Thiomolybdates — Simple but Very Versatile Reagents

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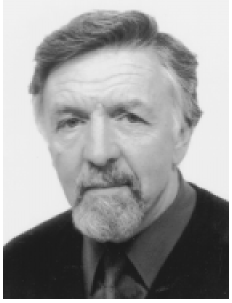
A large number of thiometallate anions, $MO_xS_{4-x}^{n-}$, and some of the seleno analogues, are known in which M is a transition metal in a high oxidation state. They are characterised by their strong colours arising from low energy S(Se)→M charge transfer transitions, by unusual redox properties and by their ability to act as ligands to produce a wide range of heterometal complexes. This review outlines some of these properties associated with the thiometallate anions of molybdenum(VI). These anions are prepared by passing H_2S through an alkaline molybdate solution, giving a sequential replacement of O atoms by S and ultimately MoS_4^{2-} (TTM) as product. The thiomolybdates, particularly TTM, have been the most intensively studied because of their ease of preparation, their relatively greater thermal and hydrolytic stabilities and their biological roles. Unusual redox changes which involve internal electron transfer have been shown by reaction with organic disulfides and with Cu^{II}. In the latter case insoluble polymeric products are readily formed which, from EPR and EXAFS studies, involve S-bridged reduced Cu and Mo centres. Reaction of TTM with Cu^I, on the other hand, produces a range of complexes in which from 1 to 6 Cu ions add across the tetrahedral faces of TTM with no redox changes. Further Cu^I ions can be added to the $[Cu_6(MoS_4)]$ moiety to produce cluster ions. This illustrates the ability of the thiometallates to act as building blocks for a very wide range of heterometal complexes ranging from simple linear ions to complex clusters, a prime example of the latter being the FeMo cofactor of the enzyme nitrogenase. TTM was identified sometime ago as the reactive intermediate in the Mo-induced Cu-deficiency that afflicts ruminants with serious consequences. Subsequently TTM, as its ammonium salt, has been successfully used in removing the excess Cu and then controlling the Cu levels of patients of Wilson's disease. It appears to act by blocking the intestinal absorption of Cu and by converting Cu into a metabolically inert form, and in these respects is different to the mode of action of chelating agents which can be used for treating this disease.

1. Introduction

There exists a number of thiometallate anions of general formula $MO_xS_{4-x}^{n-}$ in which M is a transition metal and $x = 0-3$ (Table 1). Because of their strong colours (mainly yellow to red) compounds of these ions have attracted attention since the very early studies by Berzelius in the 19th century. For some of these the corresponding selenide anions are also known − although generally less well studied. All these chalcogenide anions form a remarkably reactive series whose chemistry has still not been fully explored.

A full assignment of the UV/Vis and IR bands of these tetrahedral anions has been given by Müller and his coworkers.[1,2] Two remarkable features are first, all the metal centres are in their highest oxidation states — despite being



Professor Stuart Laurie obtained his BSc(Hons) and PhD degrees in chemistry at the University College of Wales, Aberystwyth. He then spent several years as a research worker, first at Washington State University and subsequently at the Protein Chemistry Division of the CSIRO, Australia. It was at the latter institute that he first developed his research interests in bioinorganic chemistry. He then spent two years as a Senior Research Fellow with professor R. D. Gillard's bio-inorganic group at the Univerity of Kent at Canterbury. In 1969 he joined the staff of De Montfort University (then Leicester Polytechnic) as a lecturer, subsequently being promoted to Senior Lecturer and then Reader and Professor of Inorganic Chemistry. During the time at DMU he has spent sabbatical periods at the Biochemistry Division, Hospital for Sick Children, Toronto, working with Professors B. Sarkar and (the late) A. Sass-Kortsak on Wilson's Disease therapy and, more recently, at the Marine Sciences Laboratory, University of South Florida, with Professor R. H. Byrne working on aspects of aqueous metal speciation. His current research interests are still focussed on coordination chemistry with particular reference to ternary metal chalcogenides and the recovery of metals from industrial wastes.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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Table 1. Known thio- and selenometallates

VS_4^{3-}	VOS_3^{3-}	$VO_2S_2^{3-}$	
VSe_4^{3-}	$VOSe_3^{3-}$	$VO_2Se_2^{3-}$	
NbS_4^{3-}			
TaS_4^{3-}			
MoS_4^{2-}	$MoOS_3^{2-}$	$MoO_2S_2^{2-}$	MoO_3S^{2-}
$MoSe_4^{2-}$	$MoOSe_3^{2-}$	$MoO_2Se_2^{2-}$	MoO_3Se^{2-}
WS_4^{2-}	WOS_3^{2-}	$WO_2S_2^{2-}$	WO_3S^{2-}
WSe_4^{2-}	$WOSe_3^{2-}$	$WO_2Se_2^{2-}$	WO_3Se^{2-}
ReS_4^{-}	$ReOS_3^{-}$	$ReO_2S_2^{-}$	ReO_3S^{-}

coordinated to the strongly reductive S^{2-} ions. Second, the M−S bond lengths that have been determined are all very similar, 2.15−2.18 Å. The first feature accounts for their strong colours as the S→M charge transfer bands are of relatively low energy and lie in the visible region. Linear relationships in fact have been established between the energy of the longest wavelength electronic transition with the M−S stretching force constant and with the optical electronegativity of the metal centre (for closely related species). In the latter case the transition energy increases as the χ_{opt} value decreases — consistent with charge transfer being in the S→M direction.[2]

The second feature points towards some π character in the M−S bonds — as also suggested from MO calculations.[1] Electron delocalisation through π bonding also explains why these anions do not undergo a spontaneous internal redox reaction.

Of this series it is the Mo^{VI} anions, particularly MoS_4^{2-} (TTM), which have been the most studied — this can be attributed to their ease of formation and conversion into other dimolybdenum-thiol species, their greater thermal and hydrolytic stabilities and their implication and use in biological systems.

2. Preparation and Properties of the Thiomolybdates

TTM can be most easily prepared as its ammonium salt by passing H_2S through an ammoniacal molybdate solution. [3] In 15−20 minutes $(NH_4)_2MoS_4$ precipitates from the reaction mixture as red crystals of high purity and in high yield — a chemist's dream! The Na^+ and K^+ salts [3,4] are also known but are more difficult to prepare (and keep). Attempts to prepare the Ca^{2+} salt for medical use (vide infra) have been unsuccessful.[5] Alkylammonium and phosphonium salts are particularly important for studying reactions in non-aqueous media and as starting materials for many of the known heterometal complexes. The $[R_4N]_2MoS_4$ salts can be readily prepared from aqueous solutions of the ammonium salt by elimination of the ammonium ion as ammonia. $[PPh_4]_2MoS_4$ is a particularly useful starting material for dimolybdenum compounds and is readily precipitated from aqueous solutions of $[NH_4]_2MoS_4$ by the simple addition of $[PPh_4]Cl$.[6] Preparation of salts of the intermediate oxythio anions, $MoO_xS_{4-x}^{2-}$ (x = 1−3), have all been reported — these all involve passage of H_2S but require more strictly controlled conditions in order to avoid contamination with neighbouring thiomolybdates.[1,3,7]

Formation of TTM from MoO_4^{2-} clearly proceeds via successive replacement of oxygen, as evidenced from the colour sequence change in solution: MoO_4^{2-}(colourless) → MoO_3S^{2-}(yellow) → $MoO_2S_2^{2-}$(orange) → $MoOS_3^{2-}$(orange-red) → MoS_4^{2-}(red). This colour sequence is shown in the aesthetic UV/Vis absorbance spectrum of the reaction between MoO_4^{2-} and S^{2-} as a function of time, as shown in Figure 1.

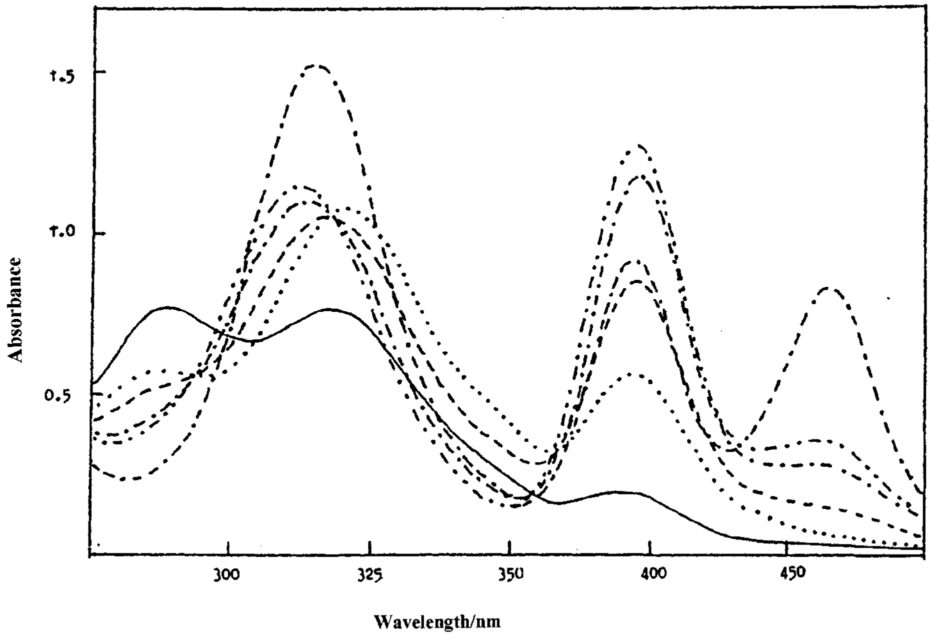


Figure 1. Formation of thiomolydate anions as a function of time (initial MoO_4^{2-} 1.3×10^{-4} M, S^{2-} 2.9×10^{-3} M, pH 7.0, 37 °C): after —————— 1 min., ········ 6 min., - - - - - - 21 min., ·-·-·-·-·- 60 min., ··-··-··-·· 110 min., --·--·--·--19 h; see Table 2 for assignment of the absorbance peaks)

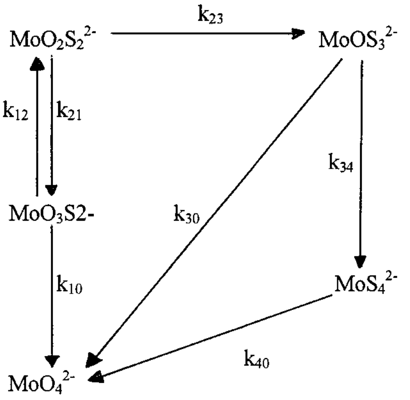
The strong UV/Vis and IR absorption bands are particularly useful diagnostic tools in determining the purity of the thiomolybdates and in following their reactions. These spectral details are given in Table 2.

Table 2. UV/Vis and IR bands of the thiomolybdate anions[a]

	UV/Vis λ/nm[b] (ε)[c]	IR[d] λ/cm^{-1}	
		Mo−S	Mo−O
MoS_4^{2-}	316 (1.76), 465 (1.24)	476	-
$MoOS_3^{2-}$	315 (0.84), 398 (0.81), 465 (0.14)	470	860
$MoO_2S_2^{2-}$	288 (0.39), 320 (0.64), 394 (0.29)	460	860, 840
MoO_3S^{2-}	288 (−), 390 (−)[e]	476	880, 860, 840

[a] From measurements made in this laboratory. − [b] In pH 7 buffered aqueous solutions, ±2 nm. − [c] 10^4 dm^3 mol^{-1} cm^{-1}. − [d] Peak positions vary depending on the nature of the solvent and cation. − [e] Difficult to obtain accurate values.

The distinctive UV/Vis spectra of TTM and the oxythiomolybdate anions (Figure 1) have been used [8] to determine the rate constants for the formation (pseudo-first order with S^{2-} in excess) and hydrolysis of the ions as in Scheme 1.



Scheme 1

The rate constants for the thiol formation reactions follow the order:

$k_{12} > k_{23} > k_{34}$

Whilst that for the hydrolysis reactions is:

$k_{10} > k_{21} \approx k_{30} > k_{40}$

All the rates increase linearly with increase in H^+ concentration. Two important results with regard to TTM formation and existence in biological systems are that its complete formation in aqueous media requires a high S:Mo ratio and that its known increasing hydrolysis rate with increasing H^+ concentration proceeds without detectable formation of the intermediate oxythio ions in the above scheme.[8]

Earlier claims that, like MoO_4^{2-}, polymerisation of TTM occurs in lower pH solutions have not been substantiated. However, treatment with polysulfide produces dimeric and trimeric species in which the Mo centres have been reduced to oxidation states V and IV respectively,[9−11] e.g. to $(NH_4)_2[Mo_2^V(S_2)_6]\cdot 2H_2O$ and $(NH_4)_2[Mo_3^{IV}S(S_2)_6]$. Cyclic voltammetry of TTM in aqueous solution shows an irreversible reduction wave at −1.08 V,[12] whilst in dimethylformamide a reversible reduction potential of −2.50 V is observed.[13]

3. Thiomolybdates as Ligands

By far the most important property of the thiomolybdates, in particular TTM, is their role as ligands in a range of complexes, In these the $MoO_xS_{4-x}^{2-}$ moieties are mostly retained. It is the sulfide ions that play the key role as bridging ligands in which they can bridge two, three or four metal centres. The complexes formed range from simple linear structures, to small cubanes (Figure 2) to more complex clusters. In these cases the thiometallate anions act as the building blocks.

These compounds have received an enormous amount of attention over recent years because of their structural diversity and potential applications, e.g. as nonlinear optical materials, industrial catalysts and as models for the active Fe−Mo−S cluster site in the metalloenzyme nitrogenase. Consequently, they have been well reviewed.[2,14−17] Mention will be made here of only the much-studied system R/Cu^I/$MoO_xS_{4-x}^{2-}$, where R typically is a phosphane PR_3, halide (Cl^- or Br^-) or CN^-. In the absence of R, polymeric products are obtained, as in $(NH_4)CuMoS_4$ and Cu_2MoS_4, which feature alternate S-linked Cu^I and Mo^{VI} centres. In the presence of the R ligands, which preferentially occupy Cu^I sites, a range of discrete complexes can be obtained

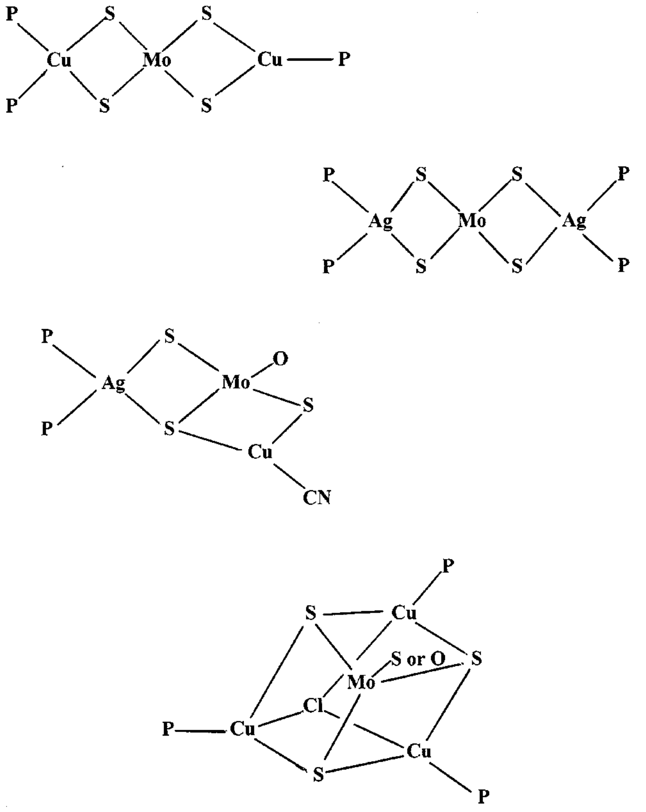


Figure 2. Some simple linear and cubane structures in schematic form illustrating the ability of thiomolybdate anions to act as ligands and as building blocks for more complex structures (P = triphenylphosphane)

depending on the reaction conditions (some examples are given in Table 3), the structures of many of these are known. Compounds have been reported from the reaction of CuCl with MoS_4^{2-} in which 1 to 6 Cu atoms occupy the six edges of the tetrahedral MoS_4^{2-} ion, i.e. of the form $[MoS_4(CuL)_n]$ ($n = 1-6$). A number of clusters with larger Cu:Mo ratios have also been synthesised, e.g. the anion $[MoS_4Cu_{10}\,Cl_{12}]^{4-}$ in which the central MoS_4^{2-} ion has six bridging Cu^I ions along its tetrahedral faces (as in the n = 6 case above) with the remaining four Cu^I ions forming an outer tetrahedral array linked by Cl^- bridges.[18] The formation of this latter complex from $(NH_4)_2MoS_4$ and CuCl illustrates how important the ratios of the starting reactants and the nature of the solvent are in terms of the final product(s) obtained. The structures of many of these heterometal compounds are known and illustrate the wide range of structural forms that they can exhibit.[19] Spectroscopic studies show that the IR ν(Mo−S) absorption modes in the 415−500 cm^{-1} region are diagnostic of the number of coordinated Cu^I ions.[20] For the diamagnetic heterometal complexes, ^{95}Mo NMR spectroscopy appears to provide a sensitive probe of the Mo environment;[21,22] for $[NPr_4]_2[Pt(MoS_4)_2]$ in DMF solution the observation of Pt−Mo coupling implies significant M−Mo interactions in these compounds.

Table 3. Examples of compounds isolated from R + Cu^I + (a) MoS_4^{2-}, + (b) $MoOS_3^{2-}$ or + (*c*) $MoO_2S_2^{2-}$

(*a*) $[Cl(PPh_3)_3Cu_3MoS_4]$	(*a*) $(PPh_3)_3[Cu_2(MoS_4)].0.8CH_2Cl_2$
(*a*) $(Bu_4N)_4[Cu_{12}(MoS_4)_8]$	(*b*) $(Bu_4N)_4[Mo_4Cu_{10}S_{16}O_3].H_2O$
(*a*) $(Me_4N)_5[MoS_4(CuCl)_6Cl_3]$	(*c*) $(Et_4N)_4[Mo_4Cu_4S_{12}O_4]$

A variation on the above is to use S^{2-} as the additional ligand leading to a further variation in structural types such as, $[Mo_4Cu_4S_{12}O_4]^{4-}$ (square type), $[Mo_8Cu_{12}S_{28}E_4]^{4-}$ E = S,O (cage), $[Mo_6Cu_6S_{19}O_6]^{2-}$ (cage).[23]

4. Redox Activity

Both the metal centres and the S ligands are redox active — either acting separately or, of more interest, acting in concert.[24] Oxidation of S^{2-} can result in a number of species with oxidation states ranging up to VI, e.g. S_2^{2-}, S_4^{2-}, S_8, SO_2, SO_3 as well as the various oxyanions. All of these are also potential ligands. As mentioned above, the occurrence of high metal oxidation state Mo^{VI} and low S state makes the occurrence and stability of the thiometallate ions somewhat surprising, especially for the thiomolybdate ions as the Mo and S redox potentials are fairly close. The potential redox activity has been realised in a number of reactions, e.g. in the reaction between TTM and organic disulfides elucidated by Stiefel and co-workers.[25,26]

$$2\,MoS_4^{2-} + RSSR \rightarrow Mo_2S_8^{2-} + 2\,RS^- \qquad (1)$$

In this reaction the disulfide *oxidant* appears to have caused reduction of the Mo^{VI} centres to Mo^V! The required four electron donation in fact comes from the conversion of sulfides to persulfides:

$$4\,S^{2-} \rightarrow 2\,S_2^{2-} + 4e^- \qquad (2)$$

The sulfide ion oxidation proceeds without M−S bond cleavage as X-ray analysis shows the persulfide ions to be coordinated to the Mo centres (Figure 3).

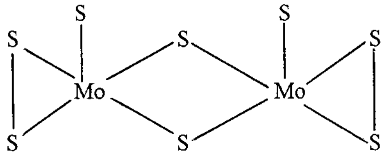


Figure 3. Structure of the anion $[Mo_2^VS_4(S_2)_2]^{2-}$ showing the coordinated persulfide ions (from ref. 25)

Under the same conditions WS_4^{2-} was found not to undergo metal reduction, but only a ligand redox reaction.[25] However, induced internal electron transfer has been observed with other tetrathiometallates. Stiefel[25] has pointed to a correlation between the ease of internal redox reactions and the lowest energy ligand-to-metal charge-transfer band (LMCT) and points to the position of the LMCT band being a "spectroscopic indicator" for such reactions. The LMCT bands in question are: ReS_4^-, 19800 cm^{-1}; MoS_4^{2-}, 21300 cm^{-1}; WS_4^{2-}, 25300 cm^{-1}. Of these ions, WS_4^{2-}, with the highest energy LMCT transition, undergoes internal redox changes the least easily. A similar intramolecular redox reaction has been reported by Coucouvanis et al.[27] involving the reaction between the oxy- and tetrathiomolybdates with elemental sulfur: under *oxidising* conditions the Mo centres were reduced to Mo^{IV} complexes with the formation of coordinated S_4^{2-} ions.

We have reported a similar redox reaction between TTM and salts and complexes of Cu^{II}, a black insoluble compound of composition $Cu_{1.6}MoS_4X_y$ was obtained (X = Cl^-, Br^-, y = 1; X = SO_4^{2-}, y = 0.5) when the Cu^{II} halide or sulfate salts were reacted with TTM in aqueous solutions.[28,29] EPR spectroscopy showed no Cu^{II} but the presence of Mo^V with a small (ca. 10%) contribution to the spectrum from an S radical species.[29] Presumably, the one electron reduction of each of the metal centres arises mainly from sulfide oxidation to persulfide, as in reactions (1) and (2) above. Some sulfide oxidation must also lead to the S radicals that were observed. EXAFS spectroscopy at the Cu and Mo K-edges show the Mo coordination to have been reduced to a trigonal MoS_3 moiety whilst the Cu is most likely a mixture of CuS_3 and CuS_4 coordination. Without some knowledge of the S species present it is difficult to predict the likely structure of this fascinating material; its insolubility does, however, suggest a multi-S bridged polymer. A further, surprising, finding was the observation that the solid irreversibly absorbs up to 2 mol O_2, with no change in either the EPR or EXAFS spectra, which suggests oxygenation at the S atoms. These EXAFS spectra are shown in Figure 4. We also found WS_4^{2-},despite its reported greater redox stability, to react with Cu^{II} identically to TTM in its reaction stoichiometry, redox changes and oxygenation.

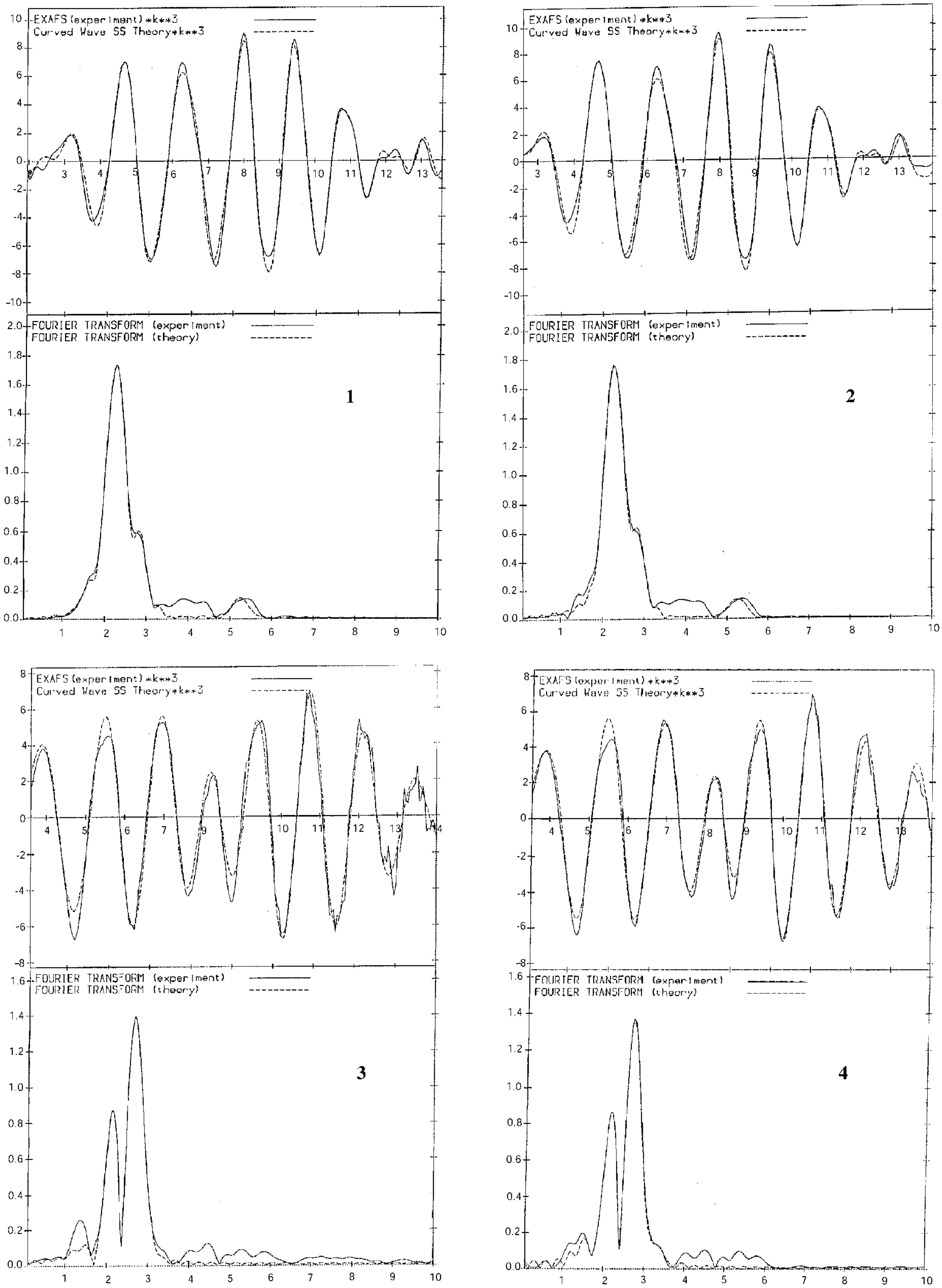


Figure 4. EXAFS spectra and Fourier transforms of [$Cu_{1.6}MoS_4Cl$] showing retention of the metal coordination sites after O_2 uptake; **1** Cu k-edge, **2** Cu k-edge of oxygenated sample, **3** Mo k-edge, **4** Mo k-edge after oxygenation

Recently, Noble et al.[30] have shown that S coordinated at a dimolybdenum centre can undergo conversion into coordinated SO (sulfoxide) and coordinated SO_2 (sulfone). Similar oxygen capture reactions have been reported for Ni thiolates.[31] It would appear that this is a reaction with unexplored potential.

The Cu:Mo ratio in the above product is very close to that in the discrete anion $[Cu_{12}Mo_8S_{32}]^{4-}$, formed from the reaction in the solid state between TTM and CuCN. Surprisingly, the CN^- ligand is not retained in this case.[31] This anion, one of the largest known of its type, contains slightly distorted $Mo^{VI}S_4$ units linking tetrahedral Cu^IS_4 centres. A fuller description is given in reference 32 and in the review by Dance and Fisher.[15]

Reaction with the oxythioanions $MoO_xS_{4-x}{}^{2-}$ (x = 1,2; M = Mo, W) with Cu^{II} has also been found to lead to mutual metal reduction to Cu^I and Mo^V from the EPR spectra of the products. However, the stoichiometry in these cases is close to 1:1 Cu:Mo rather than the 1.6:1 observed with TTM.[33] Preliminary analysis of the EXAFS Cu spectra of these compounds shows a consistent trigonal CuS_3 coordination in all samples (Cu−S 2.5−2.7 Å) and a Mo atom at 2.67−2.70 Å. The EXAFS Mo spectra are consistent with $MoOS_3$ and $MoOS_2$ environments, the latter suggesting, rather surprisingly, the cleavage of one O atom from the $MoO_2S_2{}^{2-}$ reactant; the presence of Mo−O bonds is also evident from the strong IR absorption in the 800−900 cm^{-1} region. As with the Cu K-edge spectra there is also one neighbouring Cu atom observed in the Mo spectra at 2.67−2.70 Å. Our preliminary studies also show an oxygenation reaction occurs without any change in either the EPR or the EXAFS spectra.

5. Biological Properties

The Copper−Molybdenum Antagonism

Both Cu and Mo are well-known essential elements occurring in a range of metalloenzymes. Although their enzymatic functions primarily involve redox processes there is no evidence of any direct biological interactions between them as there is, for example, between Cu and Zn and Cu and Fe; this would be as expected from their different coordination chemistry behaviour and from their very different naturally occurring forms. However, there is one exception to this, and that is the well documented Mo-induced Cu deficiency that can afflict ruminants; more correctly this should be expressed as a Mo−S−Cu interaction.

The first component of the complex digestive system of ruminants (e.g. cattle and sheep), the rumen, has a high microbial content and is anaerobic, under these conditions both inorganic and organic sulfur are reduced to sulfide. Rumen sulfide levels of up to 6.0 ppm have been observed. High dietary Mo levels have been found to inhibit sulfide production.[34] It was recognised over 50 years ago that ruminant animals grazing pastures of high Mo content (ca. ≥2 mg/kg) develop symptoms characteristic of copper deficiency, i.e. a decline in weight gain, diarrhoea, rough and discoloured coats, and skeletal abnormalities.[35] Much research on this widespread antagonism has subsequently shown that although the dietary Cu levels may be sufficient this was indeed an induced Cu deficiency. High Mo levels themselves do not necessarily induce Cu deficiency — the Mo-induced Cu deficiency also requires a high dietary S intake. Several reviews cover this earlier work.[36−38] Mills and his co-workers subsequently showed that TTM forms from molybdate ion in rumen cultures.[39] Laboratory simulation of rumen conditions also showed that the oxythiomolybdate ions and subsequently TTM can form.[40] However, because of the low natural concentrations of molybdate in the rumen it has not been possible to directly observe the presence of any thiomolybdate within a rumen.

Addition of Cu^{II} to a solution of TTM in strained rumen contents resulted in the loss of the TTM UV/Vis spectrum, with a complete loss of spectrum at an approximately 1:1 Cu:Mo ratio.[39] Our own studies[40,41] have confirmed that a rapid reaction occurs between Cu^{II} ions and its complexes with TTM and with the oxythiomolybdates: in fact, taking into account the rapidity of the reaction and the rumen concentrations it was concluded that the oxythiomolybdate ions $MoO_xS_{x-4}{}^{2-}$ (x = 1,2) were the more likely reactants.[41] Studies by Mason and co-workers show that the di-, tri-, and tetrathiomolybdates all have an effect on Cu metabolism when given intravenously to ruminants and have a reversible inhibitory effect on caeruloplasmin oxidase.[42]

Despite these latter observations the majority of studies on the biological effects of the thiomolybdate ions have concentrated on TTM because of its greater aqueous stability. The Cu depletion caused by TTM appears to result from a decreased absorption from the diet and the formation of a non-bioabsorbable form. The latter has been identified as a ternary Cu−Mo protein form in both blood plasma and in liver cells, the proteins involved being albumin and metallothionein, respectively. Molybdenum-95 NMR spectroscopy shows that TTM can bind to serum albumin protein.[43] Our own studies, using membrane filtration and UV/Vis spectroscopy, suggest this association to be a relatively weak, mainly ionic, binding between albumin and TTM, there was certainly no evidence of any S cross-linking. With Cu-albumin, however, there was rapid formation of a ternary TTM-Cu-Albumin complex with similar characteristics to the polymeric compound that we isolated in vitro, i.e. EPR evidence of Cu^I and Mo^V centres.[41] While we could find no evidence of any interaction between the Zn-thionein protein and TTM, with Cu^I-thionein TTM was strongly bound; the other thiomolybdates were found to behave in a similar manner.[41]

Administration of TTM to nonruminants such as rats causes dramatic changes to the Cu distribution within plasma and reduction in the catalytic activity of the Cu enzymes, caeruloplasmin, ascorbate oxidase, superoxide dismutase and tyrosinase. The oxythiomolybdates were found to have less marked effects. From these studies it is evident that TTM may have potential as an antidote in acute Cu intoxication, animal studies have confirmed this and showed that it could also act as an antidote against Zn and Ni toxicity but not against other metals.[44]

TTM in the Treatment of Wilson's Disease

Wilson's disease is a relatively rare human disease first described by Kinnear Wilson in 1912 as progressive lenticular degeneration, a familial disease occurring in young people. It is progressive and invariably fatal — unless treated early.[45] The cause of the disease is an accumulation of Cu resulting from a genetic defect which impairs the body′s normal excretion of dietary copper. As stated by Wilson, the disease is progressive, with severe neurological and liver deterioration. Unless treated early on, patients invariably die in their late teens or early twenties. The high Cu concentrations in the liver, low caeuloplasmin levels and Cu deposits in the cornea of the eyes (Kayser-Fleischer rings) are typical clinical symptoms used in the diagnosis of the disease. At the molecular level, free Cu ions are well-known enzyme poisons because of their potential to bind strongly to the many coordinating sites present in protein molecules. In fact, the body has well-established mechanisms for maintaining very low concentrations of free metal ions. This capacity is obviously exceeded in Wilson′s disease and the excess Cu ions are transported into the brain, the central nervous system and the liver, as well as other tissues.

Treatment of the disease is normally with chelating agents which can (a) rapidly excrete the excess Cu, and (b) over the rest of the patient′s life keep him/her in a low Cu balance. The two chelating agents of choice are D-penicillamine and triethylenetetraamine (trientine). The former is the more effective and is the usual first choice; however, penicillamine does have toxic side-effects and some patients become intolerant, in which case trientine is then used. Treatment with zinc salts has also been claimed to be beneficial, although not as effective as the above chelating agents. Another compound which is finding increasing use is TTM.

The usual criteria for successful chelation therapy is that the chelate must be nontoxic, be water soluble, resistant to metabolic degeneration, and have selective and adequate chelating ability at physiological pH. The agents and their metal chelates must be rapidly excreted by the kidneys. As shown above, TTM is very effective at removing Cu from animal tissues — even when the Cu is at normal levels — but it would not seem to fit many of the criteria for chelation therapy; it has nevertheless become another useful reagent for treating this disease. A useful summary of the prognosis of this disease and its therapy together with the related copper disorder, Menkes Disease, has recently been given by Sarkar.[46]

TTM was first used by Dr John Walshe, then at Addenbrookes Hospital, Cambridge, in 1982 on a patient who had become intolerant of all the other available treatments. She was initially treated with 50 mg twice a day, this was subsequently reduced to 30 mg twice a day and she was maintained on this regime until her death from other causes 16 years later; the longest recorded successful treatment to-date with TTM. She was initially treated with D-penicillamine but became intolerant of this, following this she responded well to trientine which reduced her liver Cu level to 90 units (ug/g wet tissue weight) but then became intolerant of this as well. She was then put on $ZnSO_4$ but after one year developed gastric problems, at this time her liver Cu level was 155 units. After a further 10 months without treatment she had deteriorated and her liver Cu level was up to 408 units. It was at this time that she was put on TTM, her health then improved and her liver Cu level decreased to 130 units. The initial follow up studies on this patient and others were reported in 1986 by Walshe.[47] TTM appears to act by blocking the intestinal absorption of Cu and by converting Cu into a metabolically inert form. The latter is most likely an S-linked Cu−Mo protein ternary complex as found in the earlier animal studies and our laboratory studies mentioned above and, more recently, in the TTM application to a rat strain that models Wilson′s disease.[48] The salt used then, and now, is the ammonium salt. Although there was some initial concern about the prolonged use of the ammonium ion there appears to have been no related adverse effect. It would have been preferable to use salts with cations such as Na^+, K^+ or Ca^{2+}, but, as noted above, these are difficult to prepare (most commercially available materials we have found to be impure, the major impurity being the highly insoluble MoS_3). The sodium salt has been found to be less toxic in rat studies than the ammonium form, LD_{50} 537 mg/kg and 176 mg/kg, respectively.[44] TTM has been successfully used by others:[44,50] in particular, a detailed study by Brewer et al. showed very promising results on using TTM as an initial treatment both to reduce Cu levels and improve neurological functions, followed by zinc administration for long term maintenance.[44] However, because of the lack of clinical data the use of TTM must still be treated as an experimental therapy. Additionally, there have been reports of it having toxic side effects,[48,49,51] although in two of these studies[48,49] the dosages used on a mg/kg body weight basis were considerably higher than those used successfully by Walshe on his patients. The applicability of some of the animal studies as models for the treatment of Wilson′s disease is also questionable. However, it is clear that continuous monitoring of a patient′s Cu and Mo tissue levels and other related clinical testing is needed during treatment with TTM.

6. Conclusions

We have shown that the unusual redox reaction between thiomolybdates and Cu^{II} occurs for a wide range of different forms of Cu^{II}. The question then arises as to how extensive this reaction is in terms of other thioanions, as listed in Table 1, and other reducible metal ions, and how common is the oxygenation reaction? I suspect that many similar reactions have previously gone undetected. Unpublished studies in our laboratory show that the thioanions of W, $WO_xS_{4-x}{}^{2-}$ ($x = 0{-}2$) undergo the same reactions with Cu^{II} as do the Mo analogues. A solid-state redox reaction between Cu^{II} and $VS_4{}^{3-}$ has also been observed. The combination of EPR and EXAFS measurements has proved particularly valuable in these studies. As regards other potentially reducible metal ions to-date we have only carried out some preliminary studies with Fe^{III}. In this latter case, redox reactions have been observed but no well-defined products have been obtained. A further area worthy of investigation is to carry out the reactions with Cu^{II} in the presence of Cu^{I} ligands so as to produce more tractable molecular species. There is also still much to be learnt about the metabolic properties of TTM and the nature of the ternary Cu-TTM-protein complex formed in the application of TTM in treating Wilson's disease.

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