Inorganica Chimica Acta, *107* (1985) 281–284

Biologically Important Coordination Compounds of 4-Acetyl-2-(acetylamino)-5-dimethyl-Δ^2-1,3,4-thiadiazole with Manganese(II), Iron(II), Cobalt(II) and Nickel(II)

K. N. THIMMAIAH*, G. T. CHANDRAPPA** and W. D. LLOYD

Department of Chemistry, University of Texas at El Paso, El Paso, Tex. 79968, U.S.A.

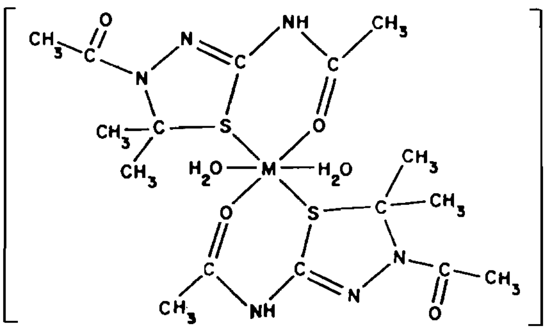
Received February 27, 1985

Abstract

The complexes of 4-Acetyl-2-(acetylamino)-5-dimethyl-Δ^2-1,3,4-thiadiazole (AAT) with Mn(II), Fe(II), Co(II) and Ni(II) have been prepared and characterized on the basis of elemental analyses, molar conductance, magnetic moments, electronic and infrared spectral studies. The most probable structures of the complexes have been proposed on the basis of their physicochemical properties. The fungitoxicity of AAT and its complexes has been evaluated on pathogenic fungi.

Introduction

Thiadiazole derivatives have proven to be biologically versatile compounds which have antiviral [1], antibacterial [2], antipyretic [3], fungicidal [4], and analgesic [5] activities. The toxicological importance of the $-\underset{|}{\overset{|}{\text{N}-\text{C}}}-\text{S}$ moiety has been well-established in many fungicides and the presence of a thiadiazole ring may be expected to impart fungicidal activity [6, 7]. Several metal chelates are also known to possess bactericidal [8], fungicidal [9] and antiviral [10] activities. In several cases the metal chelates have been found to be more fungitoxic than the chelating agent itself [9]. Thimmaiah *et al.* have proposed AAT as a chelating agent for Zn(II), Hg(II), Cd(II) and Cu(II) [11]. In the present paper, the authors report the isolation and characterization of Mn(II), Fe(II), Co(II) and Ni(II) complexes with AAT and the fungicidal activities of the ligand and the complexes in various pathogenic fungi. The proposed structure for the complexes is as follows:



M = Mn(II), Fe(II), Co(II) and Ni(II) and X = Cl.

Experimental

All the chemicals used in this work were of reagent grade and used without further purification. AAT was prepared and purified by the recommended method [12].

Preparation of the Complexes

A 50 ml portion of a 0.05 M ethanolic solution of the metal salts were mixed with an equal volume of a 0.1 M solution of AAT in ethanol and the pH of the solution was increased to 7.0 by adding dilute ammonia. The reaction mixture was digested on a water bath for about 3 h. This was cooled and the precipitate which formed was filtered off, washed with ethanol and dried *in vacuo*.

Physical Measurements

The Mn, Fe, Co, and Ni contents of the complexes were determined by standard methods. Carbon, hydrogen, nitrogen and oxygen contents of the complexes were determined using Buehler Apparatus for Microstructural Analysis, Stroehlein, Germany. The analytical results are given in Table I.

The magnetic susceptibility of the complexes was determined by Gouy's method at room temperature. The experimental magnetic susceptibilities were corrected for diamagnetism.

---

*Author to whom correspondence should be addressed.

**Department of Post-Graduate Studies and Research in Chemistry, University of Mysore, Manasa Gangotri, Mysore-570006, India.

0020-1693/85/$3.30

TABLE I. Analytical Data, Melting Point, Magnetic Moment and Conductance Data of the Complexes.

Complex	M.P. (°C)	C% Calc. (found)	H% Calc. (found)	N% Calc. (found)	O% Calc. (found)	S% Calc. (found)	M% Calc. (found)	Ω (Ohm^{-1} cm^2 mol^{-1})	μ_{eff} (BM) (27 °C)
$Mn(AAT)_2(H_2O)_2Cl_2$	>350	32.44	5.07	14.19	16.22	10.81	9.28	4.0	5.93
		(32.20)	(5.10)	(14.22)	(16.10)	(10.75)	(9.31)		
$Fe(AAT)_2(H_2O)_2Cl_2$	Charred	32.39	5.06	14.17	16.19	10.79	9.42	8.0	5.00
		(32.35)	(4.95)	(14.40)	(16.22)	(10.82)	(9.50)		
$Co(AAT)_2(H_2O)_2Cl_2$	>350	32.22	5.03	14.09	16.11	10.74	9.89	10.0	4.70
		(32.40)	(5.00)	(14.30)	(16.00)	(10.85)	(9.90)		
$Ni(AAT)_2(H_2O)_2Cl_2$	>350	32.23	5.04	14.10	16.12	10.74	9.85	12.0	3.10
		(32.42)	(4.98)	(14.20)	(16.30)	(10.90)	(9.90)		

Conductance measurements were made on 10^{-3} M solution of the complexes in nitromethane using a Toshniwal Conductivity bridge.

The UV-Vis spectra of the complexes and the ligand were recorded on a Varian Cary, model 219, automatic recording spectrophotometer in the wavelength range 200–800 nm.

The infrared spectra of the ligand and the complexes were recorded on a Perkin-Elmer model 983 G spectrophotometer in CsI pellets in the range 4000–200 cm^{-1}.

The antifungal activity of the ligand and the complexes was assayed against three pathogenic fungi, *Alternaria* (Sp.), *Paecilomyces* (Sp.) and *Pestalotia* (Sp.). Dimethylsulphoxide was used as a solvent for preparing different concentrations (0.01% and 0.1%) of the chelating agent and the metal complexes. The growth inhibition percentage was calculated on the basis of the average diameter of the fungal colony.

$$\text{Percentage Inhibition} = \frac{(C - T) \times 100}{C}$$

C = diameter of the fungus colony in the control plates after 96 h, T = diameter of the fungus colony in the treated plates after 96 h. The values of percentage inhibition of the complexes and the ligand are given in Table II.

Results and Discussion

The elemental analyses of the complexes showed that Mn(II), Fe(II), Co(II) and Ni(II) combine with AAT to form complexes of the type $[M-(AAT)_2(H_2O)_2]X_2$. All the complexes are soluble in acetone, methanol, nitromethane, DMF, DMSO, acetonitrile and chloroform.

Molar conductance values of 10^{-3} M solution of the complexes lie in the range 4–12 Ohm^{-1} cm^2 mol^{-1} which clearly indicates that all the complexes behave as nonelectrolytes.

The corrected magnetic moment data (Table I) indicate a high spin octahedral geometry for the Mn(II), Fe(II), Co(II) and Ni(II) complexes.

TABLE II. Fungicidal Screening Data of Complexes and Ligand.

Compound	Average percentage inhibition after 96 h					
	Organism *Alternaria* (Sp.) Conen used		Organism *Paecilomyces* (Sp.) Conen used		Organism *Pestalotia* (Sp.) Conen used	
	0.01%	0.1%	0.01%	0.1%	0.01%	0.1%
$Mn(AAT)_2(H_2O)_2Cl_2$	45.0	58.0	45.0	60.0	45.0	65.0
$Fe(AAT)_2(H_2O)_2Cl_2$	55.0	65.0	50.0	80.0	52.0	78.0
$Co(AAT)_2(H_2O)_2Cl_2$	60.0	75.0	60.0	80.0	64.0	86.0
$Ni(AAT)_2(H_2O)_2Cl_2$	65.0	90.0	70.0	96.0	85.0	98.0
AAT	35.0	40.0	36.0	41.0	40.0	45.0

Electronic Spectra

The electronic spectrum of the Mn(II) complex exhibits two d–d bands, one at 25 100 cm^{-1} and other at 16 000 cm^{-1} and a charge transfer band at 35 000 cm^{-1}. The two d–d bands in this complex may be assigned to $^6A_{1g} \rightarrow {}^4T_{1g}(G)$, $^4E_g(G)$ and $^6A_{1g} \rightarrow {}^4T_{2g}(G)$, $^4T_{1g}(G)$ transitions. On this basis a distorted hexacoordinate geometry may be proposed for the Mn(II) complex.

The spectrum of the Fe(II) complex shows a weak absorption band at 10 500 cm^{-1} due to $^5T_{2g} \rightarrow {}^5E_g$ transition and is characteristic of the octahedral symmetry around Fe(II) ion.

The low intensity absorption bands in the electronic spectrum of the cobalt(II) complex due to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1) and $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) transitions are observed at 9500 and 17 113 cm^{-1} respectively. Since these bands arise due to the presence of different bonding sites in the complex, hence a distorted octahedral arrangement around Co(II) may be proposed. The ν_2/ν_1 ratio ~ 2.0 lies well within the limit reported for 6-coordinate structure of the Co(II) complex.

The spectrum of the Ni(II) complex shows three bands at 8230, 14 600 and 25 640 cm^{-1} due to $^3A_{2g} \rightarrow {}^3T_{2g}$ (ν_1), $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ (ν_2) and $^3A_{2g} \rightarrow {}^3T_{1g}(P)$ (ν_3) transitions respectively. The ν_2/ν_1 ratio ~ 1.8 lies well within the limit reported for hexacoordinate geometry of the Ni(II) complex.

Infrared Spectra

The infrared spectra of the complexes and the ligand were recorded in the range 4000–200 cm^{-1} and we will only discuss selective infrared bands. An absorption band appearing at 3410 cm^{-1} can be assigned to a ν(N–H) vibration. The bands at 1630 and 915 cm^{-1} respectively can be attributed to ν(C=N) and ν(N–N) bands. The peak occurring at 655 cm^{-1} is due to a symmetric ν(C–S) vibration. The ν(C=N) and ν(N–N) bands present at 1630 and 915 cm^{-1} respectively in the ligand remain at the same positions in the spectra of the complexes suggesting that none of the nitrogen atoms of the thiadiazole ring are taking part in bonding with the metal. The ν(C–S) vibration is shifted from 655 cm^{-1} to 620 cm^{-1} on complex formation indicating the coordination through the 'S' atom of the thiadiazole ring. The ν(C=O) vibration of the $-NH-CO-CH_3$ group in free AAT located at 1680 cm^{-1} is shifted downwards by about 30 cm^{-1} in the spectra of the complexes suggesting the coordination of the oxygen of the carbonyl group to the metal ion. The new bands which appeared in the spectra of the complexes in the regions 550–520 cm^{-1} and 380–335 cm^{-1} have been assigned to the ν(M–O) and ν(M–S) bands respectively. In addition to these bands, the complexes exhibited bands in the range 1000–800 cm^{-1} assignable to the coordinated water, which is absent in the free ligand. Based on the above interpretation, it is concluded that AAT is bidentate in nature.

Evaluation of Antifungal Activity

Alternaria (Sp.), *Paecilomyces* (Sp.) and *Pestalotia* (Sp.) were employed to check the antifungal activity of the ligand and its complexes. It is clear from the fungicidal screening data (Table II) that the metal chelates are found to be more fungitoxic than the chelating agent itself. Further, it is noted that the toxicity of the metal chelates increases as the radius of the metal ion decreases.

The activity of any compound is a complex combination of steric, electronic and pharmacokinetic factors. One possible way of explaining the toxicity of the complexes may be speculated in the light of the chelation theory [13]. It was suggested that chelation reduces the polarity of the metal ion considerably probably because of partial sharing of its positive charge with the donor groups and possible π-electron delocalisation over the whole chelate ring. This increases the lipophilic character of the metal chelate which favours its permeation through lipoid layers of the fungus membranes. Furthermore, the mode of action of the compounds may involve the formation of a hydrogen bond through the $-N=C<$ group with the active centers of the cell constituents resulting in the interference with the normal cell process.

Acknowledgements

The authors thank the Microbiology Department of the Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina, U.S.A., for fungicidal screening experiments. G. T. Chandrappa acknowledges the University Grants Commission, New Delhi, for awarding a Junior Research Fellowship.

References

1 *Br. Pat. 1 045 180* (1966) to Parke Davis and Co.; *Chem. Abstr., 66,* 18720g (1976).
2 S. Vattum and S. Rao, *Proc. Indian Acad. Sci., 40,* 96 (1959).
3 *U.S. Pat. 3 127 410 (Cl. 260–370)* (1984) to A. E. Wilder Smith; *Chem. Abstr., 61,* 3118g (1964).
4 S. Giri and R. K. Khare, *J. Antibact. Antifung. Agents (Jpn.), 4,* 11 (1976).
5 *U.S. Pat. 3 127 410* to A. E. Wilder Smith; *Chem. Abstr., 61,* 3118g (1964).
6 M. C. Goldsworthy, *Phytopathology, 32,* 498 (1942).
7 K. C. Joshi and S. Giri, *J. Indian Chem. Soc., 40,* 42 (1963).
8 K. K. Chaturvedi and R. Kaushal, *Indian J. Pharmacol., 37,* 85 (1975).
9 C. L. Mason, *Phytopathology, 38,* 740 (1948).

10 F. P. Dwyer and D. P. Mellor, 'Chelating agents and metal chelates', Academic Press, London, 1964.

11 K. N. Thimmaiah, G. T. Chandrappa, W. D. Lloyd and C. Párkányi, *Inorg. Chim. Acta 107,* 1 (1985).

12 Seiju Kubota, Yashufumi Veda, Kazuichi Fujikane, Kouhei Toyooka and Masayuki Shibuya, *J. Org. Chem., 45,* 1473 (1980).

13 R. S. Srivastava, *Inorg. Chim. Acta, 56,* L65 (1981).