



COPPER THIOMOLYBDATE – A FUTURE ANSWER TO INCREASING THE BIOAVAILABILITY OF MICRONUTRIENTS IN RUMINANTS AND MONGASTRICS.

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ABSTRACT

Introduction: Copper deficiency is a common problem for ruminants. This can result from insufficient Cu intake (primary deficiency) or the presence of an antagonist that renders Cu unavailable for absorption (secondary deficiency). When Mo intake is sufficient, thiomolybdates, TM_x , form in sufficient quantities in the rumen to significantly antagonize Cu.

Aims: To synthesize the heterometallic sulphur assemblies that may be water soluble, which are kinetically inert and show relevance towards biological activities as Cu-Mo antagonism.

Materials and methods: Various types of coinage metal heterometallic sulphur systems have been synthesized using water soluble tetra-thiometallate anions for molybdenum and tungsten system. Resonance Raman spectroscopy has been utilized to determine unambiguously the structure of the symmetrically coordinated trinuclear complexes for which the suitable single crystals for a crystal structure determination have been tried but got failed due to poor experimental environment. The genesis of the heteropolynuclear species have been correlated with the polynuclear $Cu(I)$ complexes of different geometry.

Results and discussion:

The synthesized complexes in our study contain the stoichiometry between tetrathiomolybdate and copper in the ratio, 1:1, 1:2, 1:3 and 1:4, respectively. The tendency of iron in these complexes to enhance its coordination number has been demonstrated. Two equivalents of $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ (2.8gm) and one equivalent of ammonium heptamolybdate (with respect to Mo) (1.8 gm) were dissolved in 40 ml aqueous NH_3 (d, 0.7) to get a clear blue solution. Into this H_2S gas was passed for an hour. Immediately, black precipitate of CuS appeared at the first Stage followed by the gradual red colouration of the solution. The formation of multinuclear species containing Cu and Mo through the dissolution of CuS with the concomitant reduction of Cu^{++} to Cu^+ under the experimental condition.

Conclusion:

From various experiments it was concluded that high molybdenum and Sulphate intake disturb the metabolic efficiency of copper utilization and induce copper deficiency. Thus, 'Cu-Mo antagonism' may be viewed as an interaction between Cu, Mo and S. Hence, the synthesis of Copper-Thiomolybdate-Protein Complex may shed some light on the chemical implication of this phenomenon and may contribute quantitatively towards rationalizing the difference in its modus operandi in ruminants and monogastrics.

Key words: Copper Thiomolybdate, Ruminates, Monogastrates, Bioavailability.

INTRODUCTION:

Copper deficiency is a common problem for ruminants. This can result from insufficient Cu intake (primary deficiency) or the presence of an antagonist that renders Cu unavailable for absorption (secondary deficiency). When Mo intake is sufficient, thiomolybdates, TM_x , form in sufficient quantities in the rumen to significantly antagonize Cu.¹ Fortunately, the effects of copper deficiency are largely reversible with proper treatment. Reliable, efficient treatment is therefore important to be able to maximize the health of the herd and to minimize the cost and labor associated with treatment. Much of the previous work in this area has involved in vivo studies. In these cases, Cu levels are monitored under various conditions using various bio-markers.² These studies are expensive and time consuming and the results are very animal specific. Also, very little knowledge is gained about the specific chemical interactions taking place. However, thiomolybdates are known

Cu antagonists and are not as yet included in this model.³ Thiomolybdates form in the rumen from molybdate (ingested in the feed) and sulfide (formed in the rumen by reduction of various forms of sulfur). Once formed, TMs form non-labile complexes with Cu that prevent Cu from being absorbed in the body. Thiomolybdate formation is a rather slow, kinetically controlled process. Therefore, before these species can be included into the model, an accurate kinetic analysis must be performed. The TMs are most commonly analyzed by UV-visible spectroscopy. Previous work involving reactions between Cu and the TMs has consisted primarily of structural analysis.⁴ Hence in the present study we try to analyse the synthetic aspects of heterometallic-sulphur systems derived from coinage metal (i)-ions and tetrathiometalate anions and their possible biological relevance.

Thiometalates of molybdenum and tungsten are known since 1826 when Berzellius synthesized the ions MoS_4^{2-} and WS_4^{2-} . The reactivity of these thiometalates and their application in complex chemistry have been explored systematically very recently. These thiometalates reacts with other transition metal salts like CoCl_2 , FeCl_2 , NiCl_2 and also with non-transition metal salts like SnCl_2 , PdCl_2 , ZnCl_2 to form series of heterometallic-metal sulphur assemblies.⁵ The feature of iron complex is interesting the sense that essentially it contains the hetero atoms which are present in as structural component of nitrogenase active site is shown by chromatographic separation of Mo from acid treated reneutralised solution of Fe-Mo protein from *Clostridium pasteurianum* which develops as new thrust area on the investigation of $\text{Fe}_2^+/\text{MoS}_4^{2-}$ system. 'The ligation behavior of thiometalates with coinage metal Systems has not been studied in great detail until recently. This was partly due to the polymeric nature of the species formed where Structural characterization has been difficult in view of their insoluble nature.⁶

AIMS:

Hence in the present study we checked the reactivities of prepared water soluble heterometallic sulphur systems for possible biological relevance to copper-molybdenum antagonism. Since, the effect of excess molybdenum results in the depletion of copper for metabolic purpose the interaction between Copper and molybdenum is referred to as Cu-Mo antagonism.

MATERIALS AND METHOD:

Various types of coinage metal heterometallic sulphur systems have been synthesized using water soluble tetrathiomolybdate anions for molybdenum and tungsten system. The structure of synthesized $[M^1(MS_4)_n]X$ complexes when $M^1 = Cu(I), Ag(I), Au(I)$, $M=Mo, W$; $n= 2,4$ and $X = 2,3$ have been established using various types of physico-chemical spectroscopic techniques like, IR, UV-Vis., spectroscopy studies. The kinetics and thermodynamic stability of these complexes have also been studied in aqueous buffered media and their inactness *in vivo* have also get measured. Emphasis have been made to understand the perturbation caused by the complexation of closed shell $Cu(I)$ on the ligand internal transitions of the MS_4^{2-} chromophore. Resonance Raman spectroscopy has been utilized to determine unambiguously the structure of the symmetrically coordinated trinuclear complexes for which the suitable single crystals for a crystal structure determination have been tried but got failed due to poor experimental environment. The genesis of the heteropolynuclear species have been correlated with the polynuclear $Cu(I)$ complexes of different geometry.¹

RESULTS AND DISCUSSION:

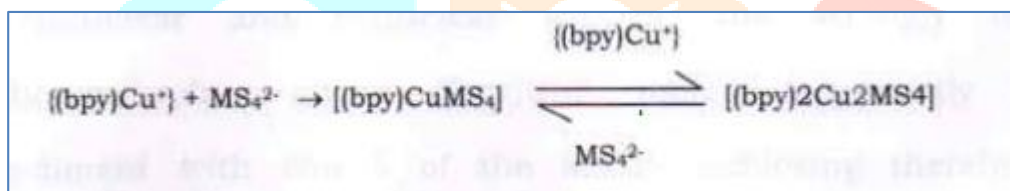
General Properties of the Complexes

The synthesized complexes in our study contain the stoichiometry between tetrathiomolybdate and copper in the ratio, 1:1, 1:2, 1:3 and 1:4, respectively. Among these only the complexes having 1:1 stoichiometry, are anionic and the rest are neutral in nature. The involvement of coligands invariably rests with copper-ligand attachment keeping the tetrathiomolybdate moiety intact which coordinates through sulphur to copper. Essentially all these complexes are red in colour; however, there is a trend of the darkening of colour when the ratio of copper is increased.⁷ All these complexes contain cuprous ion and thus have close shell $3d^{10}$ configuration and the colour is due to the internal transition of tetrathiomolybdate anion. The effect of the coligand attached to Cu^+ has little influence on the low energy band responsible for the colour. Other complexes synthesized with oxothiomolybdate are generally orange red to red in colour. The tungsten analogues of these derivatives visually show a deepening in colour on complexation with respect to the free tetrathiotungstate /oxothiotungstate anion.

The anionic complexes in this series in polar solvents like DMF and DMSO. $(NEt_4)_2[NCSCuMoS_4]$ is also soluble in acetonitrile. The neutral complexes are exceptionally stable in the solid state and they are slightly soluble in

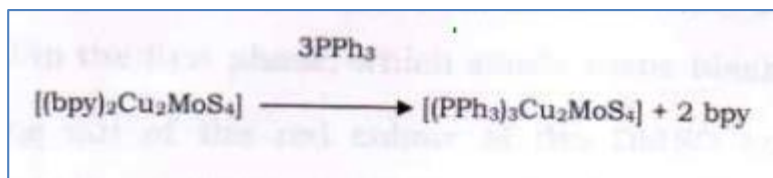
DMF and DMSO. In presence of moisture or by washing repeatedly with methanol or ethanol; apparently, hydrolysis takes place which can be seen in their infrared spectra with the appearance of Mo-O vibrational band. However, in the H₂S atmosphere this hydrolysis is sluggish. In the aromatic dimine derivative the attachment of the chelated ligand bound to copper is so strong that it takes several hours to impart the characteristic ferroin colour when, for example, [(o-phen)₂Cu₂WS₄] is treated with FeCl in DMF or DMSO. Interestingly, a slurry of [(bpy)₂Cu₂MS₄] (M= Mo or W) in little DMF immediately reacts with an equivalent amount of the respective (NH₄)₂MS₄ (M= Mo or W) to give a clear solution which gives, using appropriate cation, the 1:1 complex [(bpy)CuMS₄] (M or Mo or W).

This anionic complex variety can be directly obtained by using Cu : MS₄²⁻ in 1:1 ratio (vide supra). The interconversion of these 1:1 and 1:2 complexes is schematically summarized below:

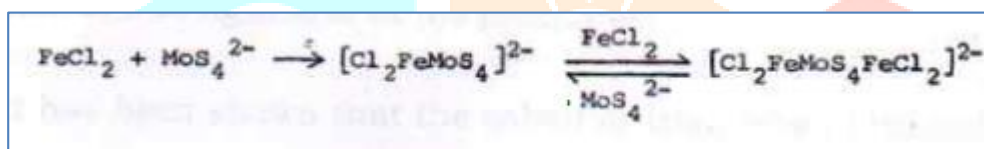


The other species, (NEt₄)₂[NCSCuMoS₄] does not give any 1:2 (MoS₄²⁻;Cu⁺) complex. Several interesting results are recently obtained on the reaction of MoS₄²⁻ with CuX (X = Cl⁻, CN⁻). Thus, when CuCN is used, MoS₄²⁻ as tetraethylammonium salt produces the simple dinuclear species, (NEt₄)₂[NCCuMoS₄], whereas the use of smaller cation like tetramethylammonium ion leads to the isolation of the polymeric species, {(NMe₄)₂NCCu(MoS₄)}.CuCN. Thus, the size of the cation plays a specific role to trap different species present in the reaction mixture. Interestingly, (NEt₄)₂MoS₄ reacts smoothly with three equivalents of CuCl to give (NEt₄)₂[MoS₄(CuCl)₃]. This monomeric tetranuclear species contains two, four coordinated Cu and one, three coordinated copper using all the four S attached to Mo. In the present case, for the interconversion of dinuclear and trinuclear species, the strongly bonded o-phenanthroline giving {(bpy)Cu}⁺ moiety apparently forces attachment with two S of the MoS₄²⁻ achieving thereby four coordination of Cu. The entire process thus can use either 1:1 or 1:2 stoichiometry. A very similar reaction of the above type with biorelevance to the nitrogenase problem has already been observed where the strong Fe-Cl bonds in FeCl do not cleave in non-

aqueous solvent and when allowed to react with MoS_4^{2-} species schematically represented below are obtained:



The symmetrical attachment of two $\{(\text{bpy})\text{Cu}\}^+$ moiety 'with one tetrathiometalate leads to the formation of the trinuclear species which contains tetracoordinate copper. However, using monodentate phosphine group as ligand the unsymmetrical complex is readily formed. Addition of triphenylphosphine into a solution of $[(\text{bpy})_2\text{Cu}_2\text{MoS}_4]$ in DMSO leads to the conversion of the symmetrical structure into an unsymmetrical one with the exchange of a α - α' bipyridyle with bulk triphenylphosphine as schematically shown below:



However, the reverse reaction of the above scheme does not take place showing the high tendency of formation of the unsymmetrical species.

Thermally the synthesized complexes are stable upto 250°C ; however, the neutral complexes slowly start decomposing with the expulsion of the organic ligand. In moist air, on heating, hydrolysis take place which is evident by the expulsion of H_2S .

$[\text{Cu}, (\text{py})_4\text{Cl}_2\text{MoS}_4]$ in DMSO reacts with AgNO_3 to give a precipitate of AgCl in the first phase, which slowly turns black in colour with the fading out of the red colour of the DMSO solution. Qualitative analysis of the black precipitate shows the presence of Cu besides Ag and No. Thus, it may be presumed that the chloride attached to copper in the complex can be exchanged with NO_3^- of AgNO_3 which may be unstable and results in the detachment of the Cu-X moiety ($\text{X} = \text{Cl}^-$, NO_3^-) followed by the attachment of the generated AgCl in the place of CuX portion. However, the black residue is not a pure compound as leaching of this with $\text{Na}_2\text{S}_2\text{O}_3$ solution shows the presence of only Ag in the leached solution without any chloride suggesting the formation of free Ag_2S also in the precipitate.

It has been shown that the cobalt or iron, when tetrahedrally complexed with the thiometallate groups can enhance their coordination number and facile nitrosylation is possible on these systems to isolate species of the type $[M'(NO)(WS_4)_2]^{2-(11)}$. Interestingly, the starting iron complex, $(PPh_4)_2[Fe(WS_4)_2]$ when tried to recrystallise in DMF, changes its colour from green to red-brown leading thereby to the isolation of $(PPh_4)_2[Fe(DMF)_2(WS_4)_2]$.

Thus, the tendency of iron in these complexes to enhance its coordination number has been demonstrated. These features in iron complex are interesting in the sense that essentially it contains the heteroatoms which are present in nitrogenase. The evidence for the possible involvement of MoS_4^{2-} anion as structural component of nitrogenase active site was shown by Zumft by chromatographic separation of MoS_4^{2-} from acid treated reneutralized solution of Fe-Mo protein from *Clostridium pasteurianum* which resulted in a new thrust on the investigation of Fe^{2+}/MoS_4^{2-} system. The synthetic methodology since then changed from aqueous to non-aqueous medium with the direct involvement of tetraalkyl ammonium tetrathiomolybdate and iron complexes for solubility reasons. Thus when iron xanthate or iron dithiocarbamate complexes are used, complex of the type $[Fe(MoS_4)_2]^{3-}$ could be isolated. In both these reactions, the formal reduction of the central iron, which was erroneously thought as the reduction of molybdenum, has occurred with the proposition that the thioligands serve as reducing agents. The previous attempt to isolate $[Fe(MoS_4)_2]^{2-}$ by analogy to corresponding tungsten analogue leads to the isolation of a polymeric amorphous compound of approximate composition $(PPh_4)_2[Fe(MoS_4)_2]$.

However, the Mossbauer Spectrum of the frozen solution containing $Fe^{2+}/MoS_4^{2-}/H_2O$ shows the presence of $[Fe(MoS_4)_2]^{3-}$ anion. The electronic spectrum also suggests the existence of this species containing MoS_4^{2-} in equilibrium. These findings are interesting which demonstrate that sulphur containing ligands are not necessary for the reduction and MoS_4^{2-} itself can serve the same purpose. As stated earlier, the reaction between MoS_4^{2-} and other metal ions in aqueous medium always leads to some polymerisation which could be avoided by appropriate choice of the solvent. 1:1 acetonitrile : water has been found to be the most effective to prevent this polymerisation step. Another point in isolating these anionic species is the proper choice of the bulky cationic group. Thus, it is possible to isolate the $[Fe(MoS_4)_2]^{5-}$ ion as tetraalkyl ammonium salt from a solution of $(NH_4)_2MoO_4$ and $FeSO_4 \cdot 7H_2O$ in $CH_3CN/H_2O(1:1)$. The mechanism for the reduction of the central

metal has not been clarified. The reduction can be facilitated by taking another iron salt. Thus a Suspension of $[\text{Fe}(\text{C}_2\text{O}_4)]$ in DMF reacts slowly but smoothly with MoS. to generate the reduced species.

So far, the ligational behaviour of thiometallate ions rests mainly on their ability to function as bidentate ligand. The only exception to this behaviour has been noticed for the tin complex where it can function as a tridentate ligand. In the containing the novel S_5^{2-} ligand is formed. From the nitrogenase point of view, Shah and Brill isolated an Fe-Mo cofactor from the Fe-Mo component protein of nitrogenase. The analytical ratio between Fe:Mo:acid labile sulphide has been reported to be 8:1:4 to 6 respectively. Molybdenum K-edge X-ray absorption fine structure (EXAFS) analyses of the Mo-Fe protein and MoFe-CO reveal that in all samples the short range order around the molybdenum should be very similar. Coucouvanis and coworkers using a complicated reaction between $[\text{((PhS)}_2\text{FeMoS}_4)]^{2-}$ and FeCl; synthesised the anionic species $[\text{(Cl}_2\text{Fe)}_2\text{MoS}_4]^{2-}$, In this trinuclear complex, MoS₂ acts as a doubly bridging ligand. By a simplified reaction produce using FeCl₂ and MoS₄²⁻, the same complex could be isolated in quantitative yield (25),

This compound may be thought to be the closest approach to the trinuclear model. The enhancement of the coordination number of central molybdenum from four to five would have polymeric $\text{NH}_4\text{CuMoS}_4$ the coordination ability is increased demonstrating its nature as a four-fold coordinating ligand. For the synthetic chemist, thus, the following facts become interesting:

- (i) To understand the ligational behavior of MS_4^{2-} ion.
- (ii) Variation of the iron compounds to know the metathetical dependence of the reaction.
- (iii) The possible involvement of any redox reaction.
- (iv) The choice of appropriate cation to stabilize the species formed.

When ferrous chloride has been used as iron source in pure anhydrous solvent, the 1:1 complex anion $[\text{Cl}_2\text{FeMoS}_4]^{2-}$ is formed which could be isolated by the use of tetraalkylammonium. Mixed tetraalkylammonium tetraphenylphosphonium and tetraphenylphosphonium cations. In this complex anion the Fe-Cl bond is fairly covalent in nature. However, with thiophenolate anion the following metathetical reaction takes place.



The influence of elemental sulphur or polysulphide ion on MoS, alone or MoS,²⁻ and iron resulted in some interesting reactive chemistry which is quite relevant to understand the role of molybdenum in the nitrogenase and in other biosystems properties are important in relevance to their application in bioinorganic field.

Possible Relevance of Cu-Mo-S Interaction to Cu-Mo Antagonism

The recent investigations on the interaction of Cu-Mo-S systems reveal that the interaction, in principle, is between copper and tetrathiomolybdate), In vitro generation of thiomolybdate by rumen contents when combined with molybdate and sulphur Sources under anaerobic conditions further supports this thiomolybdate hypothesis, Thus, it may be assumed at this stage that copper interacts with tetrathiomolybdate to form stable "Cu- Mo-S complex" which seems to be stable enough to prevent copper to be available for physiological activity. From chemical point of view it would be of prime importance to know about the exactness of the species. Chemically, the interaction between copper and tetrathiomolybdate is known even in aqueous medium where a soluble cupric salt is easily reduced by tetrathiomolybdate to cuprous which gives a polymeric highly insoluble species of the composition $\text{NH}_4\text{Cu MoS}_8$. However, there are reports that tetrathiomolybdate is rapidly bound to albumin and various other plasma proteins. These thiomolybdate protein complexes show an increased reactivity toward copper ions. When copper is present in this type of complexes it can not be liberated by TCA precipitation of the proteins.

Thus, the following points are of special interest to such interactions:

- (i) Interaction between free Cu^{n-} and MoS_4^{2-}
- (ii) Interaction between plasma proteins and MoS_4^{2-}
- (iii) Interaction between plasma apo-proteins, MoS_4^{2-} and Cu^{n-}

The situation may still be aggravated if one follows then following chemical implications:

- (a) The S^{2-} formed in the rumen reacts with MoO_4^{2-} to produce ultimately MoS_4^{2-}
- (b) A competitive reaction between Cu ion/Cu proteins with S^{2-} .

The reaction possibilities in (i) to (iii) is fully dependent on the rate of formation of MoS_4^{2-} whereas the formation of MoS_4^{2-} as in (a) is going to face the highly competitive reactive between copper and sulphide ion (b).

From the simple solubility product criterion it is evident, at least, chemically, that the S^{2-} produced in the rumen is going to interact with copper prior to MoO_4^{2-} . Thus, CuS once formed may lead Cu^{n+} out of metabolic circulation. However, if that be the only situation happening in the rumen, the antagonistic property of molybdenum remains unresolved. Several experiments on the influence of S^{2-} concentration alone on the fate of circulated copper do suggest the presence of copper for metabolic activity regardless of the plausible depletion of copper sulphide. This fact prompted thinking that if copper is precipitated as CuS Yet, by some interaction this can go into the system. Arguing on this line, one is tempted to think that possibly, MoS_4^{2-} prevents the resorption of CuS by some chemical interaction. This may be one of the possibilities emerging from simplest possible chemical rationalization. To check this possibility the following experiments were undertaken.

Reaction between cupric chloride and ammonium heptamolybdate with H_2S

Two equivalents of $CuCl_2 \cdot H_2O$ (2.8gm) and one equivalent of ammonium heptamolybdate (with respect to Mo) (1.8 gm) were dissolved in 40 ml aqueous NH_3 (d, 0.7) to get a clear blue solution. Into this H_2S gas was passed for an hour. Immediately, black precipitate of CuS appeared at the first Stage followed by the gradual red colouration of the solution. At this Stage all the molybdate had been converted into tetrathiomolybdate (monitored by electronic spectrum of a portion of the filtered solution). The mixture was kept in a glass stoppered flask with stirring overnight whereby most of the black precipitate went into the solution. The solution was quickly filtered under suction. The filtered solution was then poured into a solution of two equivalents of a-a' bipyridyl (2.0gm) dissolved in 10 ml DMSO whereby immediately a red precipitate appeared which was filtered under suction, washed

twice with ammoniacal H_2S solution followed by acetone and CS, and finally with diethylether. On analysis and spectral characterization (vide infra) this was found to be identical with $[(bpy)_2Cu_2MoS_4]$ (vide supra). It is interesting to mention here that the clear solution obtained by overnight standing, on keeping longer, precipitated the well known polymeric compound NH_4CuMoS_3 .

By following similar procedure to obtain a red solution and instead of adding a-a' bipyridyl, addition of two equivalents of $CuSCN$ in 2 ml bipyridyl and 40 ml DMSO resulted an almost clear solution. Traces of insoluble $CuSCN$ went into the solution by magnetically stirring it for about three hours. On long standing (4-5 days) a

dark red microcrystalline compound of the composition $[(bpy)_s + Cu_s(SCN)_2MoS_s]$ separated out. It is interesting to note that the above mentioned complexes can be directly synthesised using $CuSCN$, MoS_4^{2-} and appropriate ligand (vide supra). The above stated experiments do suggest the formation of multinuclear species containing Cu and Mo through the dissolution of CuS with the concomitant reduction of Cu^{++} to Cu^+ under the experimental condition.

An analogy of this type of reaction can be drawn from the reaction of Fe' with thiolate ligand. Here too, the stoichiometric dependent polymeric ferric thiolate complex can be solubilised by the use of extra thiolate ligand to give multi-nuclear cubane type $\{Fe_8S_4\}$ moiety in which partial reduction of Fe^{3+} to Fe^{2+} state takes place. In the present case the situation is not so simple as in the case of polymeric ferric thiolate complex which though insoluble, is very much reactive whereas for CuS the low solubility product and its apparent stability renders it difficult to be incorporated into a reaction so easily. However, the role of MoS_4^{2-} is interesting and though we do not have any comparison of this type of bioimportant reaction, at least, *in vivo* yet it may be reasonable to assume a similar situation whereby the precipitated CuS may be solubilized by MoS_4^{2-} to form a multinuclear species which may finally react with protein rendering copper out of circulation. Interestingly, the reaction between cupric chloride tungstate/ NH_4OH and H_2S under identical reaction condition as described above does not show any reactivity of WS_4^{2-} thus formed with the *in situ* precipitated CuS . The corresponding tungstate analogue can be directly synthesised as described earlier (vide supra). The difference in chemical reactivity of these two systems is suggestive enough to say that the involvement of such reaction with MoS_4^{2-} is of complex type wherein the possibility of the reduction of molybdenum present as MoS_4^{2-} with S^{2-} cannot be ruled out. Recently MoS_4^{2-} and S^{2-} and/or S^0 interaction do suggest this type of reduction of molybdenum to formally +5 and +4 oxidation states whereas the thiotungstate System is a sluggish one. This difference between the reactivity of MoS_4^{2-} and WS_4^{2-} reflects the natural selection of Mo in the biosystem.

CONCLUSION:

Nutritional significance of trace elements in biological systems is gaining momentum exponentially. Since the effect of excess molybdenum results in the depletion of copper for metabolic purposes, the interaction between copper and molybdenum is referred to as 'Cu-Mo Antagonism'.⁸ From various experiments it was concluded that high molybdenum and Sulphate intake disturb the metabolic efficiency of copper utilization and induce copper deficiency. Thus, 'Cu-Mo antagonism' may be viewed as an interaction between Cu, Mo and S. Hence, the synthesis of Copper-Thiomolybdate-Protein Complex may shed some light on the chemical implication of this phenomenon and may contribute quantitatively towards rationalizing the difference in its modus operandi in ruminants and monogastrics. Hence, the complexes described in the study may be considered to be the closest models of Cu-Mo interaction.¹ The resorption of CuS and MoS₄²⁻ together, and the subsequent isolation (vide supra) of α - α' bipyridyl and bipyridyl complexes from the aqueous solution (containing CuS and MoS₄²⁻), is suggestive enough to hypothesize that copper thiomolybdate N-donor complexes can be formed by direct resorption process if N-donors can be taken as representative of the protein unit. Very interesting observation that such type of reaction, namely resorption of CuS, and hence, the isolation of Multimetal complexes does not take place with WS₄²⁻), in aqueous solution, reflects the nature's choice for molybdenum over tungsten for biological incorporation (vide supra).⁹ Where the protein-Cu- MoS₄²⁻ complex have been synthesized incorporating Imidazole, Histidine, Cysteine and other N, S, O donor amino acids and one can envisage that the model would have been more realistic and comprehensive. Attempts to synthesize complexes using these ligands resulted in species varied stoichiometry. However, tailor made metal clusters using desirable units are difficult to synthesize. The difficulty is augmented by the presence of different heterometal species in the solution and hence a proper choice of counterions, solvent systems and an inherent methodology is necessary.⁶⁻⁸

References:

1. Clark RJ. Kinetics of thiomolybdate and copper-thiomolybdate interconversion processes. PhD Thesis Univ Saskatchewan. 2008;(September).
2. J.R. De Laeter, J.K. Bohlke, P. De Bièvre, H. Hidaka, H.S. Peiser KJR, Rosman, P.D.P. Taylor, Pure Appl. Chem. 75 (2003) 683. No Title.
3. J. Chandrasekaran, M.A. Ansari, S. Sarkar, Inorg. Chem. 27 (1988) 3663. No Title.
4. B.E. Erickson, The Speciation of Molybdenum in Sulfidic Natural Waters, Dept. of Chemistry and Biochemistry, University of Maryland, 1998 p. 259. No Title.
5. R.F. Jameson, in: H. Sigel (Ed.), Metal Ions in Biological Systems M, Dekker, Inc., New York, 1981 p. 1. No Title.
6. Spears JW. Comparative Trace Element Nutrition Trace Mineral Bioavailability in Ruminants. J Nutr [Internet]. 2003;133(11):1506–1509.
7. Sadr MH, Jalili AR, Razmi H, Ng SW. A new family of pyrazolyl-based anionic bidentate ligands and crystal structure of bis(N-phenyl-2-pyrazolyl-1-carboximidothioato)copper(II). J Organomet Chem. 2005;690(8 SPEC. ISS.):2128–32.
8. Langlois DK, Querubin JR, Schall WD, Nelson NC, Smedley RC. Ammonium tetrathiomolybdate treatment of copper-associated hepatopathy in dogs. J Vet Intern Med. 2019;33(3):1336–43.
9. Kegley EB, Spears JW. Bioavailability of feed-grade copper sources (oxide, sulfate, or lysine) in growing cattle. J Anim Sci. 1994;72(10):2728–34.