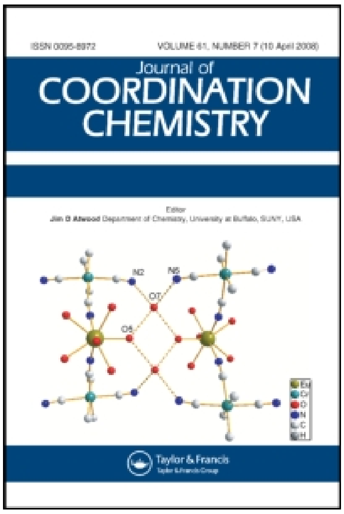

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Chromium, manganese, and zinc complexes of deoxyalliin and their bioactivity

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Chromium, manganese, and zinc complexes of deoxyalliin and their bioactivity

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Chromium, manganese, and zinc complexes of deoxyalliin were prepared and characterized by elemental analysis, spectral studies, electrospray ionization–mass spectrometry, thermogravimetric analysis, conductivity, and magnetic moment measurements. The complexes are proposed to have octahedral geometry, are water soluble, and exhibit antifungal activity against *Collectotrichum falcatum*, a fungus which causes red rot disease in sugarcane.

Keywords: Chromium, manganese, and zinc complexes; Deoxyalliin; Antifungal activity

1. Introduction

Metal amino acid complexes play a vital role in understanding the interactions between various enzymes, drugs, and metals present in living organisms. These interactions are vital for survival of the organisms because a huge number of biological functions within the living bodies depend on these interactions [1–4]. These interactions also generally produce synergistic biological effects. The amino acid interacts with metals through carboxylic and amino groups and sulfaryl group (in case of sulfur containing amino acids). Metal amino acid complexes not only elaborate the mechanism of metal amino acid interactions in living bodies but can also be a source of new therapeutic agents.

Deoxyalliin (figure 1) is a naturally occurring non-protein amino acid found in garlic and possesses many physiological properties, including antioxidant, antidiabetic, anticancer, antitumor, and antibiotic properties [5–10]. It has been shown to have reno-protective and antihypertensive effects [11]. Antihepatopathic and neurotropic activities of deoxyallin have also been reported [12–15]. Chromium(III), manganese(II), and zinc(II) have shown promising curative effects against many diseases. Deficiency of these metal ions leads to health effects.

The use of chromium supplements alleviates severe diabetic symptoms and reduces exogenous insulin requirements [16, 17]. Chromium(III) supplementation has improved glucose and/or lipid concentration level in children with protein-calorie malnutrition [18],

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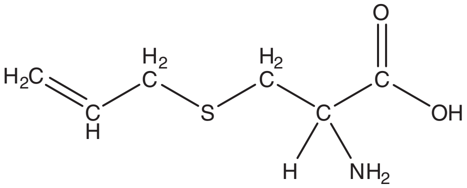

Figure 1. Structure of deoxyalliin.

elderly people [19], type 2 diabetic patients [20], and patients with impaired glucose tolerance [21, 22].

Manganese is an essential nutrient required for the formation of bones and amino acid/protein, cholesterol, and carbohydrate metabolisms [23]. Manganese is vital as it is the co-factor for manganese superoxide dismutase (SOD), arginase, glutamine synthetase, and phosphoenolpyruvate decarboxylase. It is also a regulator for many enzymes [4].

Zinc is the most abundant intracellular trace element with biochemical functions broadly classified into catalytic, structural, and regulatory functions. More than 300 specific enzymes require it for activity, e.g., alcohol dehydrogenases and alkaline phosphatase. Its structural role is demonstrated by the stabilization of tertiary structure of zinc metalloenzymes and other critical proteins, e.g., zinc fingers. It is also known to play a direct role in the regulation of gene expression. Therapeutic effects of zinc include treatment of Wilson disease, age-related macular degradation, *Human immunodeficiency virus* (HIV) infection, type 1 and 2 diabetes, wound healing, common cold, etc. [4, 23].

Physiological properties of metals can be coupled with those of biologically active ligands. The goal of the present study is to prepare chromium, manganese, and zinc complexes with deoxyalliin and to explore their synergistic effects in biological behavior.

2. Experimental

2.1. *Material and methods*

Deoxyalliin was prepared by the method of Stoll and Seebeck [24]. Chromium(III) chloride hexahydrate, manganese(II) chloride monohydrate, and zinc(II) chloride were purchased from Riedel.

Elemental analyses were performed using a CHNS-932 LECO analyzer. Fourier transform infrared (FT-IR) spectra were recorded using a Nicolet FT-IR 6700 of Thermo Scientific Company by direct probe method. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker XWIN-NMR 300 MHz. ESI–mass (ESI, electrospray ionization) spectra were recorded on a Jeol MS Route and Waters micromass triple quadrupole quarto II ESI mass spectrometer. Cone voltages ranging from 5 to 15 V were used for best results. Electrical conductivities were determined using a TPS Model 2100 conductivity meter at 20°C. Thermogravimetric analysis

Table 1. Elemental analysis of chromium, manganese, and zinc complexes.

S. No	Formula	Carbon (%)	Hydrogen (%)	Nitrogen (%)	Sulfur (%)
1.	$Zn(D.A.)_2Cl_2(H_2O)_2$	29.27 (29.13)	4.69 (4.45)	5.79 (5.66)	12.82 (12.94)
2.	$[Mn(D.A.)_2(H_2O)_4]Cl_2$	27.81 (27.69)	5.88 (5.76)	5.50 (5.38)	12.44 (12.30)
3.	$[Cr(D.A.)_2(H_2O)_3Cl]Cl_2$	27.11 (26.94)	5.35 (5.23)	5.37 (5.23)	12.08 (11.97)

D.A., deoxyalliin ($C_6H_{10}O_2NS$). Calculated percentage is given in parentheses.

(TGA), differential thermal analysis (DTA), and differential scanning calorimetry (DSC) were taken simultaneously using a Universal V4.2E TA Instruments – SDT Q600 V8.2 Build 100. Analyses were made in nitrogen with a heating rate of $10^\circ C\,min^{-1}$ from 25°C to 800°C.

2.2. *Synthesis of deoxyalliin*

Deoxyalliin was prepared by the method of Stoll and Seebeck [24] and characterized as follows: m.p. = 212–215°C (decomposition). FT–IR: $\nu = 3151$, 2909, and $2625\,cm^{-1}$ (NH_3^+), $1585\,cm^{-1}$ (COO^-), 993 and $919\,cm^{-1}$ (allyl double bond) ^1H-NMR (D_2O): $\delta = 2.77$–2.96 (2H, dd, $J = 4.5$ and 7.5 Hz, SCH_2 at β-carbon), $\delta = 3.06$–3.08 (2H, d, $J = 7.5$ Hz, SCH_2 on allyl side), $\delta = 3.75$–3.79 (1H, dd, $J = 4.2$ and 4.3 Hz, CH at α-carbon), $\delta = 5.03$–5.10 (2H, dd, $J = 10.4$ and 17.0 Hz, vinylic CH_2), and $\delta = 5.62$–5.76 (m, 1H, vinylic CH). MS; EI: $m/z = 161$ (M^+, 13.9%), 73.9 (100%), and 87 (94.51%). Anal. Calcd for ($C_6H_{11}O_2NS$)(%): C, 44.71; H, 6.88; N, 8.69; and S, 19.87. Found (%): C, 44.33; H, 6.42; N, 8.41; and S, 19.69.

2.3. *Synthesis of complexes*

Chromium, manganese, and zinc complexes were prepared by dissolving 0.01 mol of the respective metal chloride and 0.02 mol of the ligand (M : L, 1 : 2) separately in 10 mL of distilled water and then adding the ligand solution dropwise to the salt solution with constant stirring at room temperature. After the addition of the ligand solution to the salt solution, the solutions were stirred for 3 h and concentrated to a semisolid state; pH of the final solutions for manganese, chromium, and zinc complexes were 5.9, 2.2, and 6.1, respectively. The semisolid complexes were kept in an oven at 50°C for 48 h. The dried complexes were kept in a vacuum desiccator over calcium chloride until constant weight is reached.

2.4. *Elemental analysis*

The carbon, hydrogen, nitrogen, and sulfur analyses (calculated chemical analysis is given within parentheses) and proposed formulas of the complexes are summarized in table 1.

3. Results and discussion

3.1. *Thermal analysis*

3.1.1. Manganese complex. In manganese complex (figure S1), the hydration water is eliminated between 50°C and 100°C and coordinated water is lost at 180°C. The next mass loss step starts around 215°C. In the thermogram of the ligand, the mass loss starts around 200°C in a single step up to 250°C, while in that of the dehydrated complex, decomposition occurs in two steps. Derivative thermogravimetry (DTG) peak for the first step is at 235°C, while for the second step it is at 270°C. The first percentage mass loss in the dehydrated complex corresponds to loss of allyl sulfide ($CH_2=CH–CH_2–S–$) from the complex, while the second mass loss corresponds to loss of the rest of the ligand from the complex. This second mass loss step is at a higher temperature than the mass loss step of the pure ligand. The residue after the TGA was MnO, as determined by powder X-ray diffraction.

3.1.2. Zinc complex. For the zinc complex (figure S2), hydration water is lost between 50°C and 110°C and coordinated water between 170°C and 195°C. The ligand loss starts around 210°C. Unlike the manganese complex, the next two mass loss steps are not visible as two steps. DTG shows a peak for the first decomposition step up to 250°C which, while coming down, extends from its middle to 320°C as a shoulder. This broadening and mixing of peaks is due to melting of $ZnCl_2$ (m.p. = 275°C). The residue after the TGA was ZnO, as determined by powder X-ray diffraction.

3.1.3. Chromium complex. For chromium complex (figure S3), the hydration water is lost between 50°C and 100°C. Loss of some coordination water is at 170°C while loss of the rest of the coordinated water is shown around 210°C. The next two steps have the same pattern as that of dehydrated manganese complex, i.e. the first step is around 250°C and the second is at 410°C. The residue after the TGA was Cr_2O_3, as determined by powder X-ray diffraction.

The different decomposition temperatures between the complexes of the three metals for the last step are as follows: for manganese complex at 270°C, zinc complex around 280°C, while chromium complex at 410°C. This temperature difference is due to metal–oxygen (M–O) bond strength which is stronger for Cr^{+3} due to its oxidation state as compared to Mn^{+2} and Zn^{+2}.

3.2. FT-IR spectroscopy. Coordination of carboxylate (COO^-) and amino (NH_2) of amino acids in their complexes is indicated by a shift in the vibrational frequencies of these groups as compared to free amino acids. In the FT-IR spectrum of deoxyalliin, the asymmetrical (ν_{as}) and symmetrical (ν_s) vibrational frequencies of carboxylate (COO^-) are at 1585 and 1396 cm^{-1}, respectively, while for amino group, two bands are at 3150 and 2906 cm^{-1}, respectively. $\nu_s(COO^-)$ and $\nu_{as}(COO^-)$ for potassium salt of deoxyalliin are at 1571 and 1399 cm^{-1}, respectively, and a broad band from 3340 to 2590 cm^{-1} represent the frequencies for NH_2 group.

The coordination of amino group shows two well-resolved bands at about 3450 and 3280 cm^{-1} in the reported complexes of deoxyalliin [25, 26]. In all the complexes

Table 2. IR frequencies for the COO^- vibration in all the complexes.

Frequency type (cm^{-1})	Manganese complex	Zinc complex	Chromium complex
ν_{as}	1614	1632	1609
ν_s	1404	1396	1402
$\Delta\nu = (\nu_{as} - \nu_s)$	210	236	207

described in this article, no such peaks are observed. Here, the two peaks of amine present in the free ligand spectrum merge, giving a broad band from 3200 to 2875 cm^{-1}. This band rules out the coordination of amine. The broadening of amine band is due to the bonding of hydrogen with neighboring carboxylic group. Carboxylate group vibrational frequencies of all the complexes are given in table 2.

According to Nakamoto [27], $\Delta\nu$ [$\Delta\nu = (\nu_{as}(COO^-) - \nu_s(COO^-))$] is a measure of strength of M–O bond and mode of coordination of carboxylate. As the value of $\Delta\upsilon$ increases, the strength of the coordinate bond increases; $\Delta\nu$ also indicates monodentate and bidentate coordinations. Monodentate coordination gives $\Delta\nu$ values higher than $\Delta\upsilon$ value for ionic carboxylate, i.e. in amino acid salts. Bidentate coordination gives $\Delta\nu$ values closer to $\Delta\nu$ value of ionic carboxylate group. Table 2 indicates that first, for manganese and zinc complexes, the pattern of $\Delta\nu$ shows stronger M–O for zinc because zinc complexes have higher $\Delta\nu$ values than manganese complexes. This pattern is in accord with the Irving–William series for M^{+2} metal ions which gives stability of complexes of M^{+2} in the order $Mn < Co < Ni < Cu > Zn$. Second, $\Delta\nu$ for potassium salt of S-allyl cysteine is 173. So the $\Delta\nu$ values given in table 2 for the complexes indicate the monodentate coordination of carboxylate group to the metals.

3.3. *Mass spectrometry*

ESI–mass spectrum for the chromium complex showed a peak at *m*/*z* 462 corresponding to $[M + H]^+$ ion, i.e., $[CrCl(H_2O)_3(C_{12}H_{20}O_4N_2S_2) + H]^+$. Peaks at *m*/*z* 464 and 466 corresponding to ^{37}Cl were also observed. For zinc complex, peak at 495 was assigned to $[M + H]^+$ ion, i.e., $[ZnCl_2(H_2O)_2(C_{12}H_{22}O_4N_2S_2) + H]^+$. Peaks for ^{37}Cl were also observed at 497 and 499. For Mn complex, molecular ion peak $[M + H]^+$ was observed at 450 corresponding to $[Mn(H_2O)_4(C_{12}H_{22}O_4N_2S_2) + H]^+$. Isotopic distribution pattern for organosulfur compounds followed it. So, no chloride is coordinated to manganese in manganese complex. Other important peaks observed in all the spectra were of anhydrous metal ligand ion $[ML_2Cl + H/ML_2 + H]^+$ for each of the complexes and a peak for the ligand (*m*/*z* 162).

3.4. *Electronic spectra*

In the electronic spectrum of manganese complex, two weak absorptions are observed at 18,691 and 33,333 cm^{-1}, assigned to $^6A_{1g} \rightarrow {}^4T_{1g}$ and $^6A_{1g} \rightarrow {}^4E_g$ transitions. Manganese complex has light pink color showing octahedral geometry with high-spin d^5 configuration as compared to tetrahedral yellow-green complex [28]. For chromium complex, the observed absorption maxima are at 18,181, 24,691, and 34,482 cm^{-1}.

The first two bands are assigned to ${}^4A_{2g} \rightarrow {}^4T_{1g}(F)_{\nu 2}$ and ${}^4A_{2g} \rightarrow {}^4T_{2g}(F)_{\nu 1}$ transitions; the third may be due to charge transfer. These are characteristics of octahedral geometry [28].

3.5. *Magnetic moments*

The magnetic moments for the chromium and manganese complexes were 3.72 and 5.86, respectively, which correspond to three and five unpaired (d^3 and high-spin d^5 configuration, respectively) electrons and are characteristics of octahedral geometry, as supported by electronic spectra [28].

3.6. *Conductivity measurements*

The molar conductance of the chromium, manganese, and zinc complexes were 354.4, 297.6, and 96.2 $ohm^{-1}\,cm^2\,mol^{-1}$. Molar conductance value for chromium and manganese complex is higher than 1 : 2 electrolyte (235–273 $ohm^{-1}\,cm^2\,mol^{-1}$) but lower than 1 : 3 electrolyte (408–435 $ohm^{-1}\,cm^2\,mol^{-1}$) [29]. This situation may arise due to ionization of two chloride ions and partial ionization of amino acid due to its zwitterionic nature. Molar conductance for zinc is lower than 1 : 1 type electrolyte (118–131 $ohm^{-1}\,cm^2\,mol^{-1}$). This conductance may be due to ionization of amino acid.

3.7. *Bioactivity*

Neither ligand nor complexes showed any activity against Gram-positive or Gram-negative bacteria grown in Luria–Bertani (LB) medium (1% tryptone, 0.5% NaCl, and 0.5% yeast extract) at 37°C. The positive control for this test was 100 $mg\,mL^{-1}$ of ampicillin.

Antifungal activity of pure ligand and complexes was tested against *Collectotrichum falcatum*, a fungus which causes red rot disease of sugarcane. For this experiment, mycelia of the fungus were put on potato agar plates and 10 μL of each of the complexes, corresponding metal chlorides, and the ligand (10% solution in distilled water) were added 2 cm away from fungal mycelia and the plates incubated at 25°C. The experiment was performed twice and antifungal activity was observed by formation of a zone of inhibition of mycelia growth.

Manganese and zinc salts, the ligand, and manganese and zinc complexes did not show growth retarding effect on the fungus. However, chromium(III) chloride showed growth retarding effect only for 24 h, while the chromium complex showed a permanent growth inhibition effect on the fungus (figures S4 and S5).

4. Conclusion

Based on the physical and spectral data, the above complexes of deoxalliin have monodentate coordination of carboxylic group to metals and octahedral geometry around the metal. No coordination of nitrogen of amino group could be observed.

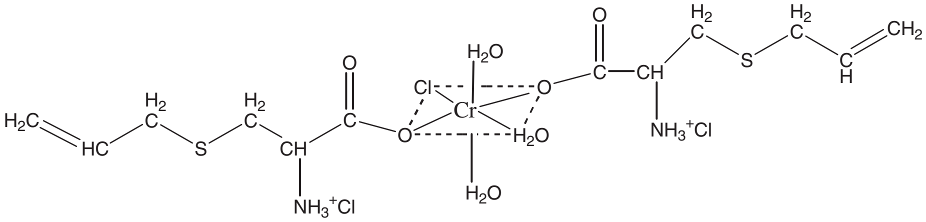

Figure 2. Proposed structure of chromium complex.

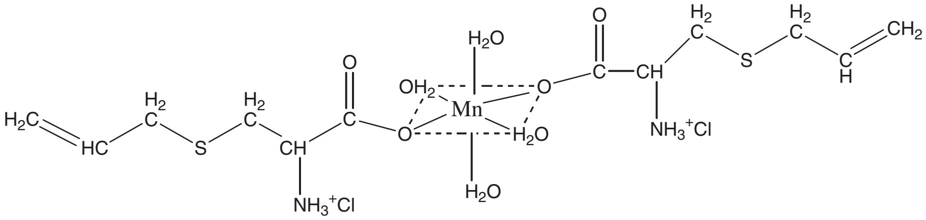

Figure 3. Proposed structure of manganese complex.

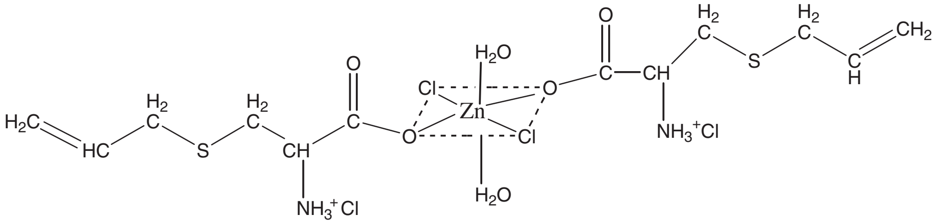

Figure 4. Proposed structure of zinc complex.

For Cr^{+3}, non-coordinating behavior toward nitrogen at low pH is also supported by the literature [30]. Conductivity measurements also suggest that amino acids are in their zwitterionic state. Only chromium complex was found to be an antifungal. The following tentative structures for the chromium (figure 2), manganese (figure 3), and zinc (figure 4) complexes have been proposed.

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