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Review

Dithiolene complexes and the nature of molybdopterin

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Contents

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ABSTRACT

The development of the coordination chemistry of dithiolene ligands is summarised, together with a consideration of the electronic structure of complexes of these 'non-innocent' ligands. This information provides a context for a consideration of the role of dithiolenes in natural systems, *i.e.* as the ligand that binds molybdenum (or tungsten) at the catalytic centre of an extensive series of enzymes. These enzymes catalyse the transfer of an oxygen atom to or from the substrate: *e.g.* the sulfite oxidases catalyse the conversion of sulfite to sulfate and the nitrate reductases catalyse the conversion of nitrate to nitrite. The nature of the catalytic centres of several of these enzymes has been determined and each involves one or two 'molybdopterin' (MPT) cofactors bound to a mononuclear metal centre *via* their dithiolene group. The biosynthesis of MPT is described and, given its nature, possible roles for this moiety in the function of the oxotransferase enzymes are discussed. The review concludes with a consideration of the coordination chemistry that has been stimulated by the present knowledge of the nature and function of the catalytic centres of these enzymes.

1. Dithiolene complexes

1.1. Development of the coordination chemistry of dithiolenes

Dithiolenes (dt) are a group of ligands, the chemistry of which commenced in the 1930s. Toluene-3,4-dithiol and 1-chlorobenzene-3,4-dithiol when reacted with halides of cadmium, mercury, tin and zinc produce highly coloured products of the formula $[M(dt)_2]^{2-}$ that were of analytical value [1,2]. This discovery led to other investigations of the properties and analytical uses of toluene-3,4-dithiol and related pro-ligands throughout the 1940s and 1950s [3,4] and various analytical protocols were developed for the detection and identification of metals [5]. However, it was not until the late 1950s that a systematic study of metal complexes of ene-1,2-dithiols occurred. In 1957 the ligand $[S_2C_2(CN)_2]^{2-}$ (maleonitriledithiolate, mnt) was synthesised and several complexes were prepared, *e.g.* Bähr and Schleitzer [6] synthesised $[Pd(mnt)_2]^{2-}$. Complexes containing quinoxaline-2,3-dithiol (qdt) bound to palladium, nickel and cobalt were reported in 1959 [7,8]. In 1960 the first example of a tris-dithiolene complex, $[Mo(S_2C_6H_3Me)_3]$, was reported; this compound was synthesised by the reaction of toluene-3,4-dithiol with $[MoO_4]^{2-}$ [9].

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In 1962 Davison et al. observed that there was a two-electron difference between two related nickel complexes that had been reported by other groups. These complexes were $[Ni(S_2C_2Ph_2)_2]$, synthesised by Schrauzer and Mayweg [10], and $[Ni(mnt)_2]^{2-}$, prepared by Gray et al. [11]. Davison et al. [12,13] demonstrated that it was possible to reduce $[Ni(S_2C_2Ph_2)_2]$ to the corresponding dianion and to oxidise $[Ni(mnt)_2]^{2-}$ to the corresponding neutral complex; in each case the conversion passed through a monoanionic intermediate. This was the first demonstration of the redox properties of dithiolene complexes. Furthermore, Davison et al. [12,13] extended the coordination chemistry of dithiolene ligands by the synthesis of complexes such as $[M(S_2C_2R_2)_2]^-$ (M = Ni, R = C_6H_5 or CF_3; M = Cu, Co, Ni, Pd, Pt or Au, R = CN).

The chemistry of dithiolenes has continued to develop since the 1960s and a wide range of complexes are now known [14–20]. These complexes involve one, two, or three dithiolene ligands with a wide variety of substituents. Homoleptic bis-dithiolene complexes invariably possess a square planar geometry and tris-dithiolene complexes are novel in manifesting a clear preference for a trigonal prismatic, rather than an octahedral, geometry. There are a very large number of heteroleptic, *i.e.* 'mixed' ligand, complexes that involve one or two dithiolenes plus a wide variety of other ligands. A notable aspect of the majority of dithiolene complexes, especially those of the *d*-transition metals, is their redox activity with many complexes capable of a change in oxidation level of one or two electrons. Many such redox changes are facile and electron addition (or loss) leads to little change in the geometry and dimensions of the complex.

1.2. Electronic structure of dithiolene complexes

Difficulty arises when the traditional description of a complex, as a central metal atom or ion bound to ligands with a defined electronic nature, is applied to a dithiolene complex [21]. Thus, a dithiolene ligand can be considered to be present in a complex as an ene-1,2-dithiolate, a radical mono-ion, or a 1,2-dithioketone (Fig. 1). This versatility has led to dithiolenes being classed as 'non-innocent' ligands [22] and the use of 'dithiolene' is useful as it avoids the need to specify the charge on the ligand [23]. Given that the charge on a dithiolene ligand is uncertain, the oxidation state of the metal in a dithiolene complex is ambiguous [24].

Schrauzer and Mayweg [25] performed molecular orbital calculations for $[Ni(S_2C_2H_2)_2]$ and concluded that the ground state of this molecule involved extensive π-electron delocalisation. Subsequent theoretical investigations by Alvarez et al. [26] proposed a molecular orbital scheme for the π-electron system of a dithiolene group based on that of 1,3-butadiene (Fig. 2). In respect of the two extreme redox states of a dithiolene (Fig. 1), an ene-1,2-dithiolate has six π-electrons and a $(\pi_1)^2(\pi_2)^2(\pi_3)^2$ electron configuration and a 1,2-dithioketone has four π-electrons and a $(\pi_1)^2(\pi_2)^2$ electronic configuration. The latter description is compatible with the valence bond description of a 1,2-dithioketone, as it involves two electrons in a π-orbital that is C–C bonding and C–S bonding and two electrons in a π-orbital that is C–C anti-bonding and C–S bonding. The addition of two electrons to π_3, to form an ene-1,2-dithiolate, leads

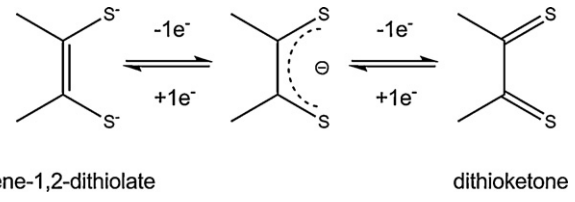

Fig. 1. Redox related forms of a dithiolene ligand.

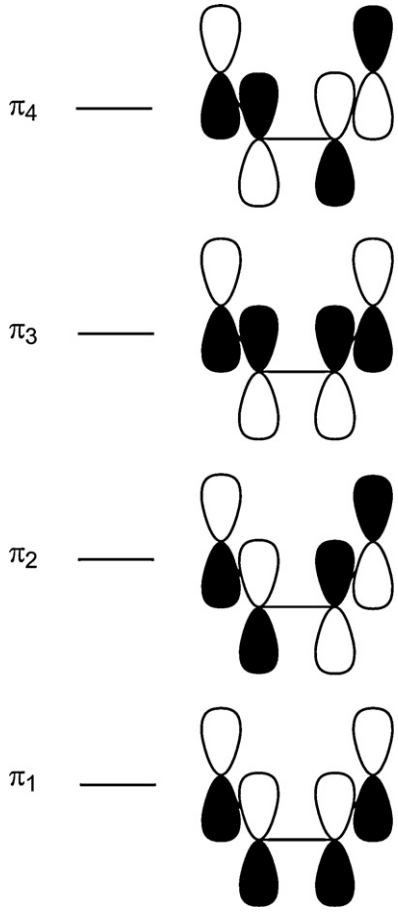

Fig. 2. Molecular orbital scheme for the π-electron system of a dithiolene [26].

to a strengthening of the C–C bond and a weakening of the C–S bond, *i.e.* π_3 is C–C bonding and C–S anti-bonding. This agreement between the valence bond and orbital description of the electronic structure of the two extreme forms of a dithiolene is encouraging and highlights the significance of the π-orbitals in determining the nature and properties of dithiolene complexes.

X-ray crystallographic information is a vital pre-requisite when attempting to determine the electronic structure of a complex that involves one (or more) non-innocent ligand(s); thus, it is important to know, not only the geometric arrangement, but also the bond lengths of the complex. In respect of the latter and with reference to Figs. 1 and 2, it would appear that the intra-ligand bond lengths should vary in accordance with the 'oxidation level' of the ligand. This has proved to be the case for the complexes of some 'non-innocent' ligands that involve nitrogen and oxygen donor atoms; *e.g. O,O′*-coordinated *o*-benzosemiquinonate or *N,N′*-coordinated *o*-iminobenzosemiquinonate π-radicals have been characterised [27–33]. In a similar manner, attempts have been made to distinguish between the various forms of dithiolene ligands by the analysis of X-ray crystallographic data [34,35]. For dithiolene complexes, however, knowledge of the molecular structure and dimensions alone has proved to be of limited value in the quest to determine the nature of the ligands and, therefore, the oxidation state of the metal [36–40]. However, in an extensive series of studies, Wieghardt et al. [41–44] have demonstrated that, by combining the information obtained from X-ray crystallography with that provided by physical techniques – notably X-ray absorption spectroscopy – and theoretical calculations, the electronic structure of a dithiolene complex can be determined.

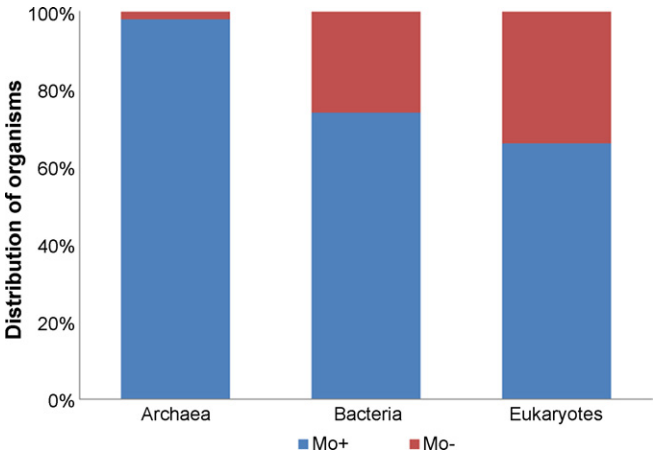

Fig. 3. Distribution of Mo-utilising organisms among those with completely sequenced genomes. All organisms were classified into two groups: Mo (+), *i.e.* utilising Mo-centred enzymes; Mo (−), *i.e.* not utilising Mo-centred enzymes [45].

2. Dithiolenes in nature

Metalloenzymes involving a dithiolene group were discovered in the late 1980s and it is now established that these enzymes are prevalent throughout biology where the metal chelated by the dithiolene ligand is either molybdenum or its Group VI counterpart tungsten.

2.1. Biological roles of molybdenum

Molybdenum is the only second-row transition metal that is an essential trace element and it is present in virtually all living systems (Fig. 3) [45].

Molybdenum is available to biological systems as molybdate, $[MoO_4]^{2-}$. Once molybdate enters the cell it is incorporated into metal cofactors by elegant and controlled biosynthetic pathways [46,47]. There are a few species that do not require molybdenum and most of these utilise its Group VI counterpart tungsten [48]; the majority of these organisms are hyperthermophilic archea that live at ~100 °C. Thus, tungstate ($[WO_4]^{2-}$) which is 100-fold less abundant than molybdate in most aqueous environments on Earth, is enriched in deep-sea hydrothermal vents. This is of particular interest as it is believed that such an environment resembles the conditions on the primitive Earth [49,50].

Molybdenum-containing enzymes play important roles in the biochemical cycles of carbon, nitrogen and sulfur [51]. The nitrogenase enzymes cleave the strongest homonuclear chemical bond, the N≡N bond in dinitrogen, under ambient conditions and produce ammonia. The molybdenum in these enzymes is present as part of a $MoFe_7S_9$ cluster (Fig. 4) [52,53].

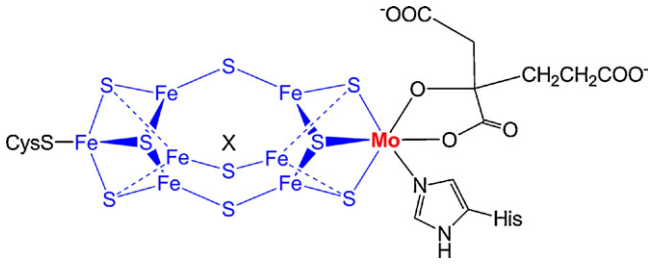

Fig. 4. The structure of the Fe–Mo–S cluster involved in the active site of the nitrogenase enzymes; X is a light atom (*e.g.* C, N, or O) but its identity has not been established unequivocally [52,53].

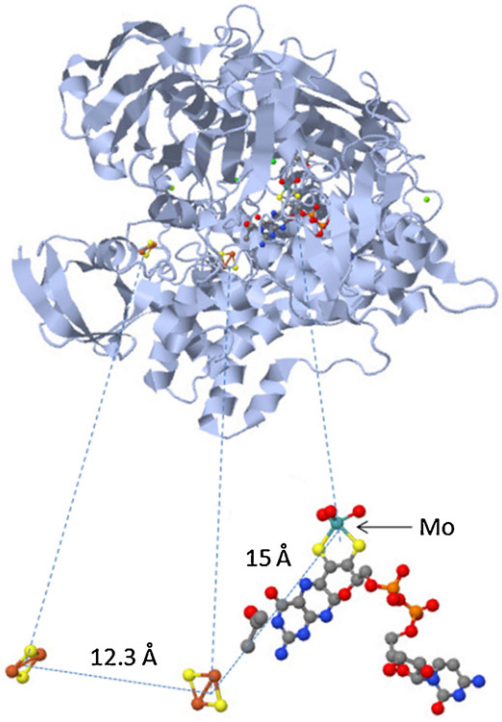

Fig. 5. The structure of *D. gigas* aldehyde oxidoreductase, as established by protein crystallography, with the nature and the location of the redox active components within the protein highlighted [56].

With the exception of the nitrogenases, all of the molybdenum-containing enzymes that have been isolated to date involve the metal bound to one (or two) dithiolene chelate(s). This represents an extensive range of enzymes, each of which catalyses a two-electron redox reaction that involves the transfer of an oxygen atom to a substrate X, or from a substrate XO, as:

$$XO + 2H^+ + 2e^- \leftrightarrow X + H_2O$$

The reactions catalysed involve a wide variety of substrates, including: (i) the oxidation of sulfite to sulfate, xanthine to uric acid, and an aldehyde to the corresponding carboxylic acid; (ii) the reduction of nitrate to nitrite and DMSO to DMS. The enzyme is named according to its function, *e.g.* sulfite oxidase or DMSO reductase [54,55].

The structure of the aldehyde oxidoreductase from the bacterium *Desulfovibrio gigas* is shown in Fig. 5; thus, the molybdenum-containing catalytic centre of this enzyme functions in conjunction with two 2Fe–2S clusters [56].

Given their biochemical function, these enzymes are often referred to as 'oxotransferases'. Each involves a mononuclear metal centre bound to one or two molecules of a special moiety, 'molybdopterin' (MPT)[1] (Fig. 6) that is unique to these enzymes [57]. The nature of MPT has been determined, following a series of biochemical [58–60] and several crystallographic [61] studies of these enzymes. MPT itself cannot be studied directly as it is highly unstable once liberated from proteins; it loses the metal and undergoes a rapid and irreversible loss of function due to oxidation [57].

Each protein crystallographic study [61] has identified MPT as a tricyclic pyranopterin, the pyran ring of which carries the dithi-

[1] Molybdopterin (or *M*etal binding *PT*erin) is the pyranopterindithiolene framework *without* any metal bound, *i.e.* molybdopterin does *not* contain molybdenum and, in the case of the tungsten oxotransferase enzymes molybdopterin is bound to tungsten. Also (see Fig. 10), molybdopterin can exist in either the pyran ring open or closed forms.

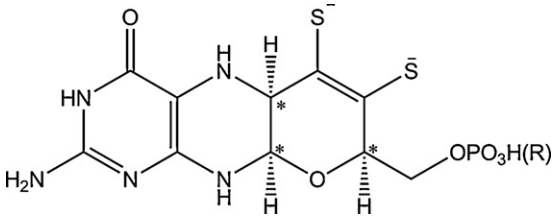

Fig. 6. Structure of 'molybdopterin' (MPT), the ligand that coordinates molybdenum or tungsten at the catalytic centre of the oxotransferase enzymes; chiral centres are indicated by *; R = H or a dinucleotide [61].

olene group and a phosphate side chain. The MPT may exist in either the mononucleotide form (where R = H), as found in many eukaryotic molybdenum enzymes, or as the dinucleotide of adenine, cytosine, guanine, or hypoxanthine, as in prokaryotic Mo-MPT enzymes. When the MPT is bound to the molybdenum centre, the complex is referred to as the "molybdenum cofactor" or Moco.

2.2. The nature of molybdenum centres in oxotransferase enzymes

A classification of the nature of the catalytic centres of the molybdenum oxotransferases, based on the coordination sphere of the metal in the oxidised form of the enzyme, was originally proposed by Hille in 1996 [54]. Since then, despite a significant increase in the number of crystallographic studies reported for these enzymes [61], this classification (see Fig. 7) has required relatively little modification. The molybdenum is bound to one or two MPT groups with the remainder of the coordination sphere taken up by a selection of non-protein ligands: oxo-, hydroxo-, water-, or sulfido-groups and/or an amino acid side chain.

- Members of the xanthine oxidase family have a single MPT coordinated to a *fac*-$Mo^{VI}OX(H_2O)$ centre (X = O or S) with no amino acid bound. CO dehydrogenase, an enzyme that catalyses the oxidation of CO to CO_2, is a special member of this family as the active site involves a Mo–S–Cu moiety [62].
- Members of the sulfite oxidase family involve one MPT bound to a *cis*-$Mo^{VI}O_2$ centre ligated by a cysteinyl residue and an additional coordination site occupied by H_2O.
- The majority of the members of the DMSO reductase family have the molybdenum ligated by two MPTs, a terminal oxo (Mo=O) group, plus the donor atom of the side chain of an amino acid residue –S of cysteine, O of serine, or Se of selenocysteine. However, for some members of this family, notably the periplasmic nitrate reductases and some formate dehydrogenases, the oxo-group is replaced by a sulfur; in the former, this sulfur atom is close (2.2–2.85 Å) to the S of the coordinated cysteine implying the formation of a (partial) disulfide bond that may well be important in the catalytic process [61,63].

All of the known tungsten oxotransferases involve two MPTs bound to the metal, *i.e.* they belong to the DMSO reductase family [61,62,64].

Spectroscopic studies indicate that the redox reaction concomitant with oxygen atom transfer in the molybdenum and tungsten oxotransferase enzymes occurs at the metal centre and that the catalytic cycle involves interconversion between the M(VI) and M(IV) oxidation states[2]; the former loses an oxo-group in the oxidases and gains one in the reductases. The M(V) state is generated by a one-electron reduction of the M(VI) state in the reductases, or by a one-electron oxidation of the M(IV) state in the oxidases, and occurs during the catalytic cycle *en route* to the regeneration of the catalytically active state by a further one-electron reduction, or oxidation, respectively [65].

2.3. Molybdopterin

2.3.1. Nature and biosynthesis

The crystallographic information presently available [61] for the molybdenum (and tungsten) oxotransferase enzymes indicates that the nature of MPT is remarkably conserved, including the conformation of the pyran and pyrazine rings and the configuration of the three chiral centres (marked * in Fig. 6). The only significant variation presently observed is that, in the nitrate reductase A from *Escherichia coli*, MPT was found to be present in both pyran ring open and closed forms [66].

The molybdenum centre of the enzymes is synthesised from guanosine-5′-triphosphate (GTP, a purine nucleotide) by a conserved biosynthetic pathway involving several identified intermediates including the cyclic pyranopterin monophosphate known as Precursor Z (Fig. 8). After MPT has been synthesised molybdenum is transferred to form 'Moco'. As indicated in Fig. 8, it has been suggested that copper is involved in this process, possibly to protect the dithiolene group until molybdenum can be bound. Evidence for the involvement of copper derives from the crystal structure of a domain (G) of the enzyme Cnx1 which catalyses one step in the insertion of molybdenum into MPT in plants [67]. However, subsequent studies have questioned if copper is essential for the formation of Moco or whether, given the affinity of this metal for sulfur-donor ligands, copper is bound adventitiously to the dithiolene group of MPT [68,69]. Moco is unstable once liberated from an enzyme and, therefore, it appears that this entity does not occur in a 'free state' but is bound to a carrier protein that protects and stores it until it is incorporated in a protein to form an enzyme (as in Fig. 5) [70].

The biosynthesis of MPT is of particular interest due to the relatively rare occurrence of 'molybdenum cofactor deficiency' in organisms where genetic errors prevent the biosynthesis of functional molybdoenzymes. Moco-deficiency in humans results in the loss of sulfite oxidase, xanthine oxidase and aldehyde oxidase activity and individuals with this deficiency are characterised by progressive neurological damage, leading to early childhood death in most cases [71]. Schwarz et al. [72] have reported successful treatment of Moco-deficient mice with Precursor Z purified from *E. coli* and this development shows promise for the treatment of human Moco-deficiency [70].

Once located within the protein, Moco is held in place by multiple hydrogen bonds between amino acid residues and the polar groups of MPT, *i.e.* the O and N atoms of the pterin and the phosphate group and – if present – the nucleotide [68,73]. In each molybdenum and tungsten oxotransferase enzyme that has been structurally defined, the active site is located close to the centre of the protein and it is of interest to note that each enzyme possesses a 'funnel' of length ca. 25 Å from the surface of the protein to the metal centre through which the substrate must travel [74].

2.3.2. Possible roles in enzyme function

The ubiquitous presence of MPT in the molybdenum (and tungsten) oxotransferase enzymes and the remarkable conservation of its nature strongly suggest that this moiety is crucial

[2] Although there is general agreement regarding the oxidation states of the molybdenum and tungsten centres of the oxotransferase enzymes at various stages of the catalytic cycle, it should be remembered that these values have *not* been unequivocally established (see Section 1.2) *e.g.* by comprehensive spectroscopic and theoretical studies of the type accomplished by Wieghardt et al. [41–44] for selected 3*d*-transition metal dithiolene complexes.

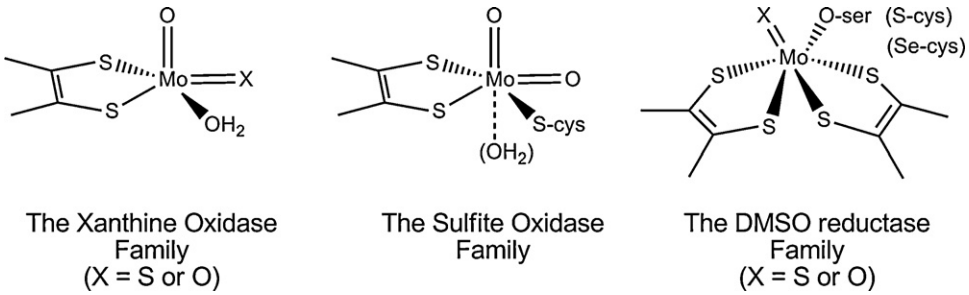

Fig. 7. A structural classification of the catalytic centres of the molybdenum oxotransferase enzymes [54].

to the catalytic process; however, the role(s) played by MPT is (are) not fully understood. Clearly, the dithiolene group is vital to the function of these enzymes. Based on the facile redox chemistry of the majority of *d*-transition metal dithiolene complexes, it seems clear that the dithiolene group supports the two-electron redox change at the metal, from the M(VI) to the M(IV) state, or *vice-versa*, that is required for oxygen atom transfer. The electronic structure of the oxo-molybdenum dithiolene complexes [LMoO(dt)] (L = hydrotris(3,5-dimethyl-1-pyrazolyl)borate; dt = 1,2-benzenedithiolate or 3,4-toluenedithiolate) has been investigated. The Mo=O interaction dominates the ligand field of these complexes, isolating the Mo d_{xy} orbital as the redox active orbital and restricting its spatial orientation to the plane perpendicular to the Mo=O vector. The Mo d_{xyo} orbital interacts with the dithiolene sulfur *p*-orbitals and this influences the redox potential of the molybdenum centre. These considerations of electronic structure have led to the proposal of an "oxo-gate" hypothesis; *viz.* a Mo=O bond oriented *cis* to the plane of a dithiolene ligand is proposed to be a necessary for efficient electron transfer to regenerate the active site of a molybdenum enzyme following oxygen atom transfer [75].

The dithiolene group of MPT could:

- Lower the activation energy for oxygen atom transfer by strong S → M σ- and π-donation [76].
- Allow electronic communication between the metal centre and the other components of MPT.
- Provide a route for the two, one-electron transfer processes required to re-oxidise, or re-reduce, the metal centre back to the catalytic state.

With respect to this last point, it has been suggested that MPT could provide a route for electron transfer to, or from, the molybdenum (or tungsten) during enzyme turnover [77,78]. This view is reinforced by the crystallographic information available for these enzymes; for virtually all of the enzymes this shows the close (typically ≤15 Å) approach of the redox active partner (an Fe–S cluster or a cytochrome) to the catalytic centre with the (or one) MPT directed towards this partner (see Fig. 5) [61].

Beyond the dithiolene group, it is important to consider the other components of MPT in terms of their possible role(s) in assisting the catalysis of oxygen atom transfer. One contribution could be to provide basic sites to handle the protons that are an integral component of the oxidation (or reduction) process ($XO + 2H^+ + 2e^- \leftrightarrow X + H_2O$). In respect of the possible participation of the pterin, as mentioned above, both the pyrimidine and pyrazine rings serve to anchor MPT to the surrounding protein *via* a series of hydrogen bonds. Furthermore, the pyrazine ring is redox active and can occur in one of three oxidation levels: the fully oxidised form; the dihydro-form (that can exist as one of several tautomers); and the tetrahydro-form, as shown in Fig. 9. These three forms are interrelated by two-proton, two-electron processes.

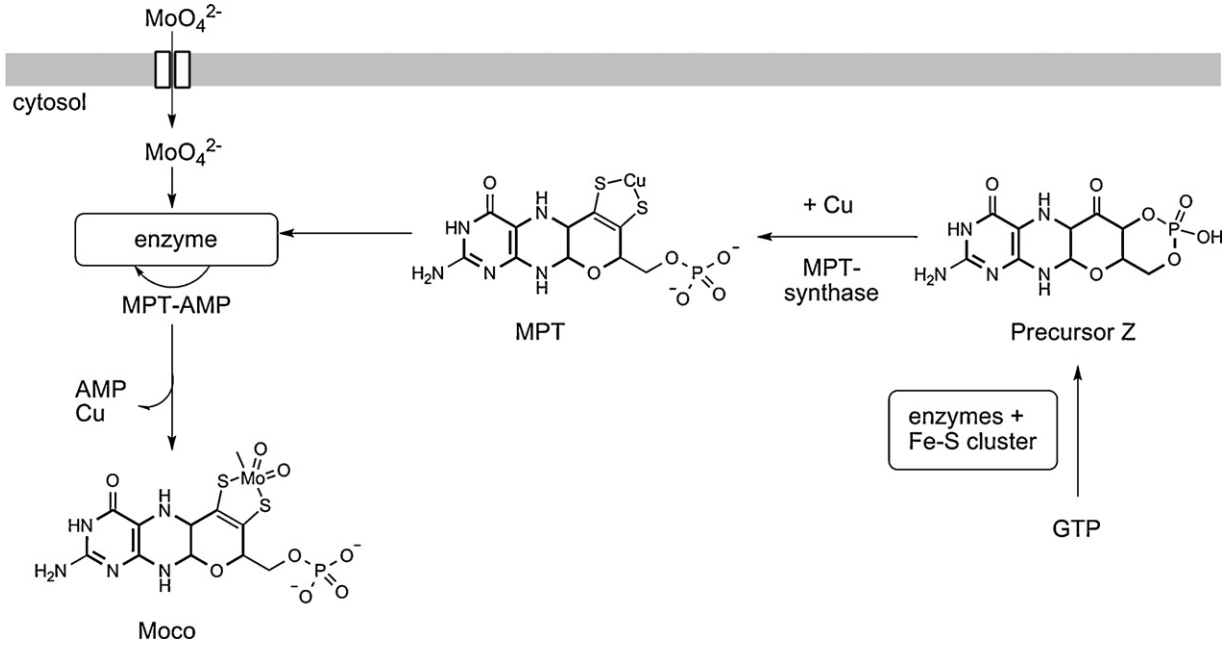

Fig. 8. Suggested route of biosynthesis and distribution of Moco in plant cells; MPT-synthase is an enzyme [70].

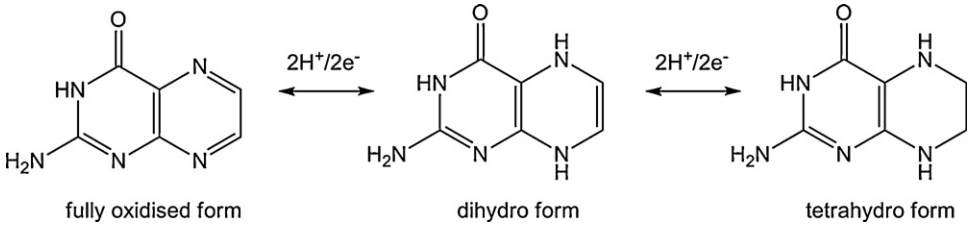

Fig. 9. The oxidation levels of a pterin.

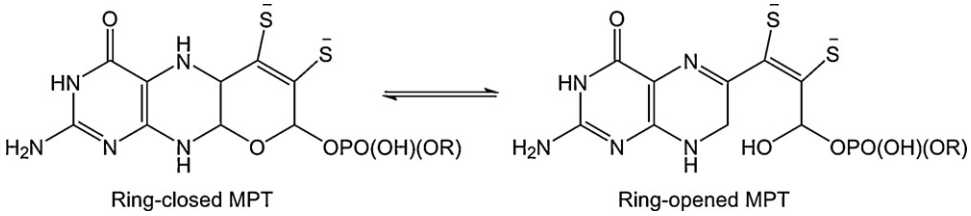

Fig. 10. The pyran ring-closed and ring-opened forms of molybdopterin (MPT) as found in the nitrate reductase A of *E. coli* [66].

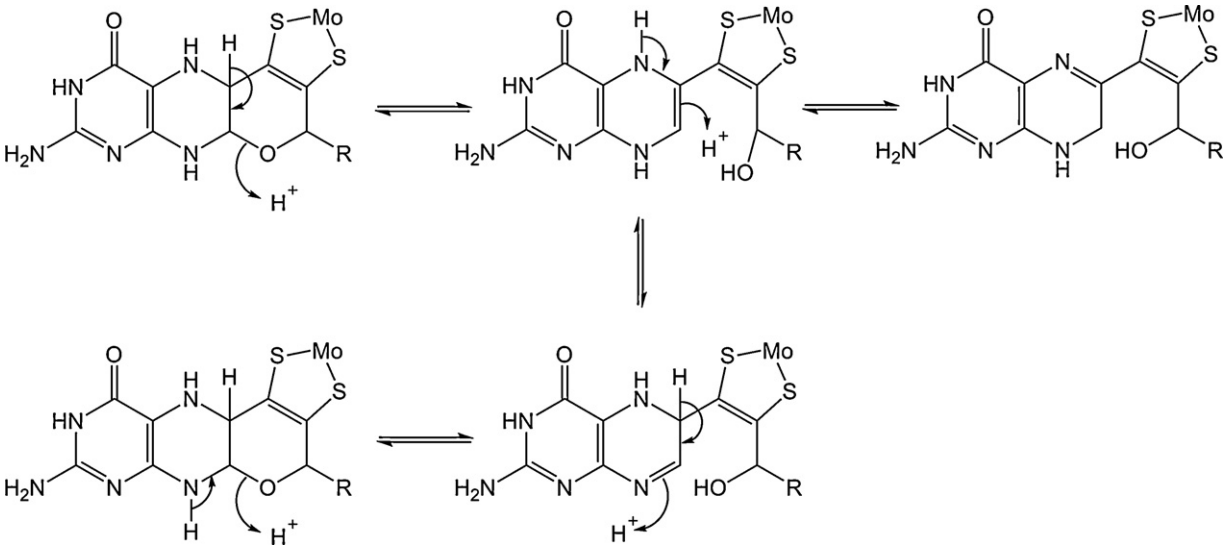

Fig. 11. The scheme proposed by Garner and Enemark [79] illustrating the proton catalysed scission/condensation of the pyran ring of the pyranopterin of MPT to generate a dihydropterin.

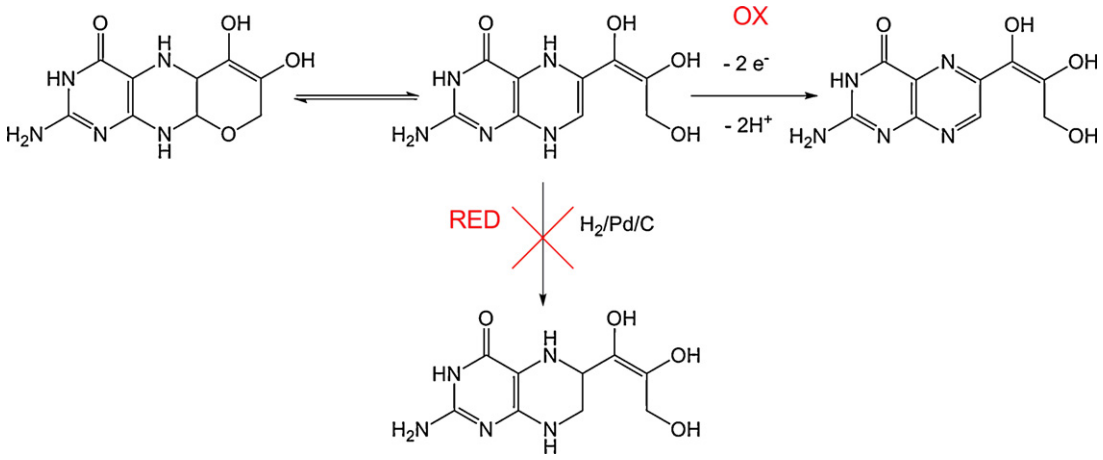

Fig. 12. The redox properties of a pyranopterin analogue of MPT showing that oxidation is possible but reduction is not [81].

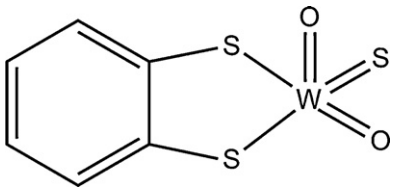

Fig. 13. A structural analogue of the catalytic centre of oxidised xanthine oxidase [84].

The reactivity of the pyran ring of MPT must be taken into account. As noted above, evidence that the pyran ring may be either open or closed (Fig. 10) has been provided by a crystal structure determination for the nitrate reductase A of *E. coli* [66].

When the state pf the pyran ring is considered in conjunction with the oxidation level of the pterin, it becomes apparent that, together, they determine the extent of the conjugation of MPT. Only when the pyrazine ring is in the dihydro-state can the opening of the pyran ring lead to a conjugation that extends from the metal centre across the pyrazine and pyrimidine rings. This is of particular interest as, in the crystal structures of the oxotransferase enzymes obtained so far, the pterin functionality in the MPT has been found in the dihydro-oxidation state and the effect of opening of the pyran ring would be that shown in Fig. 10. Enemark and Garner [79] have suggested a simple, proton catalysed, process that could facilitate the opening of the pyran ring of MPT at the dihydro-oxidation level (Fig. 11). Thus, the protons involved in the oxygen atom transfer reaction could interact with MPT to facilitate catalysis. Supporting evidence for this postulate has been provided by the theoretical calculations of Greatbanks et al. [80] that indicate the 7,8-dihydro-form of MPT is the most thermodynamically stable tautomer; this form of MPT allows electronic communication between the pyrazine ring of MPT and the metal centre.

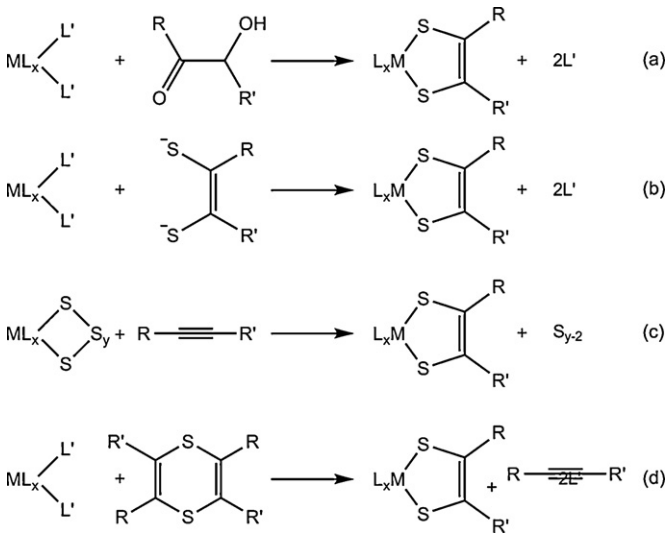

Fig. 15. Methods utilised for the synthesis of mixed ligand complexes involving an unsymmetrically substituted dithiolene.

Beyond the above considerations, if the pterin of MPT is redox active in MPT and this redox activity is linked to the state of the pyran ring, the state of the pyrazine and pyran rings could influence the redox properties of the metal centre. Burgmayer et al. [81] have provided a valuable insight into the redox capabilities of a pyranopterin. They studied how the redox properties of a pterin were affected when part of a pyranopterin (Fig. 12). They found that the pyranopterin was chemically versatile. The analogue investigated reacted as a dihydropterin in oxidations, where it was easily oxidised to the fully oxidised form after ring opening. However, under reducing conditions, which reduce dihydropterin itself it acted as a fully reduced pterin, *i.e.* no further reduction was possible.

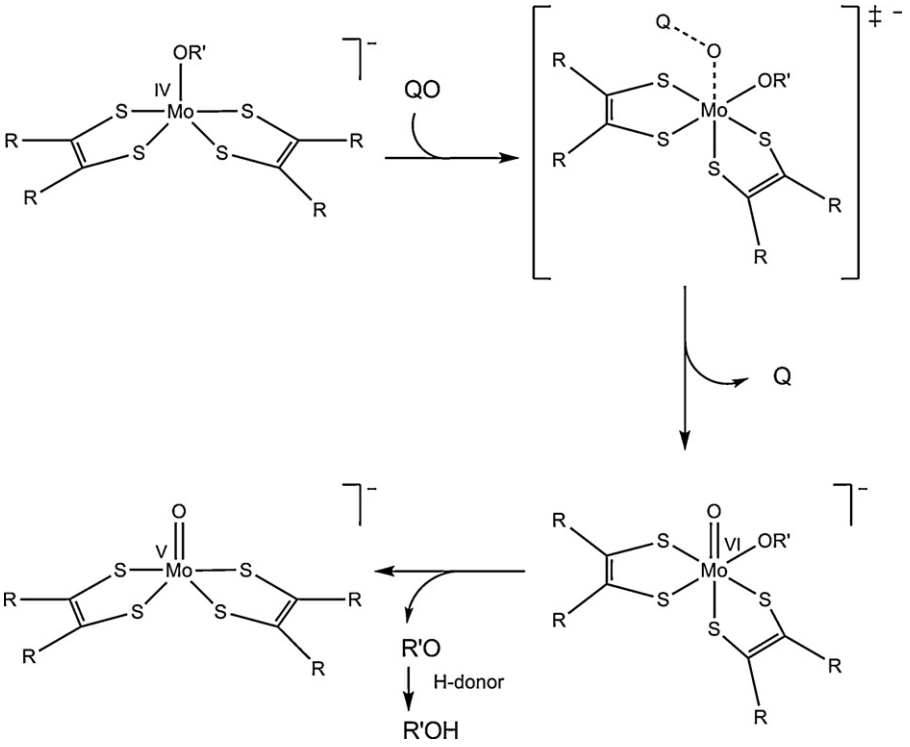

Fig. 14. Summary of an oxygen atom transfer reaction sequence, commencing with $[Mo(OR')(S_2C_2R_2)_2]^-$ (R′ = Ph, Ad, or ^{i}Pr; R = Me or Ph; QO = *N*- or *S*-oxide and ‡ = transition state) [90].

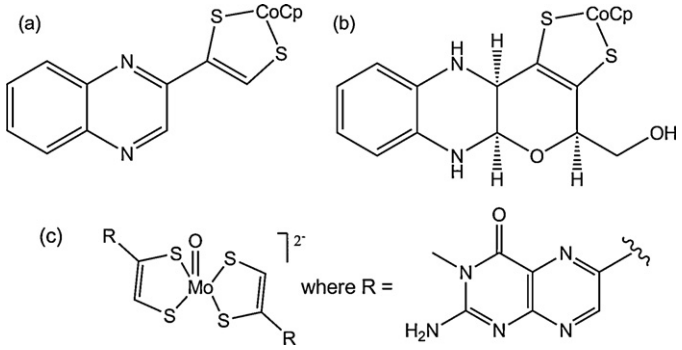

Fig. 16. (a) [CpCo{S_2C_2H(quinoxalin-2-yl)}] [103]; (b) A [CpCo(dt)] compound containing a pyranoquinoxaline analogue of MPT [106]; and (c) one of the $[Mo(O)(dt)_2]^{2-}$ complexes synthesised by Davies et al. [100,101].

3. Chemical analogues

3.1. Molybdenum centres

The synthesis of chemical analogues of the catalytic centres of the molybdenum and tungsten enzymes has led to the development of new chemistry and improved our understanding of the role of the metal in the function of the oxotransferase enzymes. The chemical analogues developed so far can be considered in two groups.

The first comprises structural models that aim to reproduce the general features of the metal's coordination sphere in at least one stage of the catalytic cycle. These compounds have provided valuable calibrations of the spectroscopic techniques used to probe the metal centres of the oxotransferase enzymes. Thus, such compounds have helped to establish the structural and spectroscopic characteristics of terminal oxo- and sulfido-molybdenum (or tungsten) complexes [82,83]. One important case study is that for the oxidised xanthine oxidase analogue shown in Fig. 13 [84]. This tungsten(VI) complex was used in place of the isostructural molybdenum analogue since molybdenum(VI) complexes are often unstable to autoreduction in anionic sulfur ligand environments [85]. Superposition of the structures of the analogue and the oxidised protein site revealed a near congruency. This is also the case for several other similar analogues [86] and indicates that interactions with the protein do not significantly perturb the coordination sphere of the metal.

A second group of studies involve reactivity analogues synthesised in attempts to reproduce the oxygen atom and/or the H^+/e^- reactions of the catalytic centres. Significant advances have been accomplished by Holm et al. [87–95] in respect of the synthesis and characterisation of simple molybdenum and tungsten dithiolene complexes that are capable of oxygen atom transfer reactions. For example, $[Mo(OR')(S_2C_2R_2)_2]^-$ (R′ = Ph, Ad, or ^{i}Pr; R = Me or Ph) complexes react readily with *N*-, *S*-, and *Se*-oxides (see Fig. 14) and kinetic investigations of these oxygen atom transfer reactions have been achieved. These reactions have been shown, by ^{18}O labelling, to proceed by direct oxygen atom transfer with second-order kinetics, an associative transition state, and an appreciable enthalpy of activation (8–15 kcal mol^{-1}). A study of the corresponding reactions of the analogous tungsten complexes has also been accomplished [91,94–96].

3.2. Towards the synthesis of molybdopterin complexes

As an initial step towards the synthesis of MPT, general strategies for the synthesis of asymmetrically substituted dithiolenes have been developed particularly those incorporating *N*-heterocycles. One such strategy involves the synthesis of asymmetrically substituted dithiolene pro-ligands [97–99]. The asymmetric pro-ligands have been used to generate a series of $[MO(S_2C_2(H)(R))_2]^{2-}$ (M = Mo or W) complexes [100,101]. The chemical shifts in the ^1H and ^{13}C NMR spectra and the $E_{1/2}$ values for the M(V)/M(IV) redox couple were shown to be modulated by the nature of the substituent (R) on the dithiolene.

Other methods utilised for synthesising unsymmetrical dithiolenes include those shown in Fig. 15. These have been utilised in the development of mixed ligand dithiolene complexes involving a CpCo or a Cp_2M (M = Mo or W) centre when bound to one dithiolene ligand [102–105]. The chemical inertness of these cyclopentadienyl centres has allowed the introduction of substituents on the dithiolene that have some relevance to MPT. Armstrong et al. [103] reported that protonation of the heterocyclic nitrogen atoms of the [CpCo(dt)] complex (Fig. 16a) resulted in a shift in the redox potential of the CpCo centre to a more positive value, indicating that the effect of protonation was communicated through the dithiolene to the metal centre. This effect has been reported for other complexes with dithiolene ligands that contain nitrogen heteroatoms that are conjugated to the dithiolene metallocycle [102–105]. Thus, such conjugation facilitates the transmission of the effects of protonation of the ligand to the metal centre, hence modulating the redox properties, *vide ultra* and Fig. 10. Davies et al. [100] extended the chemistry of $[Mo(O)(dt)_2]^{2-}$ complexes (Fig. 16c) to include a pterin moiety.

The chemistry of the [CpCo(dt)] analogues of MPT has been extended by Bradshaw et al. [106] to include the pyran ring functionality (Fig. 16b). The pyrazine ring in this system is in the dihydro-oxidation state, as in the enzymes structures determined to date.

Method (c) in Fig. 15 has been used to synthesise $[Cp_2Mo(dt)]$ and [Tp*Mo(O)(dt)] {Tp* = *tris*(3,5-dimethylpyrazolyl)borate} compounds containing an unsymmetrically substituted dithiolene [102,105,107]. Thus, Pilato et al. [102] synthesised the pterin-substituted $[Cp_2Mo(dt)]$ compound shown in Fig. 17a together with several related $[Cp_2Mo(dt)]$ compounds [105]. Subsequently, this chemistry was extended by Burgmayer et al. [107] to form [Tp*Mo(O)(dt)] complexes such as that shown in Fig. 17b.

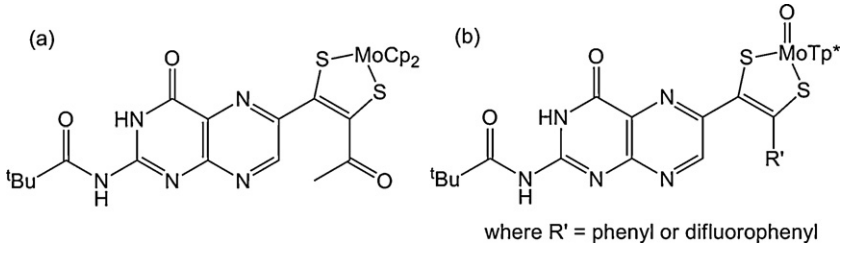

Fig. 17. (a) $[Cp_2Mo(dt)]$ and (b) [Tp*Mo(O)(dt)] complexes containing a dithiolene ligand related to MPT [102,107].

4. Conclusions

Following their introduction as analytical reagents for *d*-transition metals in the 1930s, the coordination chemistry of dithiolenes has been developed in parallel with spectroscopic and theoretical investigations of the electronic structure of the complexes of these 'non-innocent' ligands. A wide range of complexes now exist and a striking aspect of their chemistry is the ability of many of these systems to undergo facile and reversible redox reactions.

Dithiolenes play an important role in natural systems. Thus, a dithiolene group is an integral component of molybdopterin (MPT), the moiety that binds the molybdenum (or tungsten) at the catalytic centre of enzymes that transfer an oxygen atom to or from the substrate. These enzymes catalyse a wide range of reactions and are present in virtually all living systems. Several of these enzymes have been structurally characterised and each catalytic centre shown to involve a single metal atom bound to one or two MPT groups, plus other donor atoms. Spectroscopic information indicates that the oxygen atom transfer reaction takes place at the metal centre, the oxidation state of which changes from M(VI) to M(IV) (or *vice-versa*). This chemistry has been replicated by low molecular weight analogues of these centres. However, challenges remain in understanding the coordination chemistry of these centres, not the least of these is the role of the pterin and pyran ring that, together with the dithiolene, form MPT. Whether other roles for dithiolene complexes will be found in Nature remains to be seen. However, the present knowledge should encourage further investigations of dithiolene complexes as catalysts, especially when the process involves a redox change.

References

[1] W.H. Mills, R.E.D. Clark, J. Chem. Soc. (1936) 175.
[2] (a) R.E.D. Clark, Analyst 61 (1936) 242;
(b) R.E.D. Clark, Analyst 62 (1937) 661;
(c) R.E.D. Clark, Tech. Publ. Intern. Tin Res. Dev. Council, A (1936) 41.
[3] J. Hamence, Analyst 65 (1940) 152.
[4] H.G. Short, Analyst 76 (1951) 710.
[5] C.C. Miller, A.J. Lowe, J. Chem. Soc. (1940) 1258.
[6] G. Bähr, H. Schleitzer, Chem. Ber. 90 (1957) 438.
[7] G.H. Ayres, H.F. Janota, Anal. Chem. 31 (1959) 1985.
[8] D.B. Stevancevic, V.C. Drazic, Bull. Inst. Nucl. Sci. 9 (1959) 69.
[9] T.W. Gilbert Jr., E.B. Sandell, J. Am. Chem. Soc. 82 (1960) 1087.
[10] G.N. Schrauzer, V.P. Mayweg, J. Am. Chem. Soc. 84 (1962) 3221.
[11] H.B. Gray, R. Williams, I. Bernal, E. Billig, J. Am. Chem. Soc. 84 (1962) 3596.
[12] A. Davison, N. Edelstein, R.H. Holm, A.H. Maki, J. Am. Chem. Soc. 85 (1963) 2029.
[13] A. Davison, N. Edelstein, R.H. Holm, A.H. Maki, Inorg. Chem. 2 (1963) 1227.
[14] H.B. Gray, Trans. Metal Chem. 1 (1965) 239.
[15] G.N. Schrauzer, Acc. Chem. Res. 2 (1969) 72.
[16] R. Eisenberg, Prog. Inorg. Chem. 12 (1970) 295.
[17] R.H. Holm, M.J. O'Connor, Prog. Inorg. Chem. 14 (1971) 241.
[18] R.P. Burns, C.A. McAuliffe, Adv. Inorg. Chem. Radiochem. 22 (1979) 303.
[19] U.T. Müller-Westerhoff, B. Vance, in: G. Wilkinson (Ed.), Comprehensive Coordination Chemistry, Pergamon, New York, 1987, p. 595.
[20] E.I. Stiefel (Ed.), Dithiolene Chemistry: Synthesis, Properties and Applications, Progress in Inorganic Chemistry, vol. 52, John Wiley and Sons, Inc., New Jersey, 2004.
[21] G.N. Schrauzer, Trans. Metal Chem. 4 (1968) 299.
[22] Chr.K. Jørgensen, Coord. Chem. Rev. 1 (1966) 164.
[23] J.A. McCleverty, Prog. Inorg. Chem. 10 (1968) 49.
[24] M. Formigué, Coord. Chem. Rev. 178–180 (1998) 823.
[25] G.N. Schrauzer, V.P. Mayweg, J. Am. Chem. Soc. 87 (1965) 3585.
[26] S. Alvarez, R. Vincente, R. Hoffmann, J. Am. Chem. Soc. 107 (1985) 6253.
[27] P. Chaudhuri, C.N. Verani, E. Bill, E. Bothe, T. Weyhermüller, K. Wieghardt, J. Am. Chem. Soc. 123 (2001) 2213.
[28] H. Chun, T. Weyhermüller, E. Bill, K. Wieghardt, Angew. Chem. Int. Ed. 40 (2001) 2489.
[29] D. Herebian, E. Bothe, E. Bill, T. Weyhermüller, K. Wieghardt, J. Am. Chem. Soc. 123 (2001) 10012.
[30] F. Neese, J. Phys. Chem. Solids 65 (2004) 781.
[31] D. Herebian, E. Bothe, F. Neese, T. Weyhermüller, K.E. Wieghardt, J. Am. Chem. Soc. 125 (2003) 9116.
[32] S. Frantz, H. Hartmann, N. Doslik, M. Wanner, W. Kaim, H.J. Kummerer, G. Denneinger, A.L. Barra, C. Duboc-Toia, J. Fiedler, I. Ciofini, C. Urban, M. Kaupp, J. Am. Chem. Soc. 124 (2002) 10563.
[33] C.G. Pierpont, Coord. Chem. Rev. 219–221 (2001) 415.
[34] D. Sellmann, M. Geck, F. Knoch, G. Ritter, J. Denglar, J. Am. Chem. Soc. 113 (1991) 3819.
[35] H. Alves, D. Simao, H. Novais, I.C. Santos, C. Gimenez-Saiz, V. Gama, J.C. Waerenborgh, R.T. Henriques, M. Almeida, Polyhedron 22 (2003) 2481.
[36] E. Bill, E. Bothe, P. Chaudhuri, K. Chlopek, D. Herebian, S. Kokatam, K. Ray, T. Weyhermüller, F. Neese, K. Wieghardt, Chem. Eur. J. 11 (2004) 204.
[37] K. Ray, A. Begum, T. Weyhermüller, S. Piligkos, F. Neese, K. Wieghardt, J. Am. Chem. Soc. 127 (2005) 4403.
[38] T. Petrenko, K. Ray, K. Wieghardt, F. Neese, J. Am. Chem. Soc. 128 (2006) 4422.
[39] R. Kapre, K. Ray, I. Sylvestre, T. Weyhermüller, S. DeBeer George, F. Neese, K. Wieghardt, Inorg. Chem. 45 (2006) 3499.
[40] K. Ray, T. Petrenko, K. Wieghardt, F. Neese, Dalton Trans. (2007) 1552.
[41] K. Ray, S. DeBeer George, E.I. Solomon, K. Wieghardt, F. Neese, Chem. Eur. J. 13 (2007) 2783.
[42] C. Milsmann, E. Bothe, E. Bill, T. Weyhermüller, K. Wieghardt, Inorg. Chem. 48 (2009) 6211.
[43] R.R. Kapre, E. Bothe, T. Weyhermüller, S. DeBeer George, K. Wieghardt, Inorg. Chem. 46 (2007) 5642.
[44] R.R. Kapre, E. Bothe, T. Weyhermüller, S. DeBeer George, N. Muresan, K. Wieghardt, Inorg. Chem. 46 (2007) 7827.
[45] Y. Zhang, V.N. Gladyshev, Cell. Mol. Life Sci. 62 (2005) 2792.
[46] P.C. Dos Santos, D.R. Dean, Y. Hu, M.W. Ribbe, Chem. Rev. 104 (2004) 1159.
[47] G. Schwarz, Cell. Mol. Life Sci. 62 (2005) 2792.
[48] R. Hille, Trends Biochem. Sci. 27 (2002) 360.
[49] M.K. Johnson, D.C. Rees, M.W.W. Adams, Chem. Rev. 7 (1996) 2817.
[50] L.E. Bevers, P.-L. Hagedoorn, W.R. Hagen, Coord. Chem. Rev. 253 (2009) 269.
[51] J. McMaster, J.M. Tunney, C.D. Garner, in: E.I. Stiefel (Ed.), Dithiolene Chemistry: Synthesis, Properties and Applications, Progress in Inorganic Chemistry, vol. 52, John Wiley and Sons, Inc., New Jersey, 2004, p. 539.
[52] J.B. Howard, D.C. Rees, Chem. Rev. 96 (1996) 2965.
[53] B.K. Burgess, D.J. Lowe, Chem. Rev. 96 (1996) 2983.
[54] R. Hille, Chem. Rev. 96 (1996) 2757.
[55] E.I. Stiefel, D. Coucouvanis, W.E. Newton (Eds.), Molybdenum Enzymes, Cofactors and Model Systems, American Chemical Society, Washington, DC, 1993, p. 535.
[56] J.M. Rebelo, J.M. Dias, R. Huber, J.J.G. Moura, M.J. Romão, J. Biol. Inorg. Chem. 6 (2001) 791.
[57] C.D. Garner, R. Banham, S.J. Cooper, E.S. Davies, L.J. Stewart, in: I. Bertini, A. Sigel, H. Sigel (Eds.), Handbook on Metalloproteins, M. Dekker Inc., New York, 2001, p. 1023.
[58] K.V. Rajagopalan, J. Biol. Inorg. Chem. 2 (1997) 786.
[59] K.V. Rajagopalan, Adv. Enzymol. Relat. Areas Mol. Biol. 64 (1991) 215.
[60] K.V. Rajagopalan, J.L. Johnson, J. Biol. Chem. 267 (1992) 10199.
[61] M.J. Romão, Dalton Trans. (2009) 4053, and references therein.
[62] H. Dobbek, L. Gremer, R. Kiefersauer, R. Huber, O. Meyer, Proc. Natl. Acad. Sci. U.S.A. 99 (2002) 15971.
[63] S. Najmudin, P.J. González, J. Trincão, C. Coelho, A. Mukhopadhyay, N.M.F.S.A. Cerqueira, C.A. Romão, I. Moura, J.J.G. Moura, C.D. Brondino, M.J. Romão, JBIC 13 (2008) 737.
[64] C.D. Garner, L.J. Stewart, Metal Ions in Biological Systems, vol. 39, M. Dekker Inc., New York, 2002, p. 699.
[65] J. McMaster, J.M. Tunney, C.D. Garner, Prog. Inorg. Chem. 52 (2003) 539.
[66] M.G. Bertero, R.A. Rothery, M. Palak, C. Hou, D. Lim, F. Blasco, J.H. Weiner, N.C.J. Strynadka, Nat. Struct. Biol. 10 (2003) 681.
[67] J. Kuper, A. Llamas, H.-J. Hecht, R.R. Mendel, G. Schwarz, Nature 430 (2004) 803.
[68] M.S. Morrison, P.A. Cobine, E.L. Hegg, JBIC 12 (2007) 1129.
[69] M. Neumann, S. Leimkühler, FEBS J. 275 (2008) 5678.
[70] G. Schwarz, R.R. Mendel, M.W. Ribbe, Nature 460 (2009) 839.
[71] J.L. Johnson, W.R. Waud, K.V. Duran, F.A. Beemer, S.K. Wadman, Proc. Natl. Acad. Sci. 77 (1980) 3715.
[72] G. Schwarz, J.A. Santamaria-Araujo, S. Wolf, H.J. Lee, I.M. Adham, H.J. Grone, H. Schwegler, J.O. Sass, T. Otte, P. Hanzelmann, R.R. Mendel, W. Engel, J. Reiss, Hum. Mol. Genet. 13 (2004) 1249.
[73] C. Kisker, H. Schindelin, D.C. Rees, Annu. Rev. Biochem. 66 (1997) 233.
[74] F. Schneider, J. Lowe, R. Huber, H. Schindelin, C. Kisker, J. Knablein, J. Mol. Biol. 253 (1996) 53.
[75] F.E. Inscore, R. McNaughton, B.L. Wescott, M.E. Helton, R. Jones, I.K. Dhawan, J.H. Enemark, M.L. Kirk, Inorg. Chem. 38 (1999) 1401.
[76] Y. Izumi, T. Glaser, K. Rose, J. McMaster, P. Basu, J.H. Enemark, B. Hedman, K.O. Hodgson, E.I. Solomon, J. Am. Chem. Soc. 121 (1999) 10035.
[77] M.K. Chan, S. Mukund, A. Kletzin, M.W.W. Adams, D.C. Rees, Science 267 (1995) 1463.
[78] F.E. Inscore, R. McNaughton, B.L. Wescott, M.E. Helton, R. Jones, I.K. Dhawan, J.H. Enemark, M.L. Kirk, Inorg. Chem. 38 (1999) 1401.
[79] J.H. Enemark, C.D. Garner, J. Biol. Inorg. Chem. 2 (1997) 817.
[80] S.P. Greatbanks, I.H. Hillier, C.D. Garner, J.A. Joule, J. Chem. Soc., Perkin Trans. 2 (8) (1997) 1529.
[81] S.J.N. Burgmayer, D.L. Pearsall, S.M. Blaney, E.M. Moore, C. Saut-Schubert, J. Biol. Inorg. Chem. 9 (2004) 59.
[82] J.H. Enemark, J.J. Cooney, J.J. Wang, R.H. Holm, Chem. Rev. 104 (2004) 1175.
[83] H. Sugimoto, H. Tsukube, Chem. Soc. Rev. 37 (2008) 2609.
[84] S. Groysman, J.-J. Wang, R. Tagore, S.C. Lee, R.H. Holm, J. Am. Chem. Soc. 130 (2008) 12794.

[85] S. Groysman, R.H. Holm, Biochemistry 48 (2009) 2310.
[86] B.S. Lim, M.W. Willer, M. Miao, R.H. Holm, J. Am. Chem. Soc. 123 (2001) 8343.
[87] C. Lorber, J.P. Donahue, C.A. Goddard, E. Nordlander, R.H. Holm, J. Am. Chem. Soc. 120 (1998) 8102.
[88] J.P. Donahue, C.R. Goldsmith, U. Nadiminti, R.H. Holm, J. Am. Chem. Soc. 120 (1998) 12869.
[89] B.S. Lim, K.-M. Sung, R.H. Holm, J. Am. Chem. Soc. 122 (2000) 7410.
[90] K.–M. Sung, R.H. Holm, Inorg. Chem. 39 (2000) 1275.
[91] B.S. Lim, R.H. Holm, J. Am. Chem. Soc. 123 (2001) 1920.
[92] K.-M. Sung, R.H. Holm, J. Am. Chem. Soc. 123 (2001) 1931.
[93] K.–M. Sung, R.H. Holm, Inorg. Chem. 40 (2001) 4518.
[94] K.-M. Sung, R.H. Holm, J. Am. Chem. Soc. 124 (2002) 4312.
[95] J.-J. Wang, O.P. Kryatova, E.V. Rybak-Akimova, R.H. Holm, Inorg. Chem. 43 (2004) 8092.
[96] J. Jiang, R.H. Holm, Inorg. Chem. 44 (2005) 1068.
[97] A.K. Bhattacharya, A.G. Hortmann, J. Org. Chem. 39 (1974) 95.
[98] A. Dinsmore, J.H. Birks, C.D. Garner, J.A. Joule, J. Chem. Soc., Perkin Trans. 1 (6) (1997) 801.
[99] D.J. Rowe, C.D. Garner, J.A. Joule, J. Chem. Soc., Perkin Trans. 1 (1985) 1907.
[100] E.S. Davies, G.M. Aston, R.L. Beddoes, D. Collison, A. Dinsmore, A. Docrat, J.A. Joule, C.R. Wilson, C.D. Garner, J. Chem. Soc., Dalton Trans. (1998) 3647.
[101] E.S. Davies, R.L. Beddoes, D. Collison, A. Dinsmore, A. Docrat, J.A. Joule, C.R. Wilson, C.D. Garner, J. Chem. Soc., Dalton Trans. (1997) 3985.
[102] R.S. Pilato, K.A. Eriksen, M.A. Greaney, E.I. Stiefel, S. Goswami, L. Kilpatrick, T.G. Spiro, E.C. Taylor, A.L. Rheingold, J. Am. Chem. Soc. 113 (1991) 9372.
[103] E.M. Armstrong, M.S. Austerberry, J.H. Birks, R.L. Beddoes, M. Helliwell, J.A. Joule, C.D. Garner, Heterocycles 35 (1993) 563.
[104] E.M. Armstrong, M.S. Austerberry, R.L. Beddoes, M. Helliwell, J.A. Joule, C.D. Garner, Acta Crystallogr. C 49 (1993) 1764.
[105] J.K. Hsu, C.J. Bonangelino, S.P. Kaiwar, C.M. Boggs, J.C. Fettinger, R.S. Pilato, Inorg. Chem. 35 (1996) 4743.
[106] B. Bradshaw, A. Dinsmore, D. Collison, C.D. Garner, J.A. Joule, J. Chem. Soc., Perkin Trans. 1 (2001) 3232.
[107] S.J.N. Burgmayer, M. Kim, R. Petit, A. Rothkopf, A. Kim, S. BelHamdounia, Y. Hou, A. Somogyi, D. Habel-Rodriguez, A. Williams, M.L. Kirk, J. Inorg. Biochem. 101 (2007) 1601.