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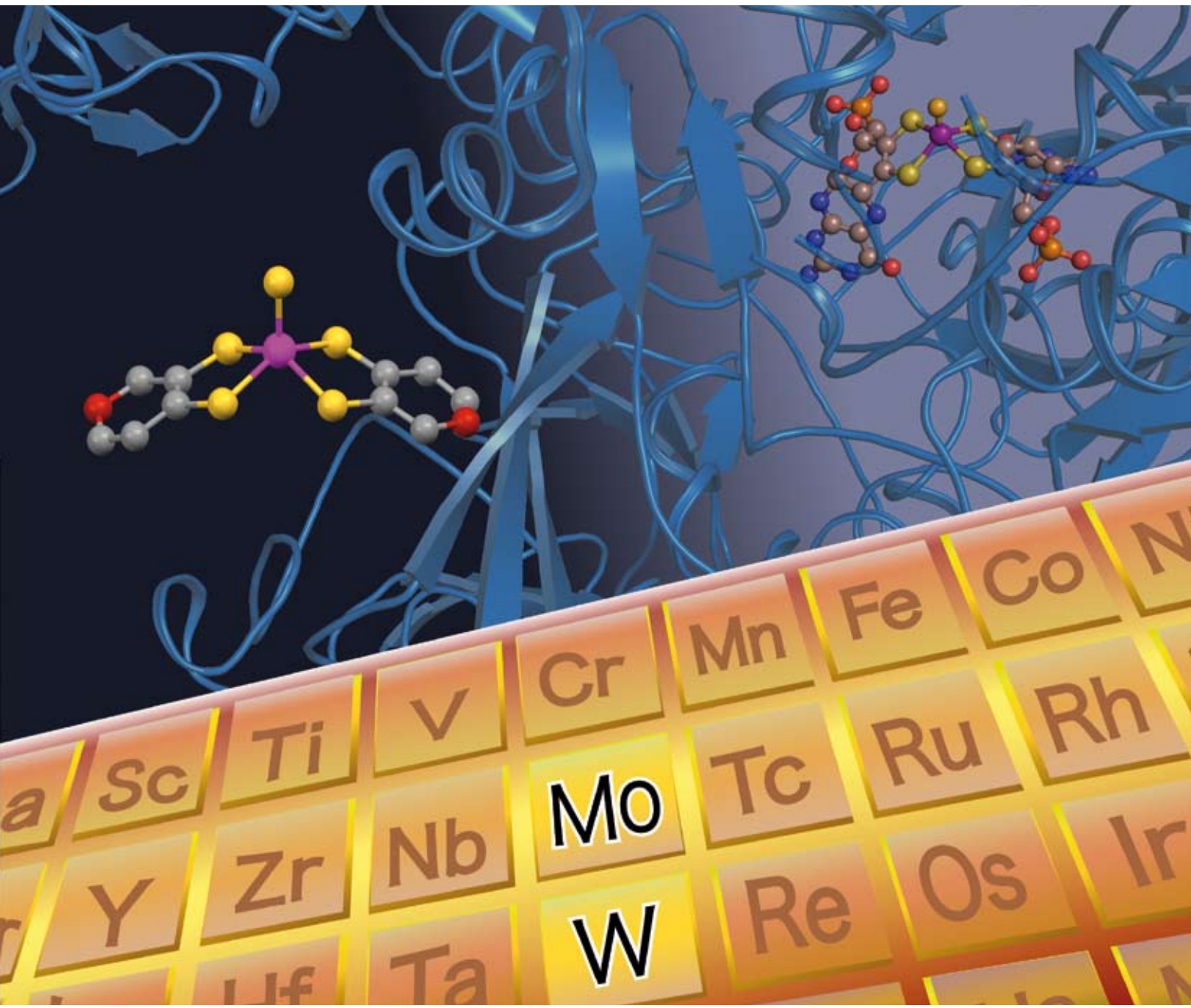

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Chemical analogues relevant to molybdenum and tungsten enzyme reaction centres toward structural dynamics and reaction diversity

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Recent characterisation of molybdenum and tungsten enzymes revealed novel structural types of reaction centres, as well as providing new subjects of interest as synthetic chemical analogues. This *tutorial review* highlights the structure/reactivity relationships of the enzyme reaction centres and chemical analogues. Chemical analogues for the oxygen atom transfer enzymes have been well expanded in structure and reactivity. Other types of chemical analogues that exhibit different coordination chemistry have recently been presented for reaction centres of the hydroxylation and dehydrogenation enzymes and others.

1. Introduction

Molybdenum (Mo) and tungsten (W) are unique 4d (Mo) and 5d (W) transition metals found in biological systems. Mo is present at a high concentration in sea water (1×10^{-2} mg L^{-1}) as $[Mo^{VI}O_4]^{2-}$, which means that biological systems take Mo from the sea. The oxidation numbers of both Mo and W vary from +4 to +6 in biological reaction cycles, whereas 3d transition metals are usually in the range from +2 to +4 in biological systems.[1] As a result, the two ions have similar ionic radii to the 3d transition metal ions although the atomic radii of Mo (1.40 Å) and W (1.41 Å) are larger than those of the latter (1.35–1.25 Å): 0.79–0.73 Å for Mo(IV)–Mo(VI); 0.80–0.74 Å for W(IV)–W(VI); and 0.91–0.67 Å for the 3d transition metal ions.[2]

Mo and W enzymes are present in all forms of life from ancient archaea to human,[1,3,4] and catalyse a wide range of reactions in carbon, sulfur and nitrogen metabolism. More than 50 Mo enzymes have been reported. With respect to W enzymes, about a dozen examples have been characterised, remarkably, most of which are found in hyperthermophilic archea living at ~100 °C.[4] The majority of Mo and W enzymes are oxotransferases and hydroxylases, which catalyse the forward reaction of the following net oxygen atom exchange or the backward reaction, coupled to proton and electron transfer between substrate E (or R–H)/EO (or R–OH) and the Fe–S cluster, heam or flavin.

$$\text{E (or R–H)} + H_2O \rightleftarrows \text{EO(or R–OH)} + 2H^+ + 2e^-$$

This type of reaction involves proton-coupled electron transfer (PCET) and utilises water as an ultimate source or sink of oxygen. PCET describes reactions in which there is a change in both electron and proton content between reactants and products, and allows buildup of multiple redox components.[5] As a result, PCET is a cornerstone of many important biological energy conversion processes such as dihydrogen oxidation in hydrogenase, dinitrogen fixation in nitrogenase,

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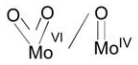
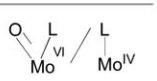
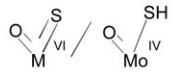
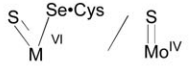
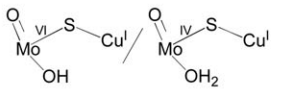
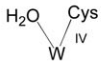
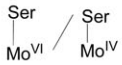
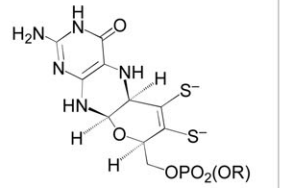
Table 1 Schematic representation of functional groups, ligand environments and reaction types in Mo and W enzymes

	Oxygen atom transfer		Hydroxylation	Dehydrogenation	
Functional Group		 (L = Ser, Cys, Asp, OH)	 M = Mo, W	 M = Mo, W	
Ligand Environment	$Mo^{VI}O_2(MPT)_2$ **1a** $Mo^{IV}O(MPT)_2$ **1b** $Mo^{VI}O_2(Cys)(MPT)$ **2a** $Mo^{IV}O(OH_2)(Cys)(MPT)$ **2b**	$Mo^{VI}O(L)(MPT)_2$ **3a** $Mo^{IV}(L)(MPT)_2$ **3b**	$Mo^{VI}O(S)(OH)(MPT)$ **4a** $Mo^{IV}O(SH)(OH_2)(MPT)$ **4b** $W^{VI}O(S)(MPT)_2$ **5a**	$Mo^{VI}S(Se{\bullet}Cys)(MPT)_2$ **6a** $Mo^{IV}S(MPT)_2$ **6b** $W^{VI}S(Se{\bullet}Cys)(MPT)_2$ **7a**	$Mo^{VI}O(OH)(MPT)(\mu\text{-}S)Cu^{I}S{\bullet}Cys$ **8a** $Mo^{IV}O(OH_2)(MPT)(\mu\text{-}S)Cu^{I}S{\bullet}Cys$ **8b**
Reaction Type	$X + H_2O \longrightarrow XO + 2H^+ + 2e^-$ (eq. 1) AO (arsenite oxidase, **1a**/**1b**) SO (sulfite oxidase, **2a**/**2b**) $XO + 2H^+ + 2e^- \longrightarrow X + H_2O$ (eq, 2) DMSOR (L=Ser, dimethylsulfoxide reductase) TMAOR (L=Ser, trimethylamine *N*-oxide reductase) NIR (L=Cys, nitrate reductase) NIR (L=Asp, nitrate reductase) SeR (L=OH, selenate reductase) } **3a**/**3b**		$R–H + H_2O \longrightarrow R–OH + 2H^+ + 2e^-$ (eq. 3) XO (xanthine oxidase) QOR (quinoline 2-oxidoreductase) Mo–AOR (Mo–aldehyde oxidoreductase) } **4a**/**4b** FOR (formaldehyde ferredoxin oxidoreductase) W–AOR (W–aldehyde oxidoreductase) GAPOR (glyceraldehyde-3-phosphate ferredoxin oxidoreductase) } **5a**/n.r.	$HCOO^- \longrightarrow CO_2 + H^+ + 2e^-$ (eq. 4) Mo–FDH (Mo–formate dehydrogenase, **6a**/**6b**) W–FDH (W–formate dehydrogenase, **7a**/n.r.) $RNH–CHO + H_2O \longrightarrow RNH_2^+ + CO_2 + H^+ + 2e^-$ (eq. 5) FMDH (*N*-formylmethanofuran dehydrogenase, **7a**/n.r.) $CO + H_2O \longrightarrow CO_2 + 2H^+ + 2e^-$ (eq. 6) CODH (CO dehydrogenase, **8a**/**8b**)	

	Other reaction		Unidentified
Functional Group			
Ligand Environment	$W^{IV}(OH_2)(Cys)(MPT)_2$ **9b**	$Mo^{VI}(Ser)(MPT)_2$ **10a** $Mo^{IV}(Ser)(MPT)_2$ **10b**	$Mo?(MPT)_2$ **11** $W?(MPT)_2$ **12**
Reaction Type	$HCCH + H_2O \longrightarrow CH_3CHO$ (eq. 7) AH (acetylene hydratase, **9b**)	pyrogallol $\longrightarrow$ 3–hydroxy–orthoquinone (eq. 8) TH (pyrogallol-phloroglucinol transhydroxylase, **10a**/**10b**)	$S_n^{2-} + 2H^+ + 2e^- \longrightarrow S_{(n-1)}^{2-} + H_2S$ (eq. 9) PSR (polysulfide reductase, **11**) $S^0 + H_2 \longrightarrow H_2S$ (eq. 10) WOR4 (fourth tungsten oxidoreductase, **12**) $RCOOH + 2H^+ + 2e^- \longrightarrow RCHO$ (eq. 11) CAR (carboxylic acid reductase, **12**)

MPT = 
R = H, nucleotide

n. r. = not reported.

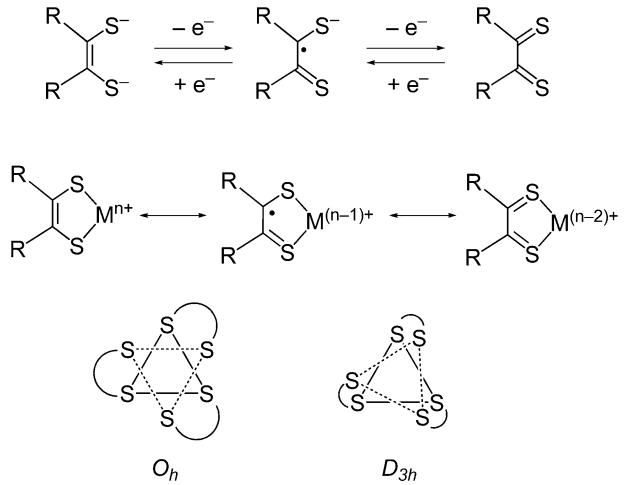


Fig. 1 Non-innocent property in dithiolene (top, redox), its transition metal compounds (middle, valence tautomerism) and tris(dithiolene) metal compounds (bottom, geometry).

dioxygen reduction in cytochrome *c* oxidase and dioxygen evolution in Photosystem II.[1]

Among the Mo and W enzymes, oxotransferases have been the most well characterised. Until 1996, the reaction centres had been considered to include the $M^{VI}O_2$ and $M^{IV}O$ functional groups in the oxidised and reduced states, respectively, because these species are very common in synthetic Mo and W compounds.[3,4] This standpoint had been widely accepted and led to a large number of $M^{VI}O_2$ and $M^{IV}O$ model compounds that catalyse oxygen atom transfer (OAT) using co-oxidants such as DMSO and NO_2^-.[6] Many model compounds are widely applicable in biomimetic oxidations and reductions,[7] and further chemical modeling is higly significant to promote hydroxylation and dehydrogenation as well as PCET. In the past decade, advanced X-ray crystallographic, EXAFS and XAS analytical techniques have provided the evidence supporting the fact that most Mo and W enzymes have other kinds of functional groups in the reaction centres. Table 1 summarises the functional groups and ligand environments of the enzyme reaction centres as well as the reaction types. The $M^{VI}O_2/M^{IV}O$ functional groups are only included in a few enzymes,[3,8] which consists of about 10% of the overall Mo and W enzymes listed. Oxidases of OAT enzymes are featured by the $Mo^{VI}O_2/Mo^{IV}O$ and $Mo^{VI}O$/desoxo Mo^{IV} types of functional groups and catalyse eqns (1) and (2) of Table 1.[3,9] Several enzymes bearing the $M^{VI}O(S)$ and $M^{VI}S$ type of functional groups promote hydroxylation and dehydrogenation (Table 1, eqn (3)–(6)), in which the sulfido groups are essential for the enzymatic activities.[3,4,9–18] Enzymes catalysing other types of the reactions (Table 1, eqn (7)–(11)) have been reported, however, some have unidentified functional groups (**11** and **12**).[3,4,19]

All functional groups in the characterised Mo and W enzymes are coordinated by one or two redox active metal-binding pyranopterin dithiolene (MPT) in the ene-1,2-dithiolate form.[3,4] Such MPT ligation is a unique feature of the Mo and W enzyme reaction centres. Dithiolenes were utilised in the 1930s as analytical reagents for metals. The d transition metal compounds of dithiolenes were extensively characterised in the 1960s and were revealed to exhibit interesting redox, valence tautomeric and geometric chemistry arising out of "non-innocent property" of dithiolenes as indicated in Fig. 1.[20] Consequently, there is one open question regarding the role of the MPT in the redox and stereochemistry of the Mo and W enzyme reaction centres. However, detailed structural and spectroscopic characterisations of the Mo and W reaction centres have been difficult. Each enzyme has a heavy Mo or W atom which prevents the clear EXAFS investigation and also includes neighboring Fe–S cluster, heam and/or flavin moieties that have strong absorbing chromophores, which obscure the electronic transitions of the metal reaction centre. Furthermore, the Mo and W reaction centres are very unstable when they are released from their protein matrices. Therefore, chemical analogues for the Mo and W enzyme reaction centres have been extensively developed to provide deep insights into the roles of the metal–ligated functional groups and MPT in the elementary OAT, hydroxylation, dehydrogenation, proton transfer and electron transfer reactions.

This review describes two classes of chemical analogues for Mo and W enzyme reaction centres: non-dithiolene compounds as functional group analogues and dithiolene compounds as ligand environment analogues (see Fig. 2). Because the reaction centres of the Mo and W enzymes have diverse reactivities in oxidation/reduction and/or PCET, excellent chemical analogues should have structural dynamics and reaction diversities *via* structural optimisation of the functional groups and the ancillary dithiolene ligands. Functional group analogues have been prepared at the primary modeling step, and the corresponding ligand environment analogues have subsequently been developed. Typically, the

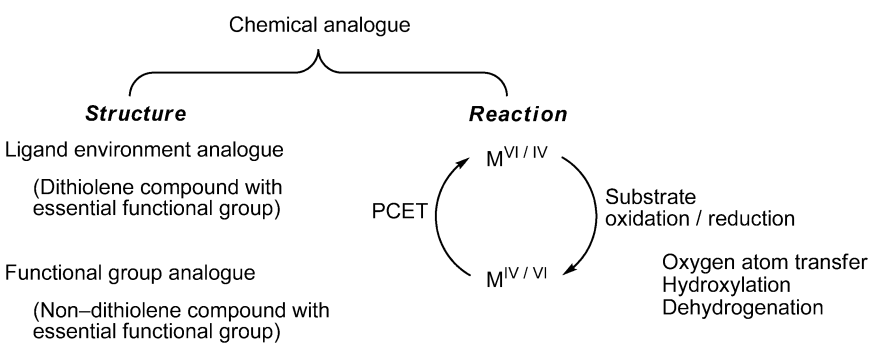


Fig. 2 Chemical analogues for reaction centres of Mo and W enzymes.

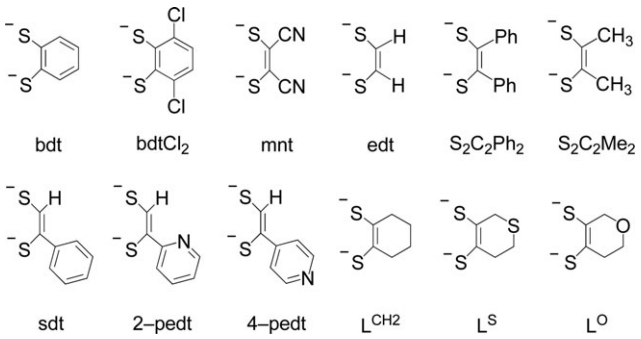


Fig. 3 Ligand structures of dithiolenes discussed in this review: Bdt = 1,2-benzenedithiolate, $bdtCl_2$ = 3,6-dichloro-1,2-benzenedithiolate, mnt = maleonitriledithiolate, edt = ethylene-1,2-dithiolate, $S_2C_2Ph_2$ = 1,2-diphenyl-1,2-ethylenedithiolate, $S_2C_2Me_2$ = 1,2-dimethyl-1,2-ethylenedithiolate, sdt = 1-phenyl-1,2-ethylenedithiolate, 2-pedt = 1-(2-pyridine)-1,2-ethylenedithiolate, 4-pedt = 1-(4-pyridine)-1,2-ethylenedithiolate, L^{CH2} = cyclohexene-1,2-dithiolate, L^{S} = 2,3-dihydro-2*H*-thiopyran-4,5-dithiolate, L^{O} = 2,3-dihydro-2*H*-pyran-4,5-dithiolate.

ligand environment analogues mimicking the OAT and PCET reactions of **1a**/**1b**, **2a**/**2b** and **3a**/**3b** have been synthesised by referring the pioneering studies of functional group analogues. On the other hand, chemical modeling studies of the hydroxylation and dehydrogenation enzymes have been behind those of the OAT enzymes (see **4a**/**4b**, **5a**, **6a**/**6b**, **7a** and **8a**/**8b**). This is due to lack of accumulated information on sulfido Mo and W compounds. The numbers of the functional group analogues characterised crystallographically are 10 for **4a**, 6 for **5a**, 9 for **6b** and 0 for **4b**, **6a**, **7a**, **8a** and **8b**. The corresponding ligand environment analogues characterised crystallographically are further limited. We first describe successful examples of chemical analogues for the OAT enzymes, and then discuss more recent examples of chemical analogues of other Mo and W enzymes. Fig. 3 represents the structures and notations of the dithiolenes that appear in this review. In the ligand environment analogues, aromatic dithiolenes were employed first and subsequently aliphatic dithiolenes were incorporated with Mo and W centres. The latter can provide ''ene-1,2-dithiolate'' ligation in a similar fashion to the biological MPT ligand.

2. Reaction centres in oxygen atom transfer enzymes and their chemical analogues

2.1 $Mo^{VI}O_2/Mo^{IV}O$ type of functional group in the enzymes and chemical analogues

The $Mo^{VI}O_2/Mo^{IV}O$ type of functional group is included in oxidases of OAT enzymes, AO and SO, and promotes net oxygen atom exchange between the substrates and water (eqn (1) in Table 1, X = AsO_2^- and SO_3^{2-}).[3,8] The ligand environments of the Mo centres in AO and SO are different. AO has the six-coordinate $Mo^{VI}O_2$ and square-pyramidal $Mo^{IV}O$ centres coordinated by two MPT in the oxidised and reduced states, respectively (**1a** and **1b** in Table 1).[8] Interestingly, the oxidised AO exhibited two ν(C=C) vibrational modes at 1525 and 1598 cm^{-1}, indicating that the two MPT are inequivalent in the π-delocalisation.[8] The oxidised and reduced SO have the square-pyramidal $Mo^{VI}O_2$ and $Mo^{IV}O$ centres with one MPT and one Cys, respectively (**2a** and **2b** in Table 1).[3] In these catalytic reactions, one oxygen atom of the $Mo^{VI}O_2$ centre is transferred to each substrate to yield the $Mo^{IV}O$ centre as well as each product, and the resultant $Mo^{IV}O$ centre is re-oxidised to the $Mo^{VI}O_2$ centre incorporating one water oxygen atom by PCET. A large number of the functional group analogues have been developed and their OAT reactivities have been summarised in the literature.[6]

In 1986, Boyde *et al.* synthesised $(Et_4N)_2[Mo^{IV}O(bdt)_2]$ and $(Ph_4P)[Mo^{V}O(bdt)_2]$ by reactions of $K_4[Mo^{IV}O_2(CN)_4]$ and $(Ph_4P)[Mo^{V}O(SC_6H_5)_4]$ with 2 equivalents of H_2bdt, respectively, as the first bis(dithiolene) Mo compounds and determined their crystal structures.[21] Since then, more than two dozen bis(dithiolene) $Mo^{IV}O$ compounds have been synthesised, in contrast the bis(dithiolene) compounds with the $Mo^{VI}O_2$ functional group remain difficult to be prepared and isolated. Yoshinaga *et al.* prepared $(Et_4N)_2[Mo^{VI}O_2(bdt)_2]$ from the corresponding $Mo^{IV}O$ species and Me_3NO in 1990.[22] Only two examples including mnt[23] and $bdtCl_2$ ligands have been reported as other pairs of crystallographically characterised bis(dithiolene) $Mo^{VI}O_2/Mo^{IV}O$ compounds.[24] In the bdt, mnt and $bdtCl_2$ compounds, the three $Mo^{IV}O$ centres adopt a square-pyramidal structure and the three $Mo^{VI}O_2$ centres possess an intermediate structure between octahedral and trigonal prismatic. The three dithiolenes differ from the MPT ligand in that the three are aromatic or electropositive with CN substituents. It is difficult for the $Mo^{VI}O_2/Mo^{IV}O$ compounds to exhibit non-innocent characteristics. In addition to various aliphatic dithiolenes such as edt, $S_2C_2Ph_2$ and $S_2C_2Me_2$,[25] which are potentially capable of being non-innocent, unsymmetric aliphatic dithiolenes such as 2-sdt, 2-pedt and 4-pedt were attached to $Mo^{IV}O$ centres.[26] In the 2-pedt and 4-pedt compounds, the dithiolenes can have a double bond character about the C–S bonds and a single bond character in the C–C bonds as a result of the resonance and inductive effects with the pyridines.[26] More recently, the aliphatic six-membered dithiolenes, L^{CH2}, L^{S} and L^{O}, were introduced into $Mo^{VI}O_2$ and $Mo^{IV}O$ centres.[27] All the $Mo^{IV}O$ compounds crystallographically characterised possess a square-pyramidal geometry. Although the three $Mo^{VI}O_2$ compounds comprising L^{CH2}, L^{O} and L^{S} were not isolated, the W counterpart of $(Et_4N)_2[Mo^{VI}O_2(L^{O})_2]$ was revealed to have an intermediate geometry between octahedral and trigonal prismatic.[28] The non-innocent characteristics of the dithiolenes employed will be investigated by various spectroscopic techniques in connection with characteristic reactivity of the $Mo^{VI}O_2/Mo^{IV}O$ compounds.

The ligand environment analogues of **1a**/**1b** were used to evaluate the Mo=O bond character of AO. As reflected in the Mo^{IV}=O bond lengths, the Mo^{IV}=O bonds of synthetic bis(dithiolene) compounds (1.67–1.72 Å) are comparable with that of **1b** (1.7 Å estimated by EXAFS) in bond strength.[8,21–27] On the other hand, synthetic bis(dithiolene) $Mo^{VI}O_2$ compounds exhibit larger values of $\nu(Mo^{VI}{=}O)_{sym}$ stretching (885–847 cm^{-1}) compared with **1a** (822 cm^{-1}),[8,22–25] suggesting the presence of other perturbations around the coordination sphere of **1a**. The hydrogen bond between the oxo groups of **1a** and the peptide backbone may weaken the Mo^{VI}=O bonds. Indeed, the hydrogen bond between the oxo group

and the ethanol molecule in the crystal structure of $(Ph_4P)_2[Mo^{IV}O(sdt)_2]\cdot C_2H_5OH$ gives a lower $\nu(Mo^{IV}{=}O)$ stretching value (879 cm^{-1}) than those of $(Ph_4P)_2[Mo^{IV}O$-(2-pedt)$_2$] (902 cm^{-1}) and $(Ph_4P)_2[Mo^{IV}O(4\text{-pedt})_2]$ (900 cm^{-1}) compounds with a distinct oxo group.[26]

Lim *et al.* reported $(Et_4N)[Mo^{VI}O_2(S\text{-}2,4,6\text{-}{}^{i}Pr_3C_6H_2)(bdt)]$ and $(Et_4N)[Mo^{VI}O_2(OSiPh_3)(bdt)]$ as the first mono(dithiolene) $Mo^{VI}O_2(SR/OR)$ compounds,[29] the latter of which is a unique ligand environmental analogue of **2a** and has a square-pyramidal geometry with the Mo^{VI} centre displaced 0.74 Å from the 3S + O equatorial plane. Further synthetic efforts toward ligand environments for **2a**/**2b** have been continued.

Catalytic cycles in AO and SO enzymes consist of OAT and PCET. Because Mo^{V} and Mo^{VI} compounds tend to irreversibly polymerise in the presence of water, few synthetic compounds have been demonstrated to combine these two reactions. The $Mo^{VI}O_2/Mo^{IV}O$ system reported by Xiao *et al.* has been the only distinct functional group analogue that combines OAT and PCET.[30] $[Tp^*Mo^{VI}O_2(S\text{-}C_6H_5)]$ was formed from $[Tp^*Mo^{IV}O(py)(S\text{-}C_6H_5)]$ (Tp* = hydrotris-(3,5-dimethylpyrazolyl)borate) by O_2 oxidation in the presence of water, and was re-reduced to the $Mo^{IV}O(py)$ species by OAT to PPh_3 in the presence of pyridine.[30] In this cycle, the $Mo^{IV}O(OH_2)$ centre derived from the $Mo^{IV}O(py)$ in H_2O is converted to the $Mo^{V}O(OH)$ centre by a type of PCET called CEPT (coupled electron–proton transfer), which undergoes sequential deprotonation and oxidation to give the $Mo^{VI}O_2$ centre. Here, CEPT defines an elementary step in which electrons and protons transfer from different orbitals on the donor to different orbitals on the acceptor.[5] The attached oxygen atom of the $Mo^{VI}O_2$ centre has been confirmed to be derived from water by a labeling experiment.[30]

Sugimoto *et al.* reported the first example of combined OAT and PCET with a ligand environment analogue of **1a**/**1b**.[31] The reaction scheme is shown in Fig. 4. The square-pyramidal $(Bu_4N)_2[Mo^{IV}O(bdtCl_2)_2]$ was oxidised to $(Bu_4N)_2$-$[Mo^{VI}O_2(bdtCl_2)_2]$ by $K_3[Fe(CN)_6]$ at pH > 9 *via* the $Mo^{V}O$ and $Mo^{V}O(OH)$ species. The square-pyramidal $Mo^{V}O$ species was characterised by X-ray crystal analysis. When the reaction was carried out in $H_2{}^{18}O$, the ^{18}O oxygen was incorporated into one of the two oxo groups of the $Mo^{VI}O_2$ compound, confirmed by the IR and ESI-MS experiments. The original $(Bu_4N)_2[Mo^{IV}O(bdtCl_2)_2]$ was regenerated by OAT from $(Bu_4N)_2[Mo^{VI}O_2(bdtCl_2)_2]$ to AsO_2^- and PPh_3. In contrast to the Tp* system, the $Mo^{V}O(OH)$ centre with $bdtCl_2$ undergoes CEPT to give the $Mo^{VI}O_2$, and the Mo centre varies its coordination number from five to six during the structural changes from the $Mo^{IV}O$ to the $Mo^{VI}O_2$ centres. Different from $(Et_4N)_2[Mo^{IV}O(bdtCl_2)_2]$, the oxidation of $(Et_4N)_2[Mo^{IV}O(bdt)_2]$ did not provide the expected $(Et_4N)_2[Mo^{VI}O_2(bdt)_2]$ even at pH = 14, but rather the one-electron oxidised square-pyramidal $Mo^{V}O$ species.[31] The bdt with no chlorine substituent provides the $Mo^{V}O$ centre with the less acidic character as not to bind OH^-. Because W compounds can have higher acidity than the isostructural Mo compounds, they are expected to exhibit different reactivities from the Mo counterparts. In fact, $(Et_4N)_2[W^{IV}O(bdtCl_2)_2]$ was revealed to be converted to $(Et_4N)_2[WO_2(bdtCl_2)_2]$ by PCET at lower pH than the corresponding Mo compound, but OAT from the $W^{VI}O_2$ centre to PPh_3 did not proceed.[32] As no OAT enzyme has been reported to include a W centre, a combination of PCET and OAT appears to be difficult with synthetic W compounds.

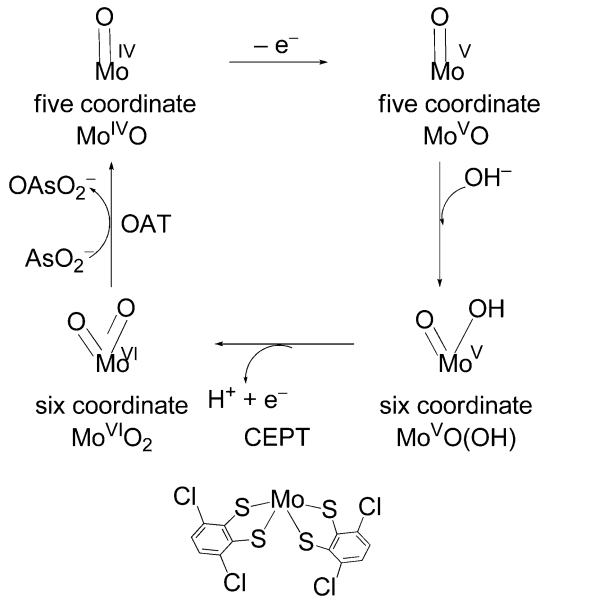


Fig. 4 Reaction scheme of PCET and OAT with $bdtCl_2$ compound. The $Mo^{IV}O$, $Mo^{V}O$ and $Mo^{VI}O_2$ compounds were characterised by X-ray crystallography.

2.2 $Mo^{VI}O/Mo^{IV}$ type of functional group in the enzymes and chemical analogues

Reductases of OAT enzymes contain $Mo^{VI}O/Mo^{IV}$ type of functional group at the reaction centres. DMSOR, TMAOR, NIR and SeR are classified into the enzymes, and the crystal structures of the former three have been determined. The Mo centre of DMSOR adopts the trigonal-prismatic $Mo^{VI}O$ and square-pyramidal desoxo Mo^{IV} structures, both of which are coordinated by two MPT and one Ser (see **3a** and **3b** in Table 1).[9] Interestingly, the two MPT of the oxidised DMSOR are inequivalent in the electronic structure as supported by the two ν(C=C) stretching bands at 1576 and 1526 cm^{-1}, whereas the two MPT of the reduced DMSOR are similar in electronic structure and characterised by one ν(C=C) vibration band at 1568 cm^{-1}.[3] These results strongly suggest the valence-tautomeric property of MPT. TMAOR Mo centre has the same ligand environment as DMSOR Mo centre, whereas Mo centres of NIRs have different protein-based ligands from that of DMSOR.[3,10] Two NIRs from *Desulfovibrio desulfuricans* and from *Escherichia coli* include a square-pyramidal Mo^{IV} centre with Cys and a trigonal-prismatic Mo^{IV} centre with Asp, respectively, instead of the Ser in DMSOR. The Mo^{IV} centres of DMSOR, TMAOR and NIR abstract one oxygen atom from the substrate ($(CH_3)_2SO$, $(CH_3)_3NO$ or NO_3^-). The oxo group of the resulting $Mo^{VI}O$ centre is converted to water by PCET and the original Mo^{IV} centre is regenerated (eqn (2) in Table 1). SeR mediates eqn (2) in Table 1, where X = SeO_3^{2-}, in a similar fashion to DMSOR, TMAOR and NIRs. Although the functional group of SeR has not been identified precisely, a six-coordinate $Mo^{VI}O(OH)$ centre

coordinated with two MPT and the corresponding square-pyramidal $Mo^{IV}(OH)$ centre have been proposed to be included in the oxidised and reduced SeR, respectively, on the basis of the EXAFS study.[11]

Nemykin *et al*. reported the first example of a reaction cycle consisting of OAT and PCET with $Mo^{VI}O$/desoxo Mo^{IV} compounds.[33] In the presence of H_2O, the desoxo $Mo^{IV}(OH_2)$ form was generated by OAT from the $Mo^{VI}O$ centre of $[Tp^*Mo^{VI}O(O\text{-}4\text{-}OC_2H_5C_6H_4)_2]NO_3$ to PPh_3, and successive CEPT and deprotonation of the $Mo^{IV}(OH_2)$ centre gave the $Mo^{V}(OH)$ species and then the $Mo^{V}O$ species. Subsequent one-electron oxidation of the $Mo^{V}O$ form by $(NH_4)_2Ce(NO_3)_6$ yielded the original $Mo^{VI}O$ state.

Discovery of biological desoxo Mo^{IV} centres has provided a hot topic in the fields of Mo-based biochemistry and coordination chemistry. Square-pyramidal desoxo Mo^{IV} structures are very rare in synthetic Mo compounds, because the well employed Mo^{IV} precursors such as $[MoO_2(CN)_4]^{2-}$, $[MoO(SC_6H_5)_4]^{2-}$ and $[MoOCl(CH_3CN)_4]^{+}$ contain at least one oxo group.[25] These synthetic problems were overcome by Holm *et al*.; two synthetic methods for bis(dithiolene) desoxo Mo^{IV} compounds were developed.[34–36] One is silylation of $(Et_4N)_2[Mo^{IV}O(\text{dithiolene})_2]$ (dithiolene = bdt and edt) and the other is substitution of the two carbonyls of $[Mo(CO)_2(S_2C_2R_2)_2]$ (R = Me and Ph) with alcoholates and thiolates. Using the two methods, ligand environment analogues of DMSOR, TMAOR and NIR from *Desulfovibrio desulfuricans* were synthesised,[35,36] the Mo^{IV} centres adopt a square-pyramidal geometry. A variety of the square-pyramidal bis(dithiolene) $Mo^{IV}(OR)$/$Mo^{IV}(SR)$ compounds were similarly obtained and discussed in detail in reviews.[25] Among them, the crystal structures of $(Et_4N)[Mo^{IV}(L)(S_2C_2Me_2)_2]$ (L = OC_6H_5 and S-2,4,6-^{i}Pr$_3$C$_6$H$_2$) are shown in Fig. 5.[35,36] Reactions of $[Mo(CO)_2(S_2C_2Me_2)_2]$ with $(Et_4N)(O_2CPh)$ and $(Et_4N)(O_2C^tBu)$ afforded the corresponding $Mo(O_2CR)$ compounds.[36] The crystal structure of $(Et_4N)[Mo^{IV}(O_2CPh\text{-}\kappa O,O)(S_2C_2Me_2)_2]$ is also presented in Fig. 5. The two carboxylate compounds have a trigonal-prismatic Mo^{IV} centre coordinated by two oxygen atoms of the carboxylate in an almost symmetrical fashion whereas an unsymmetric η^2-carboxylate binding fashion reflected by Mo–O = 1.9 and 2.4 Å has been observed in the NIR from *Escherichia coli*.[10] Bis($S_2C_2Me_2$)–$Mo^{VI}O(OR)$, –$Mo^{VI}O(SR)$ and –$Mo^{VI}O(O_2CR\text{-}\kappa O)$ compounds have not been isolated but their W counterparts have been obtained by reactions of the corresponding square-pyramidal desoxo W^{IV} precursors with R_2SO, R'_3NO or Ph_3AsO. The W^{VI} centres possess an intermediate geometry between octahedral and trigonal-prismatic as shown in Fig. 5.[25,37]

Synthesis of bis(dithiolene) $Mo^{VI}O(OH)$/$Mo^{IV}(OH)$ compounds proposed as the SeR reaction centre has proven to be challenging. The methoxo derivative, $(Et_4N)[Mo^{IV}(OMe)(S_2C_2Me_2)_2]$, was synthesised instead,[36] in which the $Mo^{IV}(OMe)$ centre possesses a square-pyramidal geometry. The Mo–O distance was determined to be 1.862(3) Å, whereas EXAFS analysis of the reduced SeR supported the Mo–OH distance at 2.22 Å. Among the bis(dithiolene) $Mo^{VI}O(OR)$ compounds reported so far (OR = silylalcoholates, alcoholates and phenolates), only $(Et_4N)[Mo^{VI}O(OSi^tBuPh_2)(bdt)_2]$ has been characterised by X-ray crystallography to have a Mo=O bond of 1.715(2) Å and a Mo–OSi bond of 1.932(2) Å.[32]

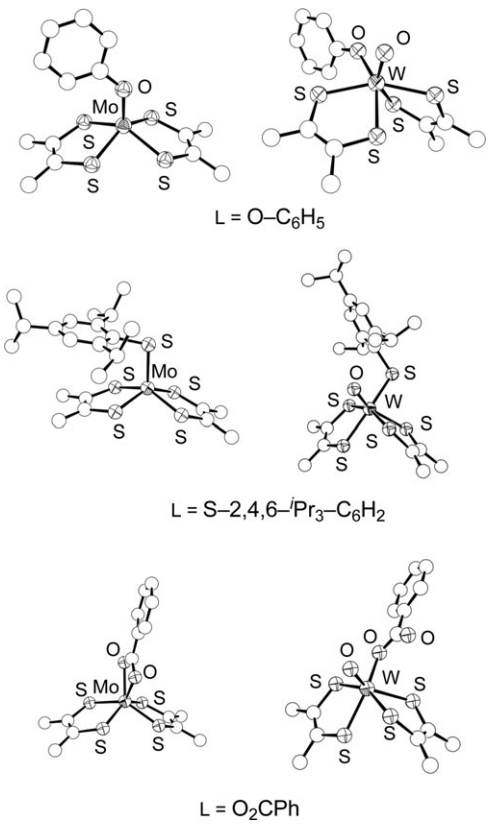


Fig. 5 Crystal structures of $[Mo^{IV}(L)(S_2C_2Me_2)_2]^-$ and $[W^{VI}O(L)(S_2C_2Me_2)_2]^-$.

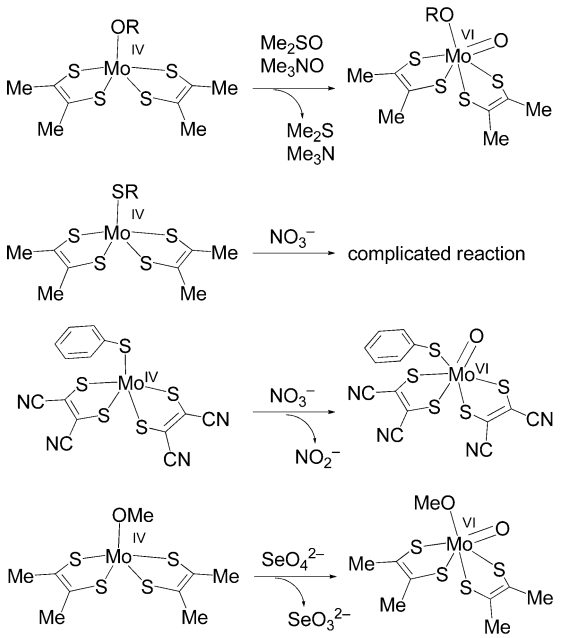


Fig. 6 OAT with ligand environment analogues.

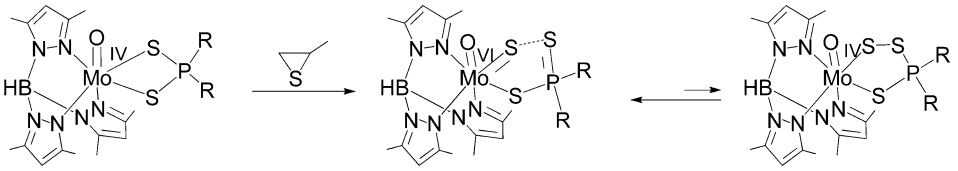


Fig. 7 Synthesis of $[Mo^{VI}O(S)]^{2+}$ complexes of Tp* (R = Et, ^{i}Pr, Ph) and their isomerisation.

Three examples of OAT with $(Et_4N)[Mo^{IV}(OR/SR)(S_2C_2Me_2)_2]$ are schematically illustrated in Fig. 6 whereas OAT from NO_3^- to bis(dithiolene) $Mo^{IV}(O_2CR\text{-}\kappa O,O)$ compounds has not been reported. Most ligand environment analogues of reduced DMSOR and TMAOR, the $Mo^{IV}(OR)$ type, readily abstract one oxygen atom from $(CH_3)_2SO$ and Me_3NO and the species is converted to the corresponding $Mo^{VI}O(OR)$ species.[25] On the other hand, $(Et_4N)[Mo^{IV}(SR)(S_2C_2Me_2)_2]$ (R = Me and Ph) compounds react with NO_3^- to give complicated mixtures.[38] Majumdar *et al.* found that $(Et_4N)[Mo^{IV}(SC_6H_5)(PPh_3)(mnt)_2]$ reacted with Bu_4NNO_3 in CH_2Cl_2 to give NO_2^-.[39] In this work, a five-coordinate $Mo^{IV}(SC_6H_5)$ centre was assumed to be generated by dissociation of PPh_3 from the trigonal-prismatic $Mo^{IV}(SC_6H_5)(PPh_3)$, and to abstract one oxygen from NO_3^-. As in the case of $Mo^{VI}O_2$ compounds (see section 2.1), mnt forms the stable $Mo^{VI}O(SC_6H_5)$ compound but $S_2C_2Me_2$ does not stabilise the $Mo^{VI}O(SR)$ centre. Jiang and Holm reported OAT with $(Et_4N)[Mo^{IV}(OMe)(S_2C_2Me_2)_2]$ (see Fig. 6).[37] This reduced SeO_4^{2-} to SeO_3^{2-} followed by second-order kinetics, but the $Mo^{VI}O(OMe)$ species generated has not been isolated.

3. Reaction centres in hydroxylation enzymes and their chemical analogues

3.1 $Mo^{VI}O(S)/Mo^{IV}O(SH)$ type of functional group in the enzymes and chemical analogues

A five-coordinate $Mo^{VI}O(S)$ reaction centre coordinated with one MPT and one hydroxo or oxo group (**4a** in Table 1) is included in the oxidised XO, Mo-AOR and QOR enzymes.[3,12] Although the reaction mechanism of eqn (3) is unclear, the $Mo^{VI}O(S)$ centre is assumed to be converted to the corresponding $Mo^{IV}O(SH)$ species, following hydride transfer from the substrates on the sulfido group (xanthine for XO, 2-quinoline for QOR and aldehydes for Mo-AOR, eqn (3) in Table 1). OH^- binds with the resulting cationic carbon to give the product hydroxylated. In the catalytic reaction, the oxo group attached on the Mo^{VI} and Mo^{IV} centres is not replaced with ^{18}O atom in the presence of $H_2{}^{18}O$.

Reaction of a tetrahedral $Mo^{VI}O_4^{2-}$ ion with excess amounts of H_2S yields an equilibrium mixture of $Mo^{VI}O_3S^{2-}$, $Mo^{VI}O_2S_2^{2-}$ and $Mo^{VI}OS_3^{2-}$, however, a very limited number of five- and six-coordinate $Mo^{VI}O(S)$ compounds have been synthesised at present.[25] In general, five- and six-coordinate $Mo^{VI}O(S)$ compounds are prone to yield the $Mo^{V}O(S\text{–}S)Mo^{V}O$ species *via* intramolecular redox or the $Mo^{VI}O_2$ and $Mo^{VI}S_2$ species through disproportionation. As representative functional group analogues, Laughlin *et al.* prepared $[Tp^*Mo^{VI}O(S)(S_2PR_2\text{-}\kappa S)]$ (R = Et, ^{i}Pr and Ph) compounds by reaction of $[Tp^*Mo^{IV}O(S_2PR_2\text{-}\kappa S,S)]$ with propylene sulfide in 80–85% yields.[40] As indicated in the centre of Fig. 7, the intramolecular redox reaction within the $Mo^{VI}O(S)$ centre is suppressed by a weak interaction between the uncoordinating sulfur atom of the monodentate S_2PR_2 and the terminal sulfido group on the Mo^{VI} centre. The S···S distances at *ca.* 2.39 Å in $[Tp^*Mo^{VI}O(S)(S_2PR_2\text{-}\kappa S)]$ (R = ^{i}Pr and Ph) are indicative of the weak interaction. In contrast, $[Tp^{iPr}Mo^{VI}O(S)(OC_6H_5)]$ with a distinct sulfido group (Tp^{iPr} = hydrotris(3-isopropyl-1-pyrazolyl)borate) dimerises to $[Tp^{iPr}Mo^{V}O(OC_6H_5)](\mu\text{-}S_2)$ by intramolecular redox reaction in solution.[41] The ligand environment analogue has not been reported yet, due to severe synthetic difficulties. Doonan *et al.* developed a method to insert a sulfur atom into the C–H bond of the benzene rings with other Tp compounds.[41] Reaction of $[Tp^{iPr}Mo^{IV}O(OAr)(OPEt_3)]$ (OAr = O-2-^{s}BuC$_6$H$_4$, O-4-^{t}BuC$_6$H$_4$ and O-2-C$_{10}$H$_7$) with propylene sulfide for 10–24 h yielded the corresponding $[Tp^{iPr}Mo^{V}O(OSAr)]$ compounds, one of which, $[Tp^{iPr}Mo^{V}O(O\text{-}1\text{-}S\text{-}2\text{-}C_{10}H_6)]$ (O-1-S-2-C$_{10}$H$_6$ = 1-mercapto-2-naphtholate), was crystallographically characterised. Fig. 8 shows the reaction scheme in the case of OAr = O-2-^{s}Bu-C$_6$H$_4$, where $[Tp^{iPr}Mo^{VI}O(S)(OAr)]$ is suggested as an intermediate for sulfur atom insertion.

3.2 $W^{VI}O(S)$ type of functional group in the enzymes and chemical analogues

A six-coordinate $W^{VI}O(S)$ centre coordinated by two MPT (**5a** in Table 1) has been thought to be involved in the oxidised FOR, W-AOR and GAPOR on the basis of the X-ray and EXAFS investigations.[4] The reduced enzymes are too air-sensitive to be characterised. The enzymatic hydroxylation may begin with hydride transfer from aldehydes to the $W^{VI}O(S)$ centre (eqn (3) in Table 1) as proposed in the reaction scheme of Mo-AOR.

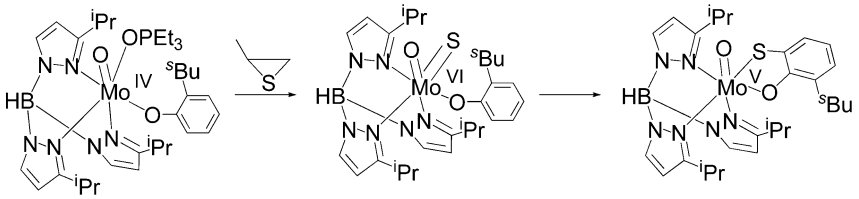


Fig. 8 C–H bond activation with $Mo^{VI}O(S)$ compound.

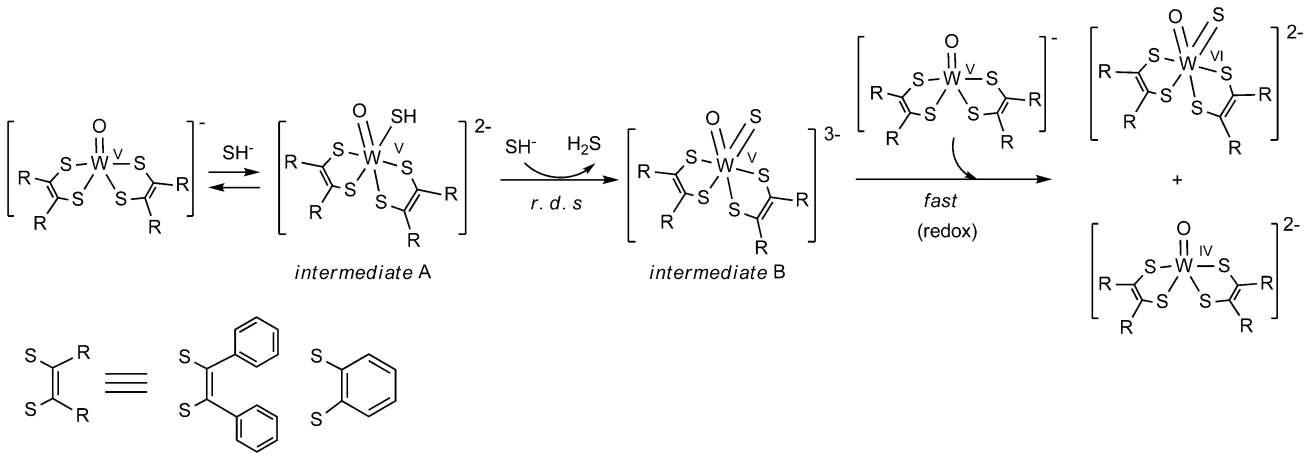


Fig. 9 Proposed mechanism for conversion of $(Et_4N)[W^{V}O(dithiolene)_2]$ into 0.5 equiv. of the $W^{VI}O(S)$ form and 0.5 equiv. of the $W^{IV}O$ form upon reaction with one equivalent of SH^-.

As most W compounds are more inert and weaker as oxidants than the isostructural Mo compounds, the $W^{VI}O(S)$ functional group analogues can be synthesised by similar synthetic procedures to that for the $Mo^{VI}O(S)$ counterparts. In phenanthroline and Tp* systems, mixtures of the $W^{VI}O(S)$, $W^{VI}O_2$ and $W^{VI}S_2$ compounds were formed by reactions of the W precursors with the sulfido donors, but the stability of the W^{VI} structures enables purification of the compounds by silica-gel column chromatography, resulting in isolation of the $W^{VI}O(S)$ compounds as well as the corresponding $W^{VI}O_2$ and $W^{VI}S_2$ ones.[25]

The ligand environment analogues of **5a** were reported for the first time by Sugimoto *et al.*, but their crystallographical characterisation has not been undertaken.[42] $(Et_4N)_2[W^{VI}O(S)(dithiolene)_2]$ (dithiolene = $S_2C_2Ph_2$ and bdt) were generated by the reaction of the corresponding square-pyramidal $W^{V}O$ compounds with an equimolar amount of Et_4NSH. As shown in Fig. 9, the $W^{V}O$ compound acts as both a reaction substrate and an oxidant, whereas the SH^- works as both a ligand and a base. The $W^{V}O$ species reacts with SH^- to generate the corresponding $W^{V}O(SH)$ species (intermediate A). Another SH^- (base) deprotonates the SH group of A, producing the $W^{V}O(S)$ species (intermediate B). Then, the redox reaction of B and another $W^{V}O$ species (oxidant) quickly occurs to yield the $W^{VI}O(S)$ compound as well as the square-pyramidal $W^{IV}O$ compound. The $W^{VI}O(S)$ centre is hydrolysed to the $W^{VI}O_2$ centre in the presence of a small amount of water, reflecting the lability of $W^{VI}{=}S$ bonds. This reaction is thought to undergo a similar process to the enzymatic inactivation process.

Wang *et al.* synthesised three types of five coordinate single dithiolene $W^{VI}O(S)$ compounds (Fig. 10).[43] $(Et_4N)_2[W^{VI}O_3(bdt)_3]$ was exposed to H_2S in CH_3CN to yield $(Et_4N)_2[W^{VI}O_2(S)(bdt)]$. Treatment of $(Et_4N)_2[W^{VI}O_2(OSi^{i}Pr_3)(bdt)]$ with 2 equiv. of $^{i}Pr_3SiSH$ gave $(Et_4N)[W^{VI}O(S)(OSi^{i}Pr_3)(bdt)]$. These two $W^{VI}O(S)$ centres adopt a distorted square-pyramidal structure with an apical oxo and basal sulfido ligation. $(Et_4N)_2[W^{VI}O(S)_2(S_2C_2Me_2)_2]$ was obtained by sulfur transfer from Ph_3SbS to $(Et_4N)_2[W^{IV}O(S_2C_2Me_2)_2]$. There are two independent molecules in the crystal structure of the $W^{VI}O(S)$ compound: one possesses a square-pyramidal geometry and the other is a trigonal bipyramid. The W centre coordinated by single dithiolene has not been observed in W enzymes yet, however, these three $W^{VI}O(S)$ compounds provide structural information for Mo-containing hydroxylation enzymes (**4a** in Table 1).

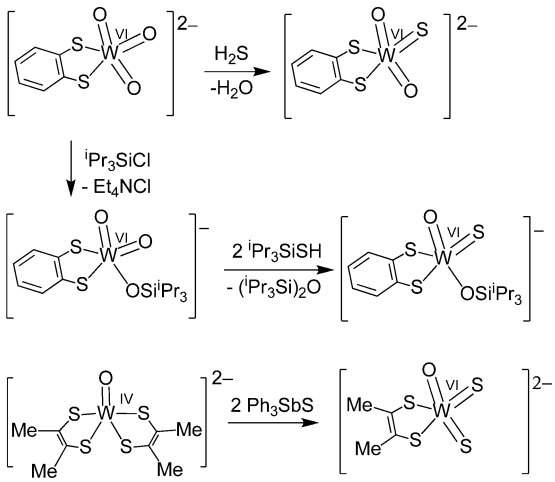


Fig. 10 Synthesis of $[W^{VI}O_2(S)(bdt)]^{2-}$ (above), $[W^{VI}O(S)(OSi^{i}Pr_3)(bdt)]^{-}$ (middle) and $[W^{VI}O(S)_2(S_2C_2Me_2)]^{2-}$ (below).

4. Reaction centres in dehydrogenation enzymes and their chemical analogues

4.1 $Mo^{VI}S(SeR)/Mo^{IV}S$ and $W^{VI}S(SeR)$ types of functional groups in the enzymes and chemical analogues

Crystal structure analysis of Mo-FDH reported by Boyington *et al.* had revealed the existence of trigonal-prismatic $Mo^{VI}S(Se{\cdot}Cys)$ (**6a** in Table 1) and square-pyramidal $Mo^{IV}(Se{\cdot}Cys)$ centres coordinated by two MPT in the oxidised and reduced states, respectively.[13] However, re-analysis of the X-ray data on the reduced Mo-FDH by Raaijimakers *et al.* has indicated that the $Mo^{IV}(Se{\cdot}Cys)$ centre reported initially is a square-pyramidal $Mo^{IV}S$ structure (**6b**).[14] As the $Mo^{VI}S(Se{\cdot}Cys)$ form is an inactive form, the detailed reaction mechanism for the formate oxidation remains unclear. Because formate is a good hydride donor, it is suggested that the formate oxidation begins

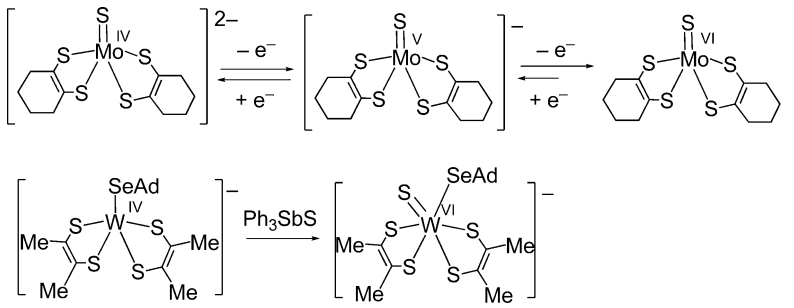


Fig. 11 Electrochemical reaction of $[Mo^{IV}S(L^{CH2})_2]^{2-}$ (above) and synthesis of $[W^{VI}S(SeAd)(S_2C_2Me_2)_2]^{-}$ (below).

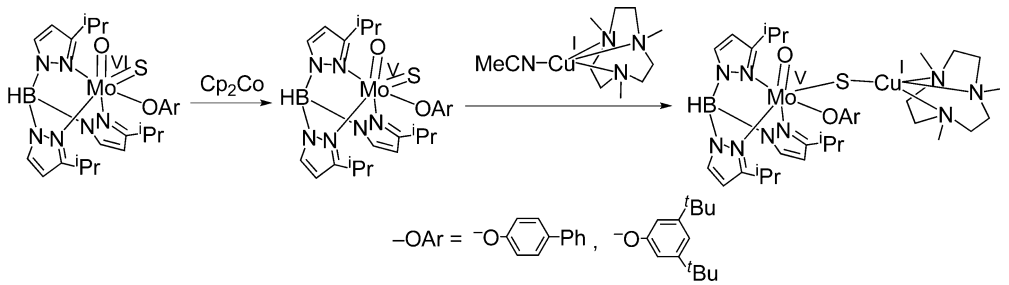


Fig. 12 Synthesis of $[Tp^{iPr}Mo^{V}O(OAr)(\mu\text{-}S)Cu^{I}(Me_3tacn)]$.

with its replacement with the Se·Cys ligand of **6a**. A subsequent hydride transfer from the formate to the sulfido group within the resulting $Mo^{VI}S(HCOO)$ species gives carbon dioxide and a square-pyramidal $Mo^{IV}(SH)$ centre, and **6b** is considered to be generated by deprotonation of the SH group (eqn (4) in Table 1).[14] W-FDH includes a trigonal-prismatic $W^{VI}S(Se{\cdot}Cys)$ centre (**7a** in Table 1), which is isostructural with the Mo^{VI} centre of Mo-FDH (**6a**).[15] The reduced W-FDH is too unstable to be characterised. FMDH also contains **7a**,[4] but its catalytic reaction mechanism remains unclear (eqn (6) in Table 1).

No ligand environment analogue of **6a** has been prepared to date. Whereas Mo-FDH is thought to include square-pyramidal $Mo^{IV-VI}S$ centres,[14] only two non-dithiolene compounds, $(Et_4N)_2[Mo^{IV}S(S_4)_2]$ and $(Et_4N)_2[Mo^{IV}S(CS_3)_2]$, had been reported as mononuclear square-pyramidal MoS compounds.[25] As these two contain redox active S_4^{2-} and CS_3^{2-} ligands, their square-pyramidal structures are decomposed by one-electron oxidation of the compounds. Sugimoto *et al.* synthesised a square-pyramidal bis(dithiolene) MoS compound for the first time by the treatment of $[Mo(CO)_2(L^{CH2})_2]$ with Na_2S.[44] As illustrated in Fig. 11, the $Mo^{IV}S$ centre undergoes two one-electron oxidation steps to generate the square-pyramidal $Mo^{V}S$ centre. Groysman and Holm synthesised $(Et_4N)[W^{VI}S(SeAd)(S_2C_2Me_2)_2]$ (SeAd = 1-adamantylselenate) as the first ligand environment analogue of **7a** from the square-pyramidal $W^{IV}(SeAd)$ species and Ph_3SbS (Fig. 11). Its crystal structure and reaction with formate have not been reported.[45]

4.2 $Mo^{VI}O(OH)(\mu\text{-}S)Cu^{I}/Mo^{IV}O(OH_2)(\mu\text{-}S)Cu^{I}$ type of functional group in the enzymes and chemical analogues

CODH catalyses oxidation of carbon monoxide to carbon dioxide as shown eqn (7) in Table 1. The X-ray and EXAFS analyses of the oxidised CODH indicated that the reaction centre consists of a unique heterodinuclear structure, $Mo^{VI}O(OH_n)(\mu\text{-}S)Cu^{I}$ (n = 0 or 1, **8a** in Table 1) in the Mo and W enzymes.[16] With the exception of the bridging sulfido group, the ligand environment of the Mo^{VI} moiety is similar to that of **4a**. The Cu^{I} ion is further coordinated by one Cys sulfur atom, adopting an almost linear geometry. OAT from the Mo^{VI} centre to carbon monoxide has been reported to give the $Mo^{IV}O(OH_2)(\mu\text{-}S)Cu^{I}$ centre (**8b** in Table 1) and carbon dioxide.

Because dinuclear Mo–Cu compounds bridged by single sulfido group are uncommon, synthesis of ligand environment analogues of CODH is a challenging issue. Unfortunately no single sulfido bridged Mo^{VI}–Cu^{I} compound has been reported to date. Gourlay *et al.* synthesised single sulfido bridged Mo^{V}–Cu^{I} compounds for the first time as shown in Fig. 12.[46] $[Tp^{iPr}Mo^{V}O(OAr)(\mu\text{-}S)Cu^{I}(Me_3tacn)]$ (OAr = O-3,5-$^{t}Bu_2C_6H_3$ and O-4-PhC_6H_4, Me_3tacn = 1,4,7-trimethyl-1,4,7-triazacyclononane) were prepared from $Cp_2Co[Tp^{iPr}Mo^{V}OS(OAr)]$ and $[Cu^{I}(CH_3CN)(Me_3tacn)]BF_4$. In the crystal structure of $[Tp^{iPr}Mo^{V}O(O\text{-}3,5\text{-}{}^{t}Bu_2\text{-}C_6H_3)\text{-}(\mu\text{-}S)Cu^{I}(Me_3tacn)]$, the Mo-Cu (3.806 Å), Mo–S (2.284(1) Å) and Cu–S (2.135(1) Å) bond distances and the Mo–S–Cu bond angle (118.90(5)°) are comparable to those of the CODH reaction centre. The dinuclear compounds exhibit EPR spectra similar to the Mo^{V}–Cu^{I} state of CODH. Detailed analysis of the functional group analogues emphasised the presence of strongly directional Mo–S π-bonding in the Mo^{V}–S–Cu^{I} moieties. Treatment with an excess of NEt_4CN in CH_2Cl_2 gave SCN^{-}, together with Mo(V) and Cu(I) monomers as observed in the reaction of CODH with cyanide.

5. $W^{IV}(H_2O)(SR)$ type of functional group in hydration enzymes and chemical analogues

AH stands out from Mo and W enzymes because it catalyses not a redox reaction but hydration of acetylene to acetaldehyde (eqn (7) in Table 1). This contains a trigonal-prismatic

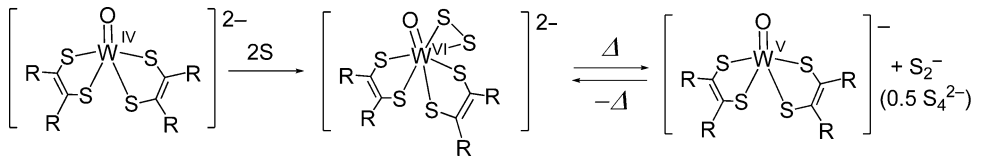


Fig. 13 Sulfur metabolism with W compounds including bdt and L^{CH2}.

$W^{IV}(H_2O)$(Cys) centre, **9b**,[17] and the coordinating H_2O attacks one of acetylene carbons to form acetaldehyde. Although both the ligand environment analogue and functional group analogue of **9b** have not been synthesised, Yadav *et al*. first converted C_2H_2 to CH_3CHO by a hydration reaction using $(Et_4N)_2[W^{IV}O(mnt)_2]$.[47] In this work, they proposed that after oxidative addition of C_2H_2 to the square-pyramidal $W^{IV}O$ centre H_2O was inserted into the resulting $W(C_2H_2)$ unit of $(Et_4N)_2[W^{VI}O(mnt)_2(C_2H_2)]$ to give the aldehyde.

6. Reaction centres in other enzymes and chemical analogues

6.1 Desoxo $Mo^{VI}(OR)/Mo^{IV}(OR)$ type of functional group in transhydroxylation enzymes and chemical analogues

In the crystal state, TH has a six-coordinate Mo^{IV}(Ser) centre coordinated by two MPT and one acetate from the crystallisation buffer.[18] The labile acetate ligand easily dissociates from the Mo^{IV} centre to give the square-pyramidal Mo^{IV} structure (**10b** in Table 1). After the two-electron oxidation, the resulting five-coordinate Mo^{VI} centre, **10a**, binds with pyrogallol to yield the Mo^{IV} and corresponding orthoquinone structures *via* intramolecular redox within the Mo^{VI}(pyrogallol) moiety (eqn (8) in Table 1). Such a desoxo square-pyramidal Mo^{VI} centre is not found in other molybdenum enzymes.

A series of square-pyramidal bis(dithiolene) desoxo $Mo^{IV}(OR)$ compounds described in section 2.2 are also good ligand environment analogues for reduced TH. Because (Et_4N)-$[Mo^{IV}(OR)(S_2C_2Me_2)_2]$ does not exhibit a reversible Mo(VI)/(V) redox couple,[35] the square-pyramidal desoxo Mo^{VI} structure is thought to be less stable than the six-coordinate Mo^{VI} structure with one additional ligand.

6.2 Unidentified functional groups in the enzymes and related reactions

PSR catalyses reduction of one sulfur atom of polysulfide to hydrogen sulfide (eqn (9) in Table 1), in which the Mo centre has two MPT ligands (**11** in Table 1).[3] WOR4 was isolated from *Pyrococcus furiosus* in 2002 and revealed to have a W centre with two MPT (**12** in Table 1).[19] Interestingly, WOR4 grows with reducing elemental sulfur to hydrosulfide in the presence of dihydrogen (eqn (10) in Table 1). CAR also has the bis(MPT) W centre (**12** in Table 1) and reduces carboxylic acids to the corresponding aldehyde (eqn (11) in Table 1). The three metal centres of PSR, WOR4 and CAR are coordinated by unidentified additional ligands. In addition, the reaction mechanisms remain unclear.

Nagarajan *et al*. reported a PSR-like reaction with $(Ph_4P)_2[Mo^{IV}(SC_6H_5)_2(mnt)_2]$.[48] This complex reacts with polysulfide and affords H_2S with replacement of the one SC_6H_5 ligand with the polysulfide anion added. Because WOR4 plays a role in S^0 reduction, several W^{IV} compounds were employed in the reaction with S^0. $(Et_4N)_2[W^{VI}O(S_2)$-(dithiolene)$_2$] (dithiolene = bdt and L^{CH2}) were prepared from the corresponding square-pyramidal $W^{IV}O$ compounds with 2S (0.25 S_8).[49] As shown in Fig. 13, the $W^{VI}O(S_2)$ com pounds are stable in MeCN–EtCN (70 : 30) at <253 K and <223 K, respectively, and completely dissociate the S_2^- to give the square-pyramidal $W^{V}O$ structures at >353 K and >293 K, respectively. The weakened W–S bonds in the WS_2 ring facilitate the dissociation due to the stronger *trans* influence by L^{CH2} compared with bdt. In contrast, $(Et_4N)_2[WO(S_2)(mnt)_2]$[50] does not dissociate the S_2 units even at 373 K.

7. Conclusions

The present review summarised ligand environments of the metal centres in Mo and W enzymes, their possible reaction mechanisms and recent advances in bio-inspired coordination chemistry of Mo and W. In efforts to understand the essentials of Mo and W enzyme reaction centres for their activities, many chemical analogues have been developed. At the present stage, most ligand environment analogues mimic at least one half-cycle of the enzymatic reactions. These analogues are expected to be advanced by theoretical, spectroscopic, catalytic and synthetic approaches.

A number of significant areas remain unclear for synthetic coordination chemists. One primary area of interest is the isolation of Mo^{VI} compounds including electron-rich aliphatic dithiolenes as potential ligand environment analogues. This will provide useful structural data such as C=C and C–S bond lengths and C–S–Mo bond angles to evaluate the non-innocent character of MPT in the enzymes. A second area of interest is activation of C–H bonds with $M^{VI}S$ compounds as seen in the hydroxylation and dehydrogenation enzymes. A third area of interest involves combination of PCET with OAT, hydroxylation and dehydrogenation in order to complete the full enzymatic reaction cycle. Another area of interest is the design of useful chemical analogues to propose structures of metal centres with unidentified functional groups in the enzymes. Chemical analogues designed along these lines will have structural dynamics and reaction diversity as observed in Mo and W enzymes. Furthermore, these compounds catalytically produce proton- and electron-gradients to form one component of a fuel cell using water and simple substrates such as formate and carbon monoxide. In addition, carbon dioxide is catalytically reduced to formaldehyde or formate in water.

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