarding model reaction of dissimilatory nitrate reductase here.

5.3.2. Model chemistry of NAP

Pentacoordinated Mo(IV)/W(IV) bis(dithiolene) monothiolate complexes $[M^{IV}(QC_6H_2\text{-}2,4,6\text{-}Pr^i_3)(S_2C_2Me_2)_2]^{1-}$ (M = Mo, W; Q = O, S) [135,136] were synthesized as possible model systems for nitrate reduction [137]. The tungsten compounds reduce nitrate to nitrite following second order kinetics (Q = O, $6.1 \times 10^{-3}\ M^{-1}\ s^{-1}$; Q = S, $1.7 \times 10^{-1}\ M^{-1}\ s^{-1}$) involving associative transition states and the oxidized tungsten species $[W^{VI}O(QC_6H_2\text{-}2,4,6\text{-}Pr^i_3)(S_2C_2Me_2)_2]^{1-}$ (Q = O [137], S [136]) were X-ray structurally characterized. However, the complex, $[Mo^{IV}(SC_6H_2\text{-}2,4,6\text{-}Pr^i_3)(S_2C_2Me_2)_2]^{1-}$ and its phenolate analogue, $[Mo^{IV}(OC_6H_2\text{-}2,4,6\text{-}Pr^i_3)(S_2C_2Me_2)_2]^{1-}$ were inadmissible for the examination of nitrate reduction. The phenolate complex showed an extremely sluggish reaction with excess nitrate in acetonitrile solution. Reaction systems containing thiolate complex and excess nitrate in both acetonitrile and DMF solutions were not well behaved and underwent decomposition to form $[Mo^{IV}(S_2C_2Me_2)_3]^{1-}$ [137], identified spectrophotometrically with a rate faster than OAT. However, an intrinsic ability of this complex to support OAT was demonstrated by the clean reduction of $(CH_2)_4SO$ to $(CH_2)_4S$. In an attempt to avail $[Mo^{IV}(SPh)(S_2C_2Me_2)_2]^{1-}$ as the active model cofactor, the irradiation on the hexacoordinated complex, $[Mo^{IV}(CO)(SPh)(S_2C_2Me_2)_2]^{1-}$ to remove CO resulted in decomposition [135] forming $[Mo^{V}(S_2C_2Me_2)_3]^{1-}$.

5.3.3. Structural–functional model chemistry of NAP

To mimic the active site of dissimilatory nitrate reductase, complexes $[Mo^{IV}(PPh_3)(SR)(mnt)_2]^{1-}$ (**5a**, R = Ph; **5d**, *p*-Me-C_6H_4, and **5e**,*o*-COOH-C_6H_4) [138,139] (Fig. 2) were synthesized. To mimic cysteinyl thiolate coordination of the native protein [131] the model study was further refined [140] by synthesizing (Fig. 2) simple aliphatic thiolate containing complexes, $[Mo^{IV}(PPh_3)(SCH_2CH_3)(mnt)_2]^{1-}$ (**5b**) and $[Mo^{IV}(PPh_3)(SCH_2Ph)(mnt)_2]^{1-}$ (**5c**). Complexes **5a**–**5c** reduce nitrate to nitrite (Eq. (3)). Reversible dissociation of PPh_3 from complexes **5a**–**5c** occur readily in solution generating the active pentacoordinated species, $[Mo^{IV}(SR)(mnt)_2]^{1-}$ responsible for nitrate reduction. Kinetics investigation of the reaction revealed Michaelis–Menten saturation kinetics with the highest rate of reaction being achieved with **5b**

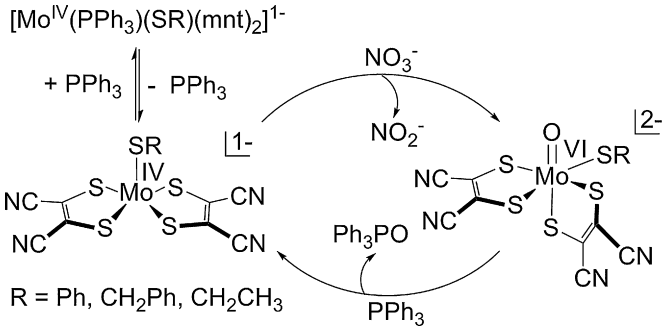

Fig. 11. Catalytic cycle for nitrate reduction using $\{[(Mo^{IV}(SR)(mnt)_2]^{1-}\}$ as the active catalyst and PPh_3 as the reductant of its putative oxidized form $\{[(Mo^{VI}O(SR)(mnt)_2]^{1-}\}$.

($V_{Max} = 3.2 \times 10^{-2}\ s^{-1}$; $V_{Max}^{5b}/V_{Max}^{5a} \sim 10$). The oxidized species, $\{[Mo^{VI}(O)(SR)(mnt)_2]^{1-}\}$ produced through the reduction of nitrate (Eq. (3)) was reduced back to $\{[Mo^{IV}(SR)(mnt)_2]^{1-}\}$ by dissociated PPh_3 (Eq. (4)). Utilizing these observations, a catalytic cycle is reported involving $[Bu_4N][NO_3]$ and PPh_3 as the oxidizing and reducing substrates respectively (Fig. 11).

$$\underset{R=-Ph\ (\mathbf{5a}),-CH_2CH_3\ (\mathbf{5b}),-CH_2Ph\ (\mathbf{5c})}{[Mo^{IV}(PPh_3)(SR)(mnt)_2]^-} + NO_3^- \rightarrow [Mo^{VI}(O)(SR)(mnt)_2]^- + NO_2^- + PPh_3 \quad (3)$$

$$\underset{R=-Ph\ (\mathbf{5a}),-CH_2CH_3\ (\mathbf{5b}),-CH_2Ph\ (\mathbf{5c})}{[Mo^{VI}(O)(SR)(mnt)_2]^-} + PPh_3 \rightarrow [Mo^{IV}(SR)(mnt)_2]^- + Ph_3PO \quad (4)$$

Complexes (**5a**–**5c**) could reduce TMNO or DMSO also [140], but the reactions did not lead to a complete conversion. In case of DMSO, the initial OAT was inhibited by the accumulated reaction product, dimethylsulfide, somewhat similar to feedback inhibition observed in enzymatic systems. In the case of TMNO reduction the product trimethylamine is basic and combines with trace amount of moisture present even in dry solvent and thereby decomposes the active species responsible for TMNO reduction.

In order to testify to the importance of the axially coordinated thiolate ligand, complexes, $[Mo^{IV}(PPh_3)(X)(mnt)_2]^{1-}$ (**6a**, X = Cl; **6b**, X = Br; **6c**, X = I, **6d**, X = NCS) isostructural to the model systems (**5a**–**5c**) have been synthesized [138–140] (Fig. 2). However, all these halide/NCS coordinated complexes did not show any reductive activity toward nitrate, TMNO or DMSO. This study indicates that halides and thiocyanate acts as dead end inhibitors [139,140] whereas in native systems they act as competitive inhibitors. Moreover, the mode of thiocyanate binding is via nitrogen [139] rather than via sulfur atom [141]. A recent DFT study [142] addressed the reactivity difference in **5a** and **6a** with nitrate [138], although these calculations failed to explain the plausible explanation for such a reactivity difference simply by changing the axial ligation at Mo center. Complexes, **5a**–**5c**, readily respond to the OAT reaction with nitrate which follows Michaelis–Menten kinetics, a characteristic signature of an enzyme like reaction (Eq. (5)).

$$E + S \rightleftharpoons [ES]' \rightleftharpoons [ES] \rightarrow [EP]' \rightarrow E' + P \quad (5)$$

Another DFT investigation has been reported [143] using computational model of nitrate reductase, $[Mo^{IV}(SMe)(S_2C_2Me_2)_2]^{1-}$ and also with protein environment model, however the nature of the first transition state ([ES]′ in Eq. (5) has not been stressed. This aspect has recently been stressed through computational effort [144] to understand the reactivity difference between thiolato and halide complexes as shown in Fig. 12. The potential donor redox orbital is the d_{xy} (Mo(IV)) orbital which is responsible for two electron enzymatic redox reaction and the accessibility of this orbital is the most important issue. The HOMO of the pentacoordinated form of **5a** and **5b** ($[Mo^{IV}(SR)(mnt)_2]^{1-}$ (R = –Ph and $-CH_2CH_3$ respectively) is predominantly a d_{xy}(Mo) orbital which is the potential electron donor and HOMO-1 of the pentacoordinated forms of **5a** and **5b** (having nearly the same energy) originates from the antibonding interaction of the Sπ and C=C π orbital of the dithiolene ligand (Fig. 12). These results indicate that when an oxo group of nitrate binds to the Mo center, electron transfer from HOMO (d_{xy})

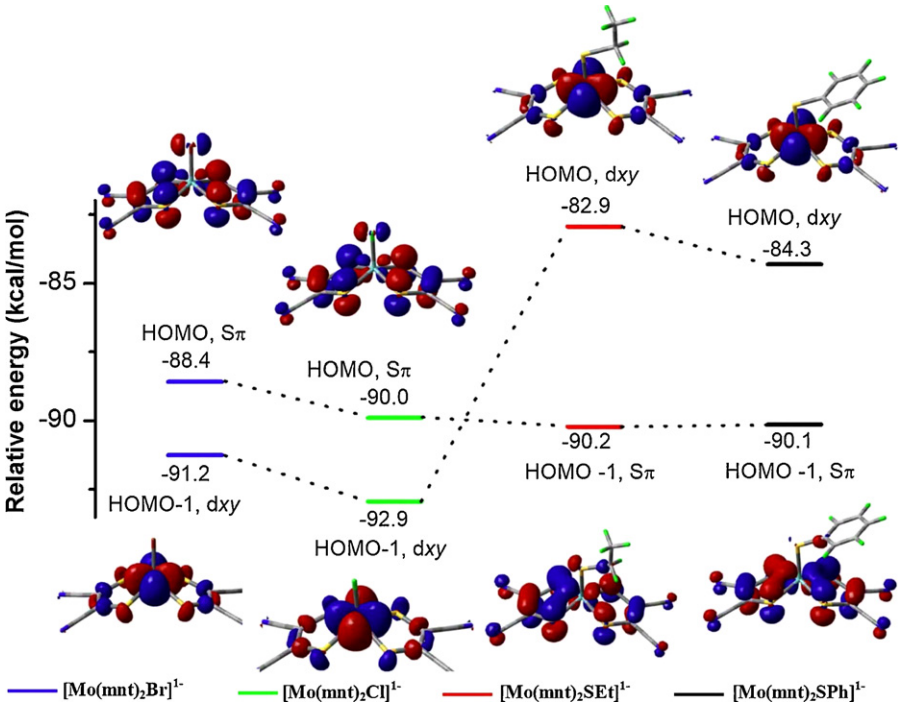

Fig. 12. Relative molecular orbital energy level diagram and FMO plot (only HOMO and HOMO-1 orbitals are shown). Reproduced with permission from Ref. [144]. Copyright Wiley–VCH Verlag GmbH & Co. KGaA.

to the nitrate coupled with OAT from nitrate to Mo can take place. The destabilization of HOMO of pentacoordinated form of **5b** by 1.4 kcal/mol with respect to that of pentacoordinated form of **5a** is supporting evidence to the faster rate of nitrate reduction by **5b** compared to **5a** [140]. In contrast, HOMO-1 of the corresponding pentacoordinated chloro and bromo derivatives are predominantly d_{xy} (Mo) orbital, stabilized by 2.8 and 2.5 kcal/mol respectively compared to their respective HOMOs which directly indicate the lack of accessibility of the salient redox orbital. Even using solvent dielectric with additional single-point calculation, such changes in the position of these orbitals retained which is originated by the effect of atomic orbital energy only as all the active states are structurally similar. Thus the nature of the axial ligation may tune the electronic criteria followed with the reactivity.

While searching for the Michaelis complex, **5a** and **5b** form a stable intermediate where nitrate is weakly bonded to the Mo center. Though in the case of **6a** a nitrate bound ES complex structurally similar to those from **5a** and **5b** may form, but energetically this is very unstable thereby responding to decomposition before the onset of OAT reaction. This type of ES complex may be a good example of non productive ES because the necessary redox orbital is also not accessible here for any such reaction to occur. The population analysis and the energetic for the reaction of the pentacoordinated species released from **6a**–**6b** with nitrate is well in agreement with the experimental results [140], that **6a**–**6b** were immediately converted to tris complex, $[Mo^{IV}(mnt)_3]^{2-}$ upon addition of nitrate.

In a parallel approach, two more thiolate ligated complexes, **5d**–**5e** were isolated (Fig. 2), which could reduce nitrate only incompletely [139]. To rationalize this fact along with the inability of a potent structural model system, $[Mo^{IV}(SC_6H_2\text{-}2,4,6\text{-}Pr^i_3)(S_2C_2Me_2)_2]^{1-}$ [135] to react with nitrate, a DFT calculation was again employed [139]. HOMOs in each case were predominantly metal centered indicating the thermodynamic ability of all these three complexes to mediate nitrate reduction. The different reactivity has been attributed to the increasing substitution at thiophenolate ring which hinders the approach of nitrate toward molybdenum center. This reaches its maximum in case of $[Mo^{IV}(SC_6H_2\text{-}2,4,6\text{-}Pr^i_3)(S_2C_2Me_2)_2]^{1-}$ thereby making it unable to reduce nitrate at all. The combined theoretical and experimental results showed that a fine tuning at the axial thiolate ligation is necessary to warrant nitrate reduction by model complexes [139].

5.4. Formate dehydrogenase (FDH)

5.4.1. Native FDH

FDH catalyze the oxidation of formate to carbon dioxide as the first step in acetogenic glucose fermentation [145–147]. As with nitrate reductase, there are several different classes of formate dehydrogenases [6]. The pyridine nucleotide-dependent enzyme from aerobes is a soluble enzyme devoid of molybdenum and other redox-active cofactors. Exceptions are the NAD^+-linked formate dehydrogenase from *Methylosinus trichosporum*, which possesses flavin cofactors and several iron–sulfur centers besides molybdenum [148] and the protein from *Clostridium thermoaceticum* which is a tungsten–Fe–S enzyme [147]. On the other hand, the enzyme from anaerobic bacteria is membrane bound and possesses molybdenum, while the enzyme from archaeal sources may contain either of molybdenum or tungsten center [147]. Active site structures of FDHs have been obtained from protein crystallography [149–151] and extended X-ray absorption fine structure (EXAFS) analyses [152,153], where it has been found that all but one refer to Mo-FDHs. Long after their first recognition [154,146], it is now well known that a substantial number of W-FDHs exist [155–159]. FDH is now known to preserve two pyranopterindithiolate cofactor, a defining feature of the DMSO reductase family, although, not all W-FDH have been shown to contain two pyranopterindithiolate ligands. Active sites of FDHs may accommodate either molybdenum or tungsten and *Desulfovibrio alaskensis* has been shown to produce active forms of Mo-FDH and W-FDH [158]. The nature of the axial ligation is not unique. Although, selenocysteinate is present in both oxidized and reduced states of most of the FDHs but there is an exception where one hydroxyl or sulfide ligand is present instead of selenocysteinate ligation.

5.4.2. Model chemistry of Mo-FDH

Due to the difficulty in preparing $[Mo(SeR)(dithiolene)_2]$ type of complexes and also due to the instability of Mo(VI) complexes with dithiolene type of ligands, there had not been much of selenothiolate ligated Mo(IV/VI) complexes reported earlier except $[Mo^{IV}(SeR)(S_2C_2Me_2)_2]^{1-}$ [160] and $[M^{IV}(CO)(SeR)(S_2C_2Me_2)_2]^{1-}$ (M = Mo, W) [13,161]. Recently complexes of the type $[Mo^{IV}Se(L)_2]^{2-}$ (L = cyclohexene 1,2-dithiolate) have been reported [162]. However, none of these complexes could demonstrate the FDH reaction.

5.4.3. Model chemistry of W-FDH

Tungsten mediated oxo transfer and related synthetic chemistry from a bioinorganic view point are far less developed, compared with molybdenum [18,109]. Relevant dithiolene chemistry of tungsten started only in 1992 with the synthesis of the set of complexes, $[W^{V}O(bdt)_2]^{1-}$, $[W^{IV}O(bdt)_2]^{2-}$ and $[W^{VI}O_2(bdt)_2]^{2-}$ [163] and four years later, the naphthalene-2,3-dithiolate complexes, $[W^{IV}O(ndt)_2]^{2-}$ and $[W^{VI}O_2(ndt)_2]^{2-}$ by Nakamura and coworkers [164]. The complex $[W^{IV}O(bdt)_2]^{2-}$ reduces TMNO to yield the dioxotungsten(VI) complex, $[W^{VI}O_2(bdt)_2]^{2-}$ in DMF medium. This was followed by the synthesis of a series of complexes, $[W^{IV}O(S_2C_2R_2)_2]^{2-}$ (R = phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl or quinoxalin-2-yl) by Garner and coworkers utilizing the reaction of $[WO_2(CN)_4]^{4-}$ with a series of dimethylamino- or thione-protected asymmetric dithiolenes (ene–1,2-dithiolates) [165]. The physical properties of all of the $[W^{IV}O(dithiolene)_2]^{2-}$ complexes were found consistent with a retention of the $(W^{IV}OS_4)$ center and each system showed a reversible electrochemical one electron oxidation to the corresponding W(V) system [165]. Various W(IV) and W(VI) dithiolene complexes have been reported by Holm and coworkers [166,167] and are summarized elsewhere [12]. Several other W(IV) and W(VI) bis(dithiolene) complexes with oxo and or sulfide ligation have been reported [162,168,169]. Some of the W(IV) complexes can be converted to the corresponding W(VI) complexes as well, but none of them could demonstrate the FDH reaction.

5.4.4. Structural–functional model chemistry of W-FDH

The model complex $[W^{IV}O(mnt)_2]^{2-}$ (**7**) was synthesized [170,171] directly from sodium tungstate upon addition of excess sodium dithionite to a mixture of Na_2WO_4 and Na_2mnt in water at pH 5.5. It is sensitive to oxygen which decomposes it. However, under anaerobic conditions it has been quantitatively oxidized by $K_3[Fe(CN)_6]$ or methylene blue leading to the formation of $[W^{VI}(O)_2(mnt)_2]^{2-}$ (**8**) in aqueous-acetonitrile medium which can be synthesized directly following the similar procedure for the preparation of **7** [170,171] but by adding sodium bisulfite instead of sodium dithionite.

To check the anaerobic dehydrogenase reaction of W-FDH, **7** was treated with CO_2/HCO_3^- at pH 7.5 in CH_3CN–H_2O where it slowly changes to **8** within a day or within 6 h upon keeping the reaction mixture at 50 °C. Chromotropic acid test for formate assay of the isolated product proved the presence of 55% formate based on **7** thus demonstrating the reaction as shown in Eq. (6), which is the first reaction of W-FDH in the pathway of CO_2 fixation in *Clostridium*

thermoaceticum [146–148].

$$[W^{IV}O(mnt)_2]^{2-} + HCO_3^- \rightarrow [W^{VI}O_2(mnt)_2]^{2-} + HCOO^- \quad (6)$$

Interestingly, displacement of W from **7** by Mo was achieved by using Na_2MoO_4 at ∼ pH 5 (CH_3COOH) in CH_3CN–H_2O (1:1). This is parallel to the reconstitution assay of W-FDH with the inactive assimilatory nitrate reductase of the *Nit-1* mutant of *Neurospora crassa* in the presence of Na_2MoO_4 in acidic medium [172].

5.5. Aldehyde ferredoxin oxidoreductase (AOR)

5.5.1. Native AOR

One of the best studied member of the hyperthermophilic archaea that thrive at high temperature (∼100 °C) near undersea hydrothermal vents is *Pyrococcus furiosus*, which contains the tungsten protein aldehyde ferredoxin oxidoreductase (AOR) and formaldehyde ferredoxin oxidoreductase (FOR) [50,51,173–177]. These tungstoenzymes catalyze atom transfer reaction with the proposed involvement of W(VI) as the catalytic center for the oxidation of aliphatic aldehydes. The reduced W(IV) center is oxidized back to W(VI) by ferredoxin centers (via FeS clusters) with the elements of water being used as the source of the additional oxygen atom of the carboxylic acid [50,51,173–177]. An inactive "red tungsten–iron–sulfur protein" (RTP) has also been isolated [50,51,173–177] during the purification procedure of AOR. Differences between the active AOR and inactive RTP forms have been speculated to be the presence of W–SH moiety in the former and a W=O group in the later [50,51,174]. Interestingly, *P. furiosus* reduces available sulfur in the growth medium to H_2S in an apparently energy conserving reaction that disposes of molecular H_2 produced from the fermentation of carbohydrates [178–180]. Active site structures of RTP, AOR and FOR contain two pyranopterindithiolate per metal atom and a $\{W(O)_2\}$(in RTP) or $\{W(O)(OH)\}$ (in AOR and FOR) moiety.

5.5.2. Model chemistry of AOR

Several monooxo W(IV) and dioxo W(VI) complexes have been reported [162,163,168,169,181–184] in relevance to W-enzyme systems. Various W(IV) and W(VI) complexes have been reported by Holm and coworkers and are summarized elsewhere [12]. Young and coworkers reported $\{HB(Me_2pz)_3\}W^{VI}OS\{(-)$-mentholate$\}$, $\{HB(Me_2pz)_3\}W^{V1}S_2(OPh)$ and $\{HB(Me_2pz)_3\}W^{IV}(OPh)\{S_2C_2(CO_2Me)_2\}$ [$HB(Me_2pz)_3$ = hydrotris(3,5-dimethylpyrazol-l-yl)borate] but as per our criterion only the latter complex has a dithiolene coordination [181]. Tungsten disulfur complexes have also been reported [185–187], although their reactivity has not been described. Some oxygen atom transfer reactions using tungsten complexes have been reported which in the case of W(VI) led to formation of W(V) dimer [163,181–184] whereas some W(IV) complexes are avid oxygen acceptors [188,189]. Therefore a true structural–functional modeling of AOR is yet to be achieved.

5.5.3. Structural–functional model chemistry of AOR

To address these enzymatic processes, the complexes, $[W^{VI}O_2(mnt)_2]^{2-}$ (**8**) and $[W^{VI}O(S_2)(mnt)_2]^{2-}$ (**9**) have been synthesized (Fig. 2) [171]. Complex **9** was prepared by refluxing **7** with elemental sulfur in acetone [171]. It is only very recently that analogous complexes, $[W^{VI}O(S_2)(L)_2]^{2-}$ (L = bdt, cyclohexene-1,2-dithiolate) have been reported [190] along with an interesting reaction with dihydrogen to form H_2S [191]. Complexes **8** and **9** contain coordination around the tungsten center which is quite similar to that found in the AOR and in the inactive RTP form with the attachment of a dihapto sulfide group in **9** instead of the proposed SH coordination. Both **8** and **9** yield **7** by reduction. Reaction of **8** with H_2S ultimately yielded **9** and **7** with a reactive intermediate possibly containing the $\{W^{VI}(O)(S)\}$ or $\{W^{VI}(O)(SH)_2\}$ moiety. Thus, to test the aldehyde oxidase activity, reactions were carried out with **8**, **8** with H_2S and with **9**, using formaldehyde and crotonaldehyde as substrates. A critical analysis of these reactions [171] showed that complex **9** is capable to mediate the transformation of aldehyde (crotonaldehyde) to acid (crotonic acid) thus demonstrating the model reaction for AOR (Fig. 13). At that stage, the disulfido ligation of tungsten was not certain in an active AOR enzyme. Ferredoxin centers are involved for the reoxidation of the reduced tungsten center of the native enzyme, whereas the release of elemental sulfur may be responsible to regenerate **9** from **7**. As suggested by Stiefel in the case of oxomolybdoenzymes [192], the electronic effect of the WS_2 moiety may be simulated by the coordination of two cysteinyl thiolates in adjacent positions of the W(IV) center in the native enzymes with partial disulfide bond formation. Hence the enzymatic oxotransfer may involve a similar heptacoordinated $\{W^{VI}(O)(SR)_2\}$ catalytic center followed by the hydrolysis of a $\{W\text{-}(SR)_2\}$ group to incorporate terminal oxo ligation to W(IV) center with the release of labile cysteinyl –SH group similar to that shown in Fig. 13. This may account for the reactivity difference between the inactive RTP and active AOR forms of the protein.

5.6. Acetylene hydratase (AH)

5.6.1. Native AH

The unique tungstoprotein, acetylene hydratase (AH) isolated from a mesophilic anaerobe *Pelobacter acetylenicus* catalyzes to the conversion of acetylene to acetaldehyde, a net hydration reaction rather than a redox one [193]. AH is a monomeric, 73 kDa protein possessing a tungsten center attached with a pterin cofactor and Fe–S cluster(s) [193], thus very closely resembling the structurally characterized aldehyde ferredoxin oxidoreductase (AOR) [50,51,173–178] from *P. furiosus*. Although Fe–S proteins catalyze non redox hydration reaction [194] but tungsten has a specific role in the functioning of AH activity [193]. Unlike other tungstoenzymes, AH was isolated in air. However, the enzyme does not show activity in air or in the presence of an oxygen scavenging system. It responds only after incubation with strong reductants like sodium

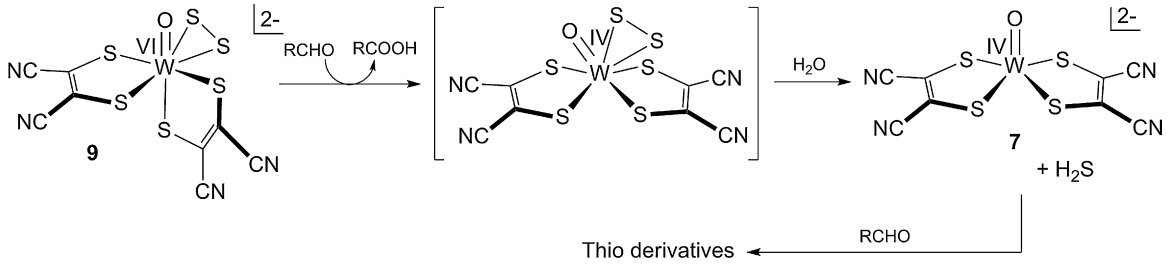

Fig. 13. AOR activity exhibited by complex **9**.

dithionite or titanium(III) citrate which invokes an alternate suggestion involving the initial reduction of acetylene to ethylene followed by hydration and subsequent oxidation [195,196]. However, the anaerobe *P. acetylenicus* neither uses ethylene as the metabolite nor does AH catalyze the conversion of ethylene to acetaldehyde or ethanol. It is also known that ethylene does not inhibit AH activity. All these facts suggest that the tungsten site of AH of anaerobe *P. acetylenicus* may get oxidized under aerobic isolation steps and thus requires strong reductants to regenerate its active form.

5.6.2. Model chemistry of AH

A number of molybdenum [197,198] and tungsten–acetylene [199,200] complexes of the form $[M(CO)(R^1C_2R^2)(S_2CNR_2)_2]$ have been reported, however with biologically irrelevant oxidation state (II) of Mo/W. A series of compounds $[MoO(R^1C_2R^2)(S_2CNR_2)_2]$ have been reported [201–204] where an oxo group has been substituted for CO and the metal can be considered as Mo(IV). All of the above types of complexes were made for $R^1C_2R^2 = C_2H_2$, making them particularly interesting species as only a few mononuclear complexes of unsubstituted acetylene were known [204]. The first synthesis of oxotungsten(IV)–acetylene complexes, $[WO(R^1C=CR^2)(S_2CNR_2)_2]$ by controlled oxidation of $[W(CO)(R^1C=CR^2)(S_2CNR_2)_2]$ with the dimeric oxygen atom transfer reagent $[Mo_2O_3(S_2P(OEt)_2)_4]$ was reported by Tempelton, McDonald and coworkers [205]. These complexes, including the parent C_2H_2 derivative, were stable toward alkyne dissociation. The complex $[MO(dtc)_2(C_2H_2)]$ (M = Mo, W; dtc = diethyldithiocarbamate) [205] was important in a sense that it was the first example of an acetylene bound Mo(IV)/W(IV) system. However, none of these complexes demonstrate the important hydration reaction of acetylene.

5.6.3. Structural–functional model chemistry of AH

The likely participation of a reduced tungsten site for catalyzing the hydration of acetylene to form acetaldehyde has been demonstrated [206] in case of the complex $[W^{IV}(O)(mnt)_2]^{2-}$ (**7**). Corresponding oxidized species did not show any catalytic activity, although after treatment with excess $Na_2S_2O_4$, it responded equally well. In a similar way, a mixture of Na_2WO_4 and Na_2mnt (1:2 ratio) in aqueous medium in the presence of KH_2PO_4 (pH ~ 6.5) did not catalyze the reaction but catalytic activity was observed upon addition of excess of $Na_2S_2O_4$. Earlier it was shown that dithionite can smoothly reduce a mixture of Na_2WO_4 and Na_2mnt to **7**. The active species, **7** was recovered with over 90% yield at different stages of the hydration reaction attesting to its function as proto-acetylene hydratase. Although no adduct formation between **7** and C_2H_2 could be observed by NMR or electronic spectroscopy, the occurrence of Eq. (7) supports the oxidative addition reaction as encountered with elemental sulfur [171].

$$[Et_4N]_2[W^{IV}O(mnt)_2] + CH_3CO_2C{\equiv}CCO_2CH_3 \rightleftharpoons [Et_4N]_2[W^{VI}O(mnt)_2\{C_2(CO_2CH_3)_2\}] \quad (7)$$

For Eq. (7), the calculated K_{eq} value {$14(\pm1)\,M^{-1}$ (CH_3CN, 25 °C)} when compared with K_{eq} values for similar reactions of $[Mo^{IV}(O)(dtc)_2]$ with C_2H_2 (~20 M^{-1}) and $CH_3CO_2C{\equiv}CCO_2CH_3$ (~20,000 M^{-1}) justifies the above observation. In this case, the short lived adduct compared to the stability of $[M^{IV}(O)(dtc)_2(C_2H_2)_2]$ (M = Mo, W) [203,205] should be the crucial requirement for the activation of acetylene for the subsequent hydration reaction. Thus Eq. (7) resembles the known Hg^{2+} catalyzed hydration of acetylene. Reduced activity of AH in the presence of $HgCl_2$ has been explained by the oxidative addition of $HgCl_2$ with **7** followed by the subsequent W(VI)–Hg(II) bond cleavage, as shown in Eq. (8). The response of **7** toward oxidative addition reactions with elemental sulfur, C_2H_2 and $HgCl_2$ suggests its involvement in activating acetylene via electron donor–acceptor (EDA) complexation. This model study clearly indicates that during the isolation procedure of AH under aerobic conditions, the active site becomes reversibly oxidized and reduction of this W center has to be carried out to regain the catalytic activity.

$$[Et_4N]_2[W^{IV}O(mnt)_2] + HgCl_2 \rightarrow [Et_4N]_2[W^{VI}O(Cl)(mnt)_2(HgCl)] \rightarrow [Et_4N]_2[W^{V}O(Cl)(mnt)_2] + 1/2\,Hg_2Cl_2 \quad (8)$$

6. Electrochemistry and Mo/W enzymes: clarification of the misconception

There has been a common practice of correlating the reduction potential data of an enzyme with that of the substrate to be oxidized or reduced enzymatically. The OAT reaction mediated by different molybdenum and tungsten containing enzyme systems cannot be directly correlated with the reduction potential value of either the intact enzyme or the substrate. For an oxo transfer reaction it is the enzyme–substrate complex (Michaelis–Menten complex) which is the active redox species quite similar to Taube's precursor complex in inner sphere mechanism. While dealing with the modeling chemistry for the tungsten sites of inactive and active forms of hyperthermophilic *P. furiosus* AOR, it was demonstrated [171] with a few interesting facts to address this misconception.

Complexes **8** and **9** showed irreversible reduction with reduction peak potentials at −1.50 and −1.45 V (vs Ag/AgCl in MeCN), respectively. The reduction peak potential of **8** was not shifted lower to −1.50 V when carried out in MeCN containing acetic acid–water (3.5 M water) at pH 5.5. Sodium dithionite has an effective reduction potential of −0.775 V vs Ag/AgCl at pH 5.5 although this value is a rough upper limit estimate, as E_0' of dithionite varies with concentration [207,208]. Therefore on the basis of simple reduction potential values, dithionite should not be capable of reducing **8**. Contrary to this expectation, dithionite smoothly reduced **8** to **7** [170,171] which indicates involvement of an inner sphere mechanism. Active site of enzyme (E) and the substrate (S) first form the Michaelis complex, ES, wherein the chemical identity of free E and unbound S are lost. The unstable ES complex can spontaneously engage in intramolecular electron transfer followed by or coupled to an atom transfer reaction with the expulsion of the oxidized substrate from the reduced E for an oxidase type half-reaction. This reaction process cautions that the cause of atom transfer reactions may not be predictable from using only the electron transfer concept [209] and reduction potential values measured by cyclic voltammetry of the complex compound or the substrate or by spectroscopy coupled to potentiometry using mediator dye for native enzymes. Thus, for the Mo(VI)/Mo(V) and Mo(V)/Mo(IV) couples of dimethyl sulfoxide (DMSO) reductase, the measured midpoint potential values range between +0.065 and −0.15 V vs NHE in the pH range 5–9 [31]. However, DMSO is electrochemically stable with a clear potential window from +2.0 V to −2.0 V and is used as a solvent for electrochemical studies. For the complexes, $[Mo^{IV}O(Et_2dtc)_2]$ and $[Mo^{IV}O(LNS)_2DMF]$ (dtc = dithiocarbamate; $LN(SH)_2$ = 2,6-bis(2,2-diphenyl-2-mercaptoethyl)pyridine), the difference of 0.12 V in the appearance of irreversible anodic peak potentials (+0.4 [210] and +0.52 V [211] vs SCE respectively) did not distinguish their thermodynamic ability to reduce DMSO. Hence the difference of only −0.03 V for the Mo(V)/Mo(IV) couples between the oxo sulfido (active) and dioxo (inactive) forms of bovine xanthine oxidase [5,212] should not be fully responsible for the difference in their activity on xanthine. These observations clearly suggest the inherent chemistry associated with a species to form the enzyme–substrate complex. The possible existence of such a

species in the reductive half-reaction of xanthine oxidase has been reported [213].

Again, the facile reductive sulfur abstraction with PPh_3 demonstrated the importance of the kinetic aspect in atom transfer reactions [171]. The irreversible reduction peak potential as high as −1.45 V vs Ag/AgCl (of **9**) suggests that such a high value does not really predict whether an atom transfer reaction will occur smoothly at ambient conditions or not.

Recently, a study of respiratory nitrate reductase from *Rhodobacter sphaeroides* (NapAB) [214] by protein film voltammetry [215] has been reported [216] which presented the first quantitative interpretation of the complex redox-state dependence of activity. It has been shown in the context of electron transfer from the proximal [4Fe–4S] cluster to the Mo active site (in NapAB) that reduction potentials cannot always be directly used to understand the behavior of an enzymatic system under turnover conditions [216]. Essentially the fact that the reduction potential of the proximal [4Fe–4S] cluster that donates electron to the Mo active site (in NapAB) is substantially higher than that of the Mo(V/IV) (−80 mV vs −225 mV) seems to make the last intramolecular electron transfer step endergonic. Although one may argue that the electron transfer could yet be fast because of the small distance between the proximal cluster and the active site but this study [216] demonstrates the fact that the reduction potential of the [4Fe–4S] cluster is sufficiently low, such that the reduction of substrate-bound Mo(V) by [4Fe–4S] cluster is exergonic and obviously the reduction potential of the substrate-free Mo(V/IV) couple is irrelevant.

7. Conclusion

The contemporary molybdenum/tungsten chemistry associated with biological perspective as summarized by Stiefel [3] has traversed a long way since then. A number of molybdenum and tungsten enzymes have been structurally characterized along with spectroscopic investigation. Re-evaluation of some long known bioinorganic modeling chemistry along with new developments in the same field has widened the prospect of bioinorganic modeling of molybdenum and tungsten containing enzymes. Elegant synthesis with the exploitation of simple and basic chemistry inspired by biological systems has been employed to synthesize model systems for some selected enzymes. These model complexes have essentially merged to a large extent the two extreme cases of modeling, namely, structural and functional modeling into a new modeling strategy, namely, structural–functional modeling which has widened the prospect of bioinorganic modeling chemistry of molybdenum and tungsten enzymes in a definitive way.

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