

CLASSIFICATION AND BIOLOGICAL ACTIVITY OF METAL COMPLEXES OF THIAZOLINES

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ABSTRACT

Thiazoline complexes play an important role in inorganic chemistry, as they easily form stable complexes with most transition metal ions. The chemistry and wide range of application of thiazoline compounds have been reported in literature. These compounds have shown wide range of applications, they can be used as industrial, anti-fungal, anti-bacterial, anticancer, anti-tubercular activities and chelating agents. Thiazoles and their thiazoline analogues are well known to coordinate to transition metal fragments and a large number of such compounds have been isolated that can potentially ligate transition metals. Complexes of transition metals ions containing ligands with N, S and N, S, O donors are known to exhibit interesting stereo chemical, electrochemical and electronic properties. Such compounds can also be used as local anesthetic, anti-radiation drugs, anti-viral and anti-protozoan agents and also in the rubber industry as vulcanization accelerators

KEY WORDS: Thiazoline complexes, metal complexes

INTRODUCTION

This paper is deals with the preparation and characterisation of Fe (III), Fe(II), Co (II), Ni (II) and Cu (II) complexes of 2-Imino phenyl-3- phenyl-4 (p-methoxy phenyl)- \square^4 - thiazoline and 2-Imino phenyl-3-phenyl-4(p-ethoxy phenyl)- \square^4 -thiazoline. On the comparison of the spectra of ligand with these complexes it has been observed that most of the band had shifted. The band observed at 1635 cm^{-1} in the ligand assigned to \square (C=N) practically remains unchanged on complexation. This shows that nitrogen of the thiazole ring does not take part in coordination. The fungicidal activity of the ligand as well as their metal complexes shows that they are more toxic. Among all the metal screened for their fungicidal activity against the three fungi, Cu (II), complexes seem to be most active fungicides. The metal complexes are less toxic than the free ligands.

Thiazolines and its derivatives have attracted the attention of several workers due to their wide range of activity. Thiazoles are mainly used as analgesic, nematocides, bacteriocides and fungicides, while some of their compounds are used as local anesthetic, antiviral and antiprotozoal agents and above all as vulcanization accelerator in rubber industry. The presence of $> \text{N}-\text{C}-\text{S}-$ linkage, in the compounds, the toxophoric importance of which has been documented in many fungicides, has shown better fungicidal activities. Transition metal complexes formed by organic ligands are essential in plant nutrition, they have been widely studied which include several amines containing sulphur cystine and merceptoacetate. It has been reported in literature that metal complexes plays an important role in biological activity of drugs. As complex formation has been suggested to one of the important mechanism for their vital action. Complexes containing thiazole and imidazole group as ligands are also of considerable interest because these groups form parts of several proteins which interact with the metal ions. Recent reviews deals with the metal complexes of sulphur donar ligands and are of special attention due to their wide range of applicability and reactivity against protoza, cancer, tuberculosis and certain kinds of tumour. Recently Srivastava et al (1993) have prepared a large number of transition metal complexes with oxazoles, oxazoline, thiazole and thiazoline and studied their structural and biological activity. Transition metal complexes of heterocyclic ligands have been prepared and characterised by several workers.

Large number of report appeared in the literature about the importance of mixed ligand complexes in the

field of medicinal, analytical and industrial chemistry. The role of mixed ligand complexes in biological process has also been recognized.

In the light of this view, the importance of metal complexes of sulphur donar ligands, we have reported a few Fe (II), Co (II), Ni (II) and Cu (II) complexes of 2-Imino-phenyl-3-phenyl-4 (p-methoxy/ ethoxy phenyl) - Δ^4 - thiazoline. In this chapter attempts have also been made to study their structure by elemental analysis, electronic spectra, and magnetic measurements. The fungicidal activity of ligands and their metal complexes were also determined against various fungi at different concentration.

PREPARATION OF THE LIGAND:

2-Imino-phenyl-3-phenyl-4-(p-methoxy/ethoxy phenyl) - Δ^4 - thiazoline]

The ligand was prepared according to the literature procedure. The ligand was prepared from methoxy/ethoxy acetophenone. A solution of Br₂ (0.054 mole) in ethanol (40 ml) was added slowly with constant stirring to a solution of methoxy/ ethoxy aceto-phenone (0.051 mole) in ethanol (10ml) Sym- diphenyl thiourea (0.053 mole) was than added to above mixture. The reaction mixture was heated on a water bath using reflux condenser for 12 hours and finally for 4 hours without condenser. It was then kept in contact with ether for overnight to remove the unreacted ketone. Ether was removed by decantation.

The product was then boiled with water (50 ml). The water was decanted hot and the residue obtained was treated with ammonia to triburated the free base and kept as such for overnight. The mass solidified this product was finally recrystallized from acetone. Analysis gave following influence as to their formulae.

Ligands	% found/ Calculated			
	C	H	N	S
C ₂₂ H ₁₈ N ₂ OS	73.76 (73.74)	5.06 (5.03)	7.78 (7.82)	8.88 (8.94)
C ₂₃ H ₂₀ N ₂ OS	74.20 (74.19)	5.40 (5.38)	7.58 (7.53)	8.56 (8.60)

PREPARATION & ISOLATION OF METAL COMPLEXES:

(1) TRICHLORO/ TRIACETATO AND TRINITRATO TRIS (2-IMINO- PHENYL-3- PHENYL-4-(p METHOXY/ETHOXY PHENYL)- Δ^4 -THIAZOLINE Fe(III) COMPLEXES:

These complexes have been synthesized by mixing ethanolic solution of ligand (0.03 moles) with Fe (III) salts (0.01 mole) in the same solvent under stirring and refluxed for two hours. The contents were concentrated and cooled. Brownish black crystals were obtained which were filtered washed thoroughly with ethanol and dried. The chemical analysis corresponds to the following molecular formulae.

COMPLEX	% found / calculated				
	C	H	N	S	Fe
[Fe(C ₂₂ H ₁₈ N ₂ OS) ₃ Cl ₃]	64.02 (64.10)	4.40 (4.37)	6.76 (6.79)	7.72 (7.76)	4.54 (4.53)
[Fe (C ₂₂ H ₁₈ N ₂ OS) ₃ (NO ₃) ₃ .H ₂ O]	59.48 (59.47)	4.19 (4.20)	9.48 (9.46)	7.22 (7.21)	4.22 (4.20)
[Fe (C ₂₂ H ₁₈ N ₂ OS) ₃ (CH ₃ COO) ₃]	66.06 (66.11)	4.80 (4.82)	6.42 (6.43)	7.36 (7.35)	4.30 (4.28)
[Fe (C ₂₃ H ₂₀ N ₂ OS) ₃ Cl ₃]	64.76 (64.76)	4.68 (4.69)	6.58 (6.57)	7.54 (7.51)	4.36 (4.38)
[Fe(C ₂₃ H ₂₀ N ₂ OS) ₃ (NO ₃) ₃ .H ₂ O]	60.24 (60.26)	4.50 (4.51)	9.20 (9.17)	4.64 (4.66)	4.06 (4.06)
[Fe (C ₂₃ H ₂₀ N ₂ OS) ₃ (CH ₃ COO) ₃]	66.70 (66.72)	5.16 (5.12)	6.22 (6.23)	7.16 (7.12)	4.14 (4.15)

2. [DICHLORO/ DINITRATO AND DIACETATO BIS (2-IMINO- PHENYL-3- PHENYL-4- (p-METHOXY/ ETHOXY PHENYL)- Δ^4 THIAZOLINE-Co (II) COMPLEXES].

Anhydrous Co (II) salts (0.01 moles) dissolved in minimum quantity of dry ethanol, were added to a solution of ligand (0.02 moles) also in minimum volume of ethanol. The pH of the reaction mixtures were slightly raised by addition of ammonia and the contents refluxed for one hour. On cooling the precipitates separate out, which were filtered, washed with ethanol and finally with ether, dried and analysed.

COMPLEX	% found/Calculated				
	C	H	N	S	Co
[Co(C ₂₂ H ₁₈ N ₂ OS) ₂ Cl ₂]	62.42 (62.41)	4.24 (4.26)	6.60 (6.62)	7.58 (7.57)	7.00 (6.97)
[Co(C ₂₂ H ₁₈ N ₂ OS) ₂ (NO ₃) ₂]	58.72 (58.73)	4.00 (4.01)	9.28 (9.34)	7.10 (7.12)	6.58 (6.56)
[Co(C ₂₂ H ₁₈ N ₂ OS) ₂ (CH ₃ COO) ₂]	64.52 (64.50)	4.72 (4.70)	6.30 (3.27)	7.18 (7.17)	6.62 (6.61)
[Co(C ₂₃ H ₂₀ N ₂ OS) ₂ Cl ₂]	63.18 (63.16)	4.56 (4.58)	6.40 (6.41)	7.30 (7.32)	6.76 (6.75)
[Co(C ₂₃ H ₂₀ N ₂ OS) ₂ (NO ₃) ₂]	59.54 (59.55)	4.28 (4.31)	9.00 (9.06)	6.92 (6.90)	6.40 (6.36)
[Co (C ₂₃ H ₂₀ N ₂ OS) ₂ (CH ₃ COO) ₂]	65.16 (65.15)	5.00 (4.99)	6.00 (6.08)	6.96 (6.95)	6.42 (6.41)

MAGNETIC MOMENT & ELECTRONIC SPECTRAL STUDIES:

The present work is an attempt in the direction of seeking a correlation between magnetic moment and ligand field parameters.

Fe (III) Complexes:

The magnetic moment of Fe (II) complexes observed at room temperature lie in the range 5.62-5.65 B.M. The value is however, suggestive of high- spin six coordinated Fe (III) complexes. The octahedral Fe (III) complexes exhibit broad bands assignable to $^5T_{2g} \rightarrow ^5E_g$ transition. Here two bands are observed near 8650 and 10550 cm^{-1} which are split components of one band assignable to $^5T_{2g} \rightarrow ^5E_g$. This splitting of the E_g state may be due to distortion of the octahedron since tetragonal and rhombic distortion split 5E_g excited state but static distortion of the octahedron is not expected to occur for a variety of electronic reasons, in the molecules having T_{2g} ground state. The possibility of trigonal distortion is not anticipated because such a distortion would not warrant the lifting of degeneracy of 5E_g states. Thus in this case it appears that the splitting of spin- allowed band is attributed only to Jahn- Teller effect and all other explanations seen to be invalid.

Co (II) Complexes:

The theory of magnetic susceptibility of Co (II) was given originally by Schalp and Penney while the best summary of recent results is given by Figgis Nyholm. The observed value of magnetic moment 4.40-4.45 B.M. at room temperature lie well with in the range expected for tetrahedral Co (II) complexes and are generally diagnostic of the coordination geometry around the metal ion.

The spectra of present Co (II) complexes were very similar and three spin- allowed transitions $^4A_2 \rightarrow ^4T_2$ (γ_1), $^4A_2 \rightarrow ^4T_1$ (F) (γ_2), and $^4A_2 \rightarrow ^4T_1$ (P) (γ_3), are expected to occur in tetrahedral field. The reflectance spectra exhibit bands at 19000-19250, 16050, 8700-8850 and 7050 cm^{-1} . In confirmity with the spectra of other tetrahedral Co (II) compelxes . The doublet in the region 7000- 8850 is assigned to the split component of γ_2 transitions. The doublet in the visible region with maxima at 19250 and 16050 can be assigned to the split components of the γ_3 transitions. Using the method of Cotton Goodgame

various crystal field parameters for Co (II) complexes have been calculated.

Ni (II) Complexes:

The present six- coordinated Ni(II) complexes exhibit a magnetic moment 2.80-3.10 B.M. expected for two unpaired electrons in an octahedral field. The electronic spectra indicates an octahedral or tetragonal arrangements of the ligands. Although the complexes formally have D_{4h} symmetry, the electronic spectra in the range 8000-8350 cm^{-1} and magnetic moment values are typical of octahedrally coordinated Ni (II) complexes the observed energies of three spin- allowed transitions ${}^3A_{2g} \rightarrow {}^3T_{2g}$ at 8400-8750, ${}^3A_{2g} \rightarrow {}^3T_{1g}$ (F) at 14000 – 14100 and ${}^3A_{2g} \rightarrow {}^3T_{1g}$ (P) at 24000-24150 cm^{-1} agree well with those predicted from Liehe and Ballhausen⁴⁷ energy level diagram for Ni (II) in a ligand field of octahedral symmetry. The ligand field parameter $10 Dq$ was taken equal to the observed energy of the first triplet transition (γ_1) and the Racah parameter B was calculated by substitution of (γ_1), (γ_2) and (γ_3) band energies in the secular equation. Furthermore, observed value of 1.61-1.66 for ratio (γ_2/γ_1) are in accord with commonly reported value of 1.60-1.70 for Ni (II) complexes of octahedral symmetry.

Cu (II) Complexes:

The room temperature magnetic moment for the present complexes have been found in the range 1.50-1.52 B.M. which is lower than the spin only value of 1.73 B.M. required for an $S=1/2$ system. Some what subnormal magnetic moment values can be attributed to the anti ferromagnetic exchange between the interacting Cu^{+2} ions, thus dimerisation or polymerization in the solid state either through Cu^{+2} - Cu^{+2} interaction or through ligand participation cannot be ruled out in the present case.

The square planar geometry have been confirmed by the nature of absorption bands which appear in the visible spectra of the complexes. Two bands have been observed in their electronic spectra in the region 15300-15600 and 19200-19300 cm^{-1} which may be attributed to d-d transition ${}^2B_{1g} \rightarrow {}^2A_{1g}$ and ${}^2B_{1g} \rightarrow {}^2E_g$ respectively in a planer field. Distortion of the planer complexes towards a tetrahedral configuration lowers the band frequency. Bands at 10050 and 13850-12000 cm^{-1} have been assigned from their frequency and relatively low intensities to crystal field transition of Cu(II) in a pseudo tetrahedral environment. Hence the absence of a band below 10050 cm^{-1} in these complexes eliminates the possibility of tetrahedral structure. However, a distorted, effectively planer structure is likely as the ${}^3B_{1g} \rightarrow {}^3E_g$ transition is likely to be more intense.

FUNGICIDAL ACTIVITY

The mechanism of action of sulphur containing ligands and their metal complexes has been a subject of interest for many years. It is presumed that sulphur compounds acts as hydrogen acceptor in metabolic system and in doing so, disturb the normal hydrogenation and dehydrogenation reaction in the fungal cells. The views are however based on the presumption that sulphur being next to oxygen, acts much like oxygen. The work of Tweedy however suggests that the cytochrome system is involved in the reduction of sulphur compounds. Owens advocated an interesting theory and suggested that reaction polysulphide free radicals might form stable cross linkages with protein and other cellular compounds of fungus. This theory however provides one of the most intriguing unsolved problems in fungicidal mechanism. The thiazolines and its Fe (III), Co (II), Ni (II) and Cu (II) complexes have been assayed for their fungicidal action against *Phoma-exigua*, *Macrophomia- phascoli* and *Colletotrichum-Capsici* at different concentrations 100, 50 and 20 ppm. and an attempt has been made to establish a relationship between fungicidal activity and chemical structure.

The result obtained shows that there exists a gradual decline of growth with the increasing dose of the complexes. The ligand possesses good fungicidal activity which seems to be related with the size of substituents. The ligand exhibit greater activity in comparison to its complexes which might be due to the fact that the ligand in the free state can easily combine with fungal cells and check their growth. However on complex formation adduct compounds are formed. Solubility of the complexes also constitutes an important factor responsible for the biological activity.

Table 1

Growth responses of *Phoma-exiqua*, *Macrophomina- phaseoli* and *Colletotrichum capsici* (After 168 hours at $25 \pm 1^{\circ}$ on Czepecks Dox Agar Medium) at different concentration (in ppm) in relation to the ligand 2--Imino phenyl-3-phenyl –4- (p- methoxy phenyl)- \square^4 Thiazoline (IPPMPT)

Test Samples	Average percentage inhibition after 168 hours								
	Phoma-exiqua			Macro phomia- phaseoli concentration used in ppm			Colletotrichum- capsici		
	100	50	20	100	50	20	100	50	20
Ligand	91.6	76.0	58.0	91.2	76.4	58.6	91.4	76.2	58.8
[Fe (L) ₃] Cl ₃]	63.6	42.6	29.0	64.0	76.4	29.2	64.2	42.4	29.2
[Fe (L) ₃ (NO ₃) ₃ H ₂ O]	62.8	41.2	28.8	63.2	42.8	28.8	63.3	41.6	28.4
Fe (L) ₃ (CH ₃ COO) ₃]	60.4	40.8	27.6	61.2	41.6	28.2	61.4	40.8	27.9
[Co (L) ₂ (Cl ₂]	67.5	44.8	30.2	68.0	40.6	30.8	68.2	45.2	31.4
[Co (L) ₂ (NO ₃) ₂]	68.8	45.2	31.6	69.3	45.6	32.0	69.5	45.8	32.3
[Co (L) ₂ CH ₃ COO) ₂]	65.4	43.8	29.6	66.6	44.0	30.6	66.8	44.0	30.2
[Ni (L) ₂ Cl ₂ 2H ₂ O]	70.8	47.8	34.6	71.2	48.2	64.8	70.6	48.4	34.9
[Ni (L) ₂ (NO ₃) ₂ 2H ₂ O]	71.6	50.0	35.4	72.2	50.8	65.8	72.4	50.6	35.2
[Ni (L) ₂ (CH ₃ COO) 2H ₂ O]	70.5	46.2	32.8	70.8	46.4	32.8	70.8	46.8	32.6
[Cu (L) ₂ Cl ₂]	75.0	52.3	40.0	75.8	52.4	41.4	75.6	52.4	40.6
[Cu (L) ₂ (NO ₃) ₂]	74.7	51.8	38.7	74.9	52.0	39.6	75.0	52.2	39.8
[Cu (L) ₂ (CH ₃ COO) ₂]	72.8	50.6	36.2	73.0	51.2	36.8	72.9	51.8	36.8

Table 2

Growth responses of *Phoma-exiqua*, *Macrophomina- phaseoli* and *Colletotrichum capsici* (After 168 hours at $25 \pm 1^{\circ}$ on Czepecks Dox Agar Medium) at different concentration (in ppm) in relation to the ligand 2--Imino phenyl-3-phenyl –4- (p-ethoxy phenyl)- \square^4 thiazoline (IPPEPT).

Test Samples	Average percentage inhibition after 168 hours								
	Phoma-exiqua			Macro phomia- phaseoli concentration used in ppm			Colletotrichum- capsici		
	100	50	20	100	50	20	100	50	20
Ligand	91.4	75.9	57.9	91.2	76.3	58.4	91.1	76.0	59.2
[Fe (L) ₃ Cl ₃]	61.2	41.5	28.9	64.0	76.1	29.0	64.1	42.1	29.1
[Fe (L) ₃ (NO ₃) ₃ H ₂ O]	63.2	42.3	28.5	63.1	41.1	28.1	62.0	41.3	28.4
Fe (L) ₃ (CH ₃ COO) ₃]	62.5	41.3	27.4	61.1	41.1	28.0	60.9	40.2	27.1
[Co (L) ₂] (Cl ₂]	67.5	44.2	30.0	68.0	40.1	30.2	68.1	45.0	31.0
[Co (L) ₂ (NO ₃) ₂]	65.1	43.6	29.2	66.1	43.8	30.1	66.4	43.5	29.5
[Co (L) ₂ (CH ₃ COO) ₂]	64.1	43.1	29.0	65.3	43.1	29.3	66.0	43.5	29.1

[Ni (L) ₂ Cl ₂ 2H ₂ O]	70.2	47.3	34.1	71.0	48.1	34.2	70.5	48.1	34.2
[Ni (L) ₂ (NO ₃) ₂ 2H ₂ O]	71.2	49.2	35.1	72.1	50.2	35.4	72.2	50.3	35.1
[Ni (L) ₂ (CH ₃ COO) ₂ 2H ₂ O]	70.2	45.8	32.3	70.6	46.2	32.2	70.3	46.4	32.3
[Cu (L) ₂ Cl ₂]	74.9	52.1	39.0	65.1	52.2	40.3	75.1	52.1	40.5
[Cu (L) ₂ (NO ₃) ₂]	74.3	51.3	38.2	74.2	51.6	39.2	74.2	52.1	39.3
[Cu (L) ₂ (CH ₃ COO) ₂]	72.2	50.3	36.0	73.1	51.2	36.8	72.9	51.83	36.8

CONCLUSION

The ligand, because of its strongly soluble nature in acetone and alcohol can be easily absorbed by fungal hyphae but the complexes are not much soluble which accounts for the differences in toxicity between the ligand and the complexes. The analysis of the results showed that among all the metal complexes screened for their fungicidal activity against the three fungi, Cu (II), complexes seem to be most active fungicides. The toxicity of metal ions in the decreasing order has been observed in the following manners: Cu (II) > Ni (II) > Co (II) > Fe (III). Again from the data of toxicological studies, it is observed that 1:2 complexes are more active than 1:3 complexes. The anions attached to metal complexes also govern the result to some extent. In case of Ni (II) and Co (II) complexes the nitrate complexes are most effective, next in order of efficiency where the acetate complexes while in Cu (II) and Fe (III) complexes the order of toxicity as $\text{Cl}^- > \text{NO}_3^- > \text{CH}_3 \text{COO}^-$ were observed most effective.

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