BIOLOGICALLY POTENT HETEROCYCLIC SULPHONAMIDE IMINES AND THEIR MANGANESE (II) COMPLEXES.

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Abstract

Imines derived from different sulphadrugs and heterocyclic ketones and their Mn (II) complexes have been synthesized and characterized by their elemental analysis, molecular weight determinations, conductance and magnetic measurements. A high spin tetrahedral geometry around this metal ion has been proposed on the basis of magnetic and spectral studies. The unimolar and bimolar reactions of hydrated manganese acetate and chloride with monobasic, bidentate heterocyclic ligands resulted in the formation of the coloured solids which are soluble in DMF and DMSO. The molecular weight determinations indicate them to be monomers and their conductivity measurements in dry DMF show them to be non-electrolytes. All the ligands and their corresponding complexes have been screened for their fungicidal, bactericidal and nematicidal activities.

Introduction

The chemistry of heterocyclic imines have occupied a place of considerable importance because of their well established biological activities. They are well known antibacterial as well as antifungal agents. Metal complexes of such ligands and particularly of sulfur containing ligands are also drawing enormous attentions mainly due to their practical utility. Several manganese complexes are know to exhibit antifungal activity[1]. The role of metal chelates in all aspects of biological studies has gained considerable importance, as these provide valuable approaches to the metabolic studies, oxidative phosphorylation, transmethylation and principles of chemotherapy[2].

The chemistry of manganese in higher oxidation state is the subject of current interest[3] owing to its involvement in a number of biological systems e.g., in superoxide dismutase[3], an azide insensitive catalase[4] and photasystem-II (PS II)[5-7]. The interest in coordination chemistry is increasing continuously with the preparation of organic ligands containing a variety of donor groups[8-10] and it is multiplied many folds when the ligands have biological importance[11,12]. It was therefore considered worth while to synthesize such type of complexes with biologically potent ligands and particularly with manganese.

Experimental

All reagents were dried and distilled before use. The imines were prepared by the condensation of sulphathiazole, sulphaguanidine and sulphapyridine and with 2-acetylfuran in 1:1 molar ratio in alcohol. The reaction mixture was refluxed in ethanol (50 mL) for about five hours on a water bath. On cooling crystals of the imines separated out which were washed with ethanol, dried and recrystallized with acetone and dried *in vacuo*. These were characterized and analysed before use.

1. 2-Acetylfuran sulphathiazole (2-Ac-F-StH) (light yellow), 124-130°C
2. 2-Acetylfuran sulphaguanidine (2-Ac-F-SgH) (cream), 132-134°C
3. 2-Acetylfuran sulphapyridine (2-Ac-F-SpH) (brown), 138-140°C

Synthesis of Manganese (II) Complexes

For the preparation of manganese (II) complexes equimolar and bimolar reactions of $Mn(CH_3COO)_2.4H_2O$ and $MnCl_2.4H_2O$ with imines were carried out in dry methanol. To a hot solution of ligands in 30 mL methanol, the metal acetate and chloride in methanol were added dropwise. The reaction mixture was refluxed for 15-18 hrs. by column method and then cooled to room temperature. The solvent was removed, residue was dried *in vacuo* after being repeatedly washed with dry cyclohexane and finally the complexes were recrystallized in methanol. The important properties and physical data of the complexes are reported in Table I.

Table I - Physical properties of manganese complexes.

Compound	Colour and M.P. (°C)	Yield (%)	Analyses % Mn Found (Calcd.)	N Found (Calcd.)	S Found (Calcd.)	Mol. Wt. Found (Calcd.)
[Mn (CH_3COO)(2-Ac-F-St)H_2O]	Light yellow 139-141°C	84	11.38 (11.48)	8.67 (8.78)	13.20 (13.41)	451.21 (478.39)
[Mn (2-Ac-F-St)$_2$]	Dim yellow 135-137°C	76	7.29 (7.35)	11.16 (11.23)	17.00 (17.15)	701.88 (747.71)
[Mn (CH_3COO)(2-Ac-F-Sg)H_2O]	Light brown 242-244°C	79	12.48 (12.56)	12.75 (12.81)	7.14 (7.33)	390.25 (437.29)
[Mn (2-Ac-F-Sg)$_2$]	Light brown 165-167°C	79	8.17 (8.25)	16.75 (16.84)	9.50 (9.63)	614.29 (665.51)
[Mn (CH_3COO)(2-Ac-F-Sp)H_2O]	Brown 126-128°C	81	11.58 (11.63)	8.84 (8.89)	6.65 (6.79)	430.48 (472.39)
[Mn (2-Ac-F-Sp)$_2$]	Light yellow 136-138°C	86	7.41 (7.47)	11.39 (11.42)	8.61 (8.72)	698.43 (735.71)
[MnCl (2-Ac-F-St)H_2O]	Off white 142-145°C	77	2.00 (2.08)	9.18 (9.24)	14.01 (14.10)	421.91 (454.79)
[MnCl (2-Ac-F-Sg)H_2O]	Creamish 153-155°C	82	13.20 (13.28)	13.47 (13.54)	7.59 (7.75)	376.52 (413.69)
[MnCl (2-Ac-F-Sp)H_2O]	Brownish white 168-170°C	85	12.21 (12.24)	9.30 (9.36)	7.05 (7.14)	410.88 (448.79)

The analytical methods and procedures of physical measurements are the same as reported earlier[2].

Antifungal Screening

The antifungal activity of all the ligands and their corresponding complexes was evaluated against *Aspergillus niger* by the agar plate technique[2]. The compounds were dissolved in 100 ppm concentration in methanol and then were mixed with the medium. The linear growth of the fungus was obtained by measuring the diameter of colony in petri plate after 96 hours and the percentage inhibition was calculated as 100 (C-T)/C, where C and T are the diameters of the fungus colony in the central and test plates, respectively.

Antibacterial Activity

Bactericidal activity evaluated by the paper disc plate method[7]. The nutrient agar medium (peptone, beaf extract, NaCl and agar-agar) and 5mm diameter paper discs of Whatman No. 1 were used. The compounds were dissolved in methanol in 1000 ppm concentration. The filter paper discs were soaked in different solutions of the compounds dried and then placed in the petriplates previously seeded with the test organisms *E. coli*. The plates were incubated for 24-30 hrs. at 28 ± 2°C and the inhibition zone around each disc was measured.

Results and Discussion

Reactions of hydrated Manganese(II) acetate and chloride with monobasic bidentate ligands in 1:1 and 1:2 molar ratios in methanol may be represented by the following equations :

$Mn(CH_3COO)_2.4H_2O$ + N–NH → [Mn(CH_3COO)(N–N)H_2O] + CH_3COOH + $3H_2O$

$Mn(CH_3COO)_2.4H_2O$ + 2N–NH → [Mn (N–N)$_2$] + $2CH_3COOH$ + $4H_2O$

$MnCl_2.4H_2O$ + N–NH → [MnCl (N–N)H_2O] + HCl + $3H_2O$

$MnCl_2.4H_2O$ + 2N–NH → [Mn (N–N)$_2$] + 2HCl + $4H_2O$

These reactions are quite facile and the yields are almost quantitative. The products so obtained are soluble in methanol, benzene, DMF and DMSO. These were washed repeatedly with cyclohexane and were recrystallized in methanol. The molecular weight determinations indicate them to be monomers and their conductivity measurements in dry DMF (10-15 ohm^{-1} cm^2 mol^{-1}) show them to be non-electrolytes.

I.R. Spectra : In the IR spectra of the free ligands the -NH stretching and deformation bands appear at 3370-3200 and 1670-1705 cm^{-1}, respectively. However in the spectra of manganese(II) complexes, bands due to NH vibrations disappear indicating deprotonation of the ligands and chelation of nitrogen with the manganese atom. In the spectra of 1:1 metal complexes, a new band also appears in the region 676-690 cm^{-1} and which is due to the coordinated water molecule[13]. This is not observed in the corresponding 1:2 complexes. Further, a broad band around 3400 cm^{-1} may be due to νOH of water molecule[13]. The coordination of ligands through azomethine nitrogen further gets support by the appearance of new bands of medium to weak intensity in the region 410-370, attributable to ν M ← N vibrations[14].

Electronic Spectra : Manganese complexes show a maximum absorption band at ca. 420 nm and a charge transfer band at ca. 270nm indicating a tetrahedral geometry[15] for these complexes. In tetrahedral field, the transitions are spin forbidden and are no longer parity forbidden. Thus the tetrahedral compounds are some what more intensely coloured[14].

The magnetic susceptibilities of manganese (II) complexes have been determined by the Gouy's method. The magnetic moment values of Mn(II) complexes have been found to be 5.9 ± 0.1 B.M. and which suggests a high spin state for these complexes with a tetrahedral geometry[16].

Electron Spin Resonance Spectra :The electron spin resonance spectral studies of 1:1 and 1:2 Mn (II) complexes of 2-acetylfuran with sulphadrugs at the room temperature show only one isotropic signal centered at 2.145 g and which once again suggests a four coordinated geometry for these complexes. Thus on the basis of the above evidences a tetrahedral geometry has been proposed for 1:1 and 1:2 manganese complexes of sulpha drugs.

Antifungal and Antibacterial Activities : All the complexes of manganese(II) along with the ligands have been tested on various fungi and bacteria. The results given in Table II reveal that the activity increases on complexation, i.e., the newly synthesized complexes have been found to be more active in inhibiting the growth of fungi and bacteria than the parent ligands themselves. However, the solubility and concentration of the compounds also plays an important role in ascertaining the degree of inhibition.

Nematicidal Activity : Plant parasitic nematodes cause about 20.6% world wide yield loss[17]. Yield losses in India due to root-knot nematodes (*Meloidogyne* spp.) range from 39.7 to 46.0%[18,19]. Nematode *Meloidogyne incognita* was responsible for 44.87 percent yield loss in brinjal[20]. Plants infected with root-knot nematode *Meloidogyne* spp. develop root gall alongwith eggs and eggmasses.[21]

In the present studies the nematicidal activity was tested on nematode *Meloidogyne* spp. *Meloidogyne* eggsmasses were isolated from heavily infected brinjal roots and washed them under running water. Quantities of clean *Meloidogyne incognita* eggs were obtained by step by step procedure as cutting the roots, addition of 1% sodium hypochloride solution, shaking it and than sieving through 150 and 400 mesh sieves.[22] Two hundred and thirty eggs of nematode *M. incognita* were used per replicate sample and each treatment was replicated three times. The experiment was conducted at room temperatures 30 ± 2°C. The eggs were treated with complexes dissolved in 100 ppm for 24 hrs. and observation in relation to hatching of *Meloidogyne* eggs were noted. Results revealed that maximum hatching was recorded in control (H_2O) but in eggs treated with chemicals very poor hatching was recorded. The rate of occurrence for each stage of nematode (larvae) *Meloidogyne* eggs was calculated by determining the absolute frequency[23].

$$\text{Absolute frequency} = \frac{\text{No. of samples containing a species}}{\text{No. of samples collected}} \times 100$$

All the ligands and their complexes have been tested on nematode *Meloidogyne*. It reveals that the activity increases on complexation, i.e., the newly synthesized complexes have been found to be more active in inhibiting the hatching of eggs than the parent ligands, themselves.

Table 2. Biological activity index

Compound	Fungicidal % inhibition (100 ppm) *Aspergillus niger*	Bactericidal *E.coli* (1000 ppm) (diameter)	Nematicidal (*Meloidogyne spp.*) hatching % (100ppm)
(2-Ac-F-StH)	61	6.5	15
$[Mn(CH_3COO)(2\text{-Ac-F-St})H_2O]$	65.6	7.2	13.8
$[MnCl(2\text{-Ac-F-St})H_2O]$	65	7.1	14
$[Mn(2\text{-Ac-F-St})_2]$	74	8.0	12
(2-Ac-F-SgH)	60.1	6.1	15.9
$[Mn(CH_3COO)(2\text{-Ac-F-Sg})H_2O]$	65.0	6.6	15.0
$[MnCl(2\text{-Ac-F-Sg})H_2O]$	63.8	6.3	15.5
$[Mn(2\text{-Ac-F-Sg})_2]$	73	7.2	12
(2-Ac-F-SpH)	60.6	6.4	16.3
$[Mn(CH_3COO)(2\text{-Ac-F-Sp})H_2O]$	64.8	7.0	15.2
$[MnCl(2\text{-Ac-F-Sp})H_2O]$	63.9	6.8	15.1
$[Mn(2\text{-Ac-F-Sp})_2]$	74	7.9	12.4

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