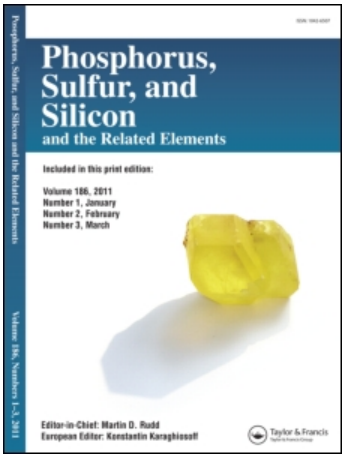

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BIOCHEMICAL STUDIES ON BIOLOGICALLY ACTIVE THIO-LIGANDS BENZOTHIAZOLINES AND THEIR MANGANESE(II) COMPLEXES

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The coordination behaviour of benzothiazolines having the donor group N⌒S towards manganese(II) has been studied. The unimolar and bimolar reactions of hydrated manganese acetate with monobasic bidentate benzothiazolines resulted in the formation of coloured solids which have been characterised by elemental analysis, molecular weight determinations conductance and magnetic measurements. The infrared, electronic and electron spin resonance spectral studies indicate a high spin tetrahedral geometry for the resulting complexes. All the ligands and their corresponding complexes have been screened for their fungicidal and bactericidal activity.

Key words: Manganese(II) complexes; benzothiazolines; heterocyclic ketones; monobasic bidentate ligand; spectral studies; biological activity.

INTRODUCTION

The chemistry of azomethines have occupied a place of considerable importance because of their well established biological activities.[1] They are well known antibacterial[2] as well as antifungal agents.[3] Metal complexes of such ligands and particularly of sulfur containing ligands are also drawing enormous attention mainly due to their practical utility. They are active against tuberculosis,[4] cancer,[5] viruses,[6] malaria,[7] smallpox[8] and certain kinds of tumor.[9] Several manganese complexes are known to exhibit antifungal activity, e.g., Maneb, the coined name for manganous ethylene bisdithiocarbamate has been successfully used against a wide variety of diseases, particularly of vegetables and fruits.[10] 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. It was, therefore, considered worth while to synthesize such type of complexes with sulphur containing ligands and particularly with manganese. Benzothiazolines, the cyclic products obtained by the condensation of 2-mercaptoaniline with a carbonyl compound constitute an extremely important class of sulfur donor ligands which are also of biological significance as well. Further, it has been observed that the metal-nonmetal ion acts as a template and favours the formation of a Schiff base rather than the thiazoline form.[11–12] Later on, it has been described[13] that even in the absence of metal ion, the condensation products of an aldehyde or ketone and 2-mercapto aniline is an equilibrium mixture of benzothiazoline and the Schiff base (shown below). The results of the following four types of benzothiazolines derived from heterocyclic ketones and their manganese(II) derivatives form the subject of this paper.

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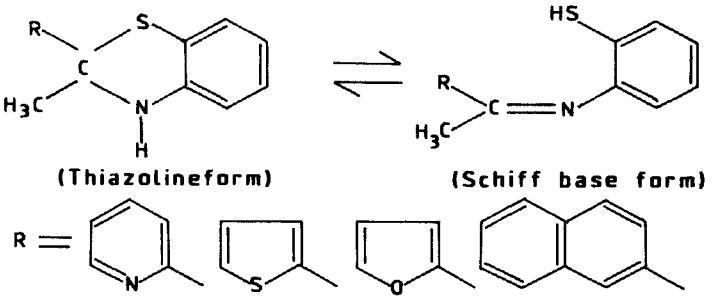


EXPERIMENTAL

All reagents were dried and distilled before use. The benzothiazolines were prepared by the condensation of 2-acetylnaphthalene, 2-acetylthiophene, 2-acetylfuran and 2-acetyl pyridine with 2-mercaptoaniline in 1:1 molar ratio in alcohol. The reaction mixture was stirred magnetically for ca. 3–4 hrs and the solid which separates out was filtered, purified by recrystallization from alcohol and dried in vacuo. These were characterized and analysed before use.

1. 2-Acetylnaphthalene benzothiazoline (2-Acnaph.BztH), Yellow solid, M.P. 78°C.
2. 2-Acetylthiophene benzothiazoline (2-Acthio.BztH), Yellow solid, M.P. 88°C.
3. 2-Acetylfuran benzothiazoline (2-Acfur.BztH), Brown solid, M.P. 73°C.
4. 2-Acetylpyridine benzothiazoline (2-Acpyd.BztH), Yellow solid, M.P. 84°C.

Synthesis of Manganese(II) Complexes. For the preparation of manganese(II) complexes equimolar and bimolar reactions of $Mn(CH_3COO)_2 \cdot 4H_2O$ with benzothiazolines were carried out in dry methanol. After the addition of yellow solution of ligand to $Mn(CH_3COO)_2 \cdot 4H_2O$, the yellow colour changes to brown and complex formation takes place instantly. However, to ensure the completion of the reaction, the reaction mixture was shaken thoroughly refluxed for 4 hrs and then cooled to room temperature. The solvent was removed and residue was dried in vacuo after being repeatedly washed with dry cyclohexane. Finally the complexes were recrystallized in methanol. The important properties and physical data of the complexes are reported in Table I.

Physical Measurements and Analytical Methods. The analytical methods and procedures of physical measurements are the same as reported earlier.[14]

Antifungal Screening. The antifungal activity of all the ligands and their corresponding complexes was evaluated against *Macrophomina phaseolina*, *Fusarium oxysporum* and *Aspergillus niger* by the agar plate technique.[15] The compounds were dissolved in 50, 100 and 200 ppm concentrations in methanol and then were mixed with the medium. The linear growth of the fungus was obtained by measuring the diameter of colony in petriplate 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 control and test plates, respectively.

Antibacterial Activity. Bactericidal activities were evaluated by the paper-disc plate method.[16] The nutrient agar medium (Peptone, Beaf Extract, NaCl and agar agar) and 5 mm diameter paper discs of Whatman No. 1 were used. The compounds were dissolved in methanol in 500 and 1000 ppm concentrations. The filter paper discs were soaked in different solutions of the compounds, dried and then placed in the petri plates previously seeded with the test organisms (*Pseudomonas cepacicola*, *E. coli*, *Klebsiella aerogenous*). The plates were incubated for 24–30 hrs at 28 ± 2°C and the inhibition zone around each disc was measured.

RESULTS AND DISCUSSION

Reaction of hydrated manganese(II) acetate with monobasic bidentate benzothiazolines in 1:1 and 1:2 molar ratios in methanol may be represented by the following equations:

TABLE I

Physical properties of manganese complexes.

Compound	Colour and M.P. (°C)	Yield (%)	Analyses (%) Mn Found (Calc.)	N Found (Calc.)	S Found (Calc.)	Molecular weight Found (Calc.)
$[Mn(CH_3COO)(2\text{-}Achaph.Bzt)H_2O]$	Brown 130	84	13.41 (13.45)	3.34 (3.43)	7.54 (7.85)	384.78 (408.39)
$[Mn(2\text{-}Acnaph.Bzt)_2]$	Brown 120	78	9.01 (9.04)	4.43 (4.61)	10.24 (10.55)	624.43 (607.73)
$[Mn(CH_3COO)(2\text{-}Acthio.Bzt)H_2O]$	Reddish brown 120	86	15.00 (15.08)	3.71 (3.84)	17.21 (17.60)	341.78 (364.33)
$[Mn(2\text{-}Acthio.Bzt)_2]$	Reddish brown 90	79	10.43 (10.57)	5.28 (5.39)	24.22 (24.68)	530.79 (519.61)
$[Mn(CH_3COO)(2\text{-}Acfur.Bzt)H_2O]$	Brown 100	77	15.45 (15.77)	4.00 (4.02)	9.13 (9.21)	319.83 (348.26)
$[Mn(2\text{-}Acfur.Bzt)_2]$	Brown 80	82	11.15 (11.27)	5.68 (5.74)	13.01 (13.15)	463.84 (487.47)
$[Mn(CH_3COO)(2\text{-}Acpyd.Bzt)H_2O]$	Dim green 120	74	15.34 (15.29)	7.48 (7.79)	8.73 (8.92)	324.96 (359.30)
$[Mn(2\text{-}Acpyd.Bzt)_2]$	Dim green 100	76	10.81 (10.78)	10.77 (10.99)	12.62 (12.58)	524.18 (509.55)

$$Mn(CH_3COO)_2 \cdot 4H_2O + BztH \rightarrow [Mn(CH_3COO)(Bzt)H_2O] + CH_3COOH + 3H_2O$$

$$Mn(CH_3COO)_2 \cdot 4H_2O + 2BztH \rightarrow [Mn(Bzt)_2] + 2CH_3COOH + 4H_2O$$

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. The absence of νSH at 2500–2600 cm^{-1} and >C=N at 1600–1620 cm^{-1} are indicative of the benzothiazoline rather than the Schiff bases structures. However, in the spectra of manganese(II) complexes, bands due to NH vibrations disappear indicating deprotonation of the ligand and chelation of nitrogen with the manganese atom and a new band at ~1600 cm^{-1} is observed, which may be assigned to νC=N vibrations. The appearance of this band suggests that the complexes are metal Schiff base derivatives as in presence of metal ions the cyclic structure of benzothiazolines rearranges to give the Schiff base metal chelates. Due to the overlapping of bonding vibrations of H_2O molecule with νC=N frequencies it could not be possible to distinguish bending vibrations of water molecule around 1600 cm^{-1}. In the spectra of 1:1 metal complexes, a new band also appears in the region 675–690 cm^{-1} and which is due to the coordinated water molecule.[17] 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.[17] The coordination of ligands through azomethine nitrogen and thialo sulfur further gets support by the appearance of new bands of medium to weak intensity in the regions 410–370, 340–290 and 490–450 attributable to νM ← N, νM – S and νM – O vibrations, respectively.[18]

Electronic Spectra

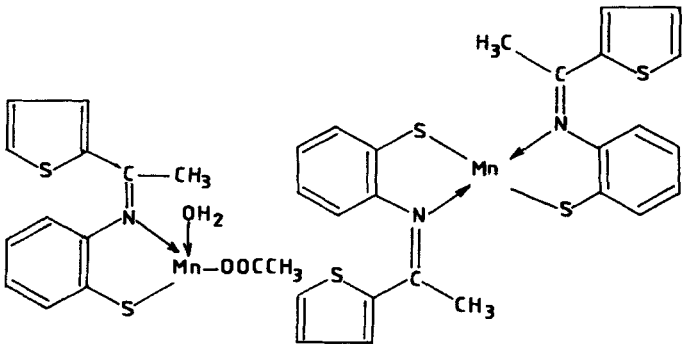
Manganese complexes show a maximum absorption band at ca. 420 nm and a charge transfer band at ca. 270 nm indicating a tetrahedral geometry[19] for these complexes. In tetrahedral fields, the transitions are spin forbidden and are no longer parity forbidden. Thus the tetrahedral compounds are some what more intensely coloured.[18]

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.[20]

Electron Spin Resonance Spectra

The electron spin resonance spectral studies of 1:1 and 1:2 Mn(II) complexes of 2-acetylthiopene benzothiazoline 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.[21] Thus on the basis of the above evidences a tetrahedral geometry has been proposed for 1:1 and 1:2 manganese complexes of benzothiazolines.



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 Tables II and III 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. The antimicrobial activity of these ligands can be ascribed to the hydrogen bond formation between the azomethine nitrogen atom of the ligands and some bioreceptors in the cells of fungi and bacteria,[22] as a result of which protein synthesis is inhibited. They might combine with 50S ribosome subunits and interferes with translocation, i.e. movement of the m-RNA on the ribosome to expose the next codone for aminoacyl-t-RNA attachment. Thus, synthesis of larger proteins is specifically suppressed. The activity of the complexes is thought to be enhanced due to introduction of metal ions in the ligands.[23] One might reason that complexation would reduce such hydrogen bonding, but bioactivity increases on complexation. It may also be postulated that these complexes might act as uncoupling agents of oxidative phosphorylation. The first uncoupling agent to be described, by W. F. Loomis and F. Lipmann was 2,4-dinitrophenol. Today many different uncoupling agents are known. Most are lipid soluble substances containing an acidic group and usually an aromatic ring. These agents allow electron transport to continue but prevent the phosphorylation of ADP to ATP, i.e., they uncouple the energy-yielding from the energy-conserving reactions. Uncoupling agents function by breaking down a high-energy intermediate or state generated by electron transport. They can promote the passage of H^+ ions through the cell membrane, which is normally impermeable to them.[24] However, these agents are less effective for bacteria. The greater toxicity of metal complexes than the ligands can also be explained on the basis of chelation theory.[25,26] Chelation reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with the donor groups and possible π-electron-delocalisation over the whole chelation ring. This increases the lipophillic character

TABLE II

Antibacterial screening data of the ligands and their complexes. Inhibition (mm) after 24 hours (conc. in ppm).

Compound	E.coli		Klebsiella aerogenous		Pseudomonas cepacicola	
	500	1000	500	1000	500	1000
2-Acnaph.BztH	5	8	4	7	4	7
[Mn(CH_3COO)(2-Acnaph.Bzt)H_2O)]	7	9	5	8	6	9
[Mn(2-Acnaph.Bzt)$_2$]	8	10	6	9	7	9
2-Acthio.BztH	4	8	4	5	5	8
[Mn(CH_3COO)(2-Acthio.Bzt)H_2O]	6	10	5	7	6	9
[Mn(2-Acthio.Bzt)$_2$]	7	10	6	10	7	11
2-Acfur.BztH	3	4	2	3	2	3
[Mn(CH_3COO)(2-Acfur.Bzt)H_2O]	4	6	3	5	3	4
[Mn(2-Acfur.Bzt)$_2$]	5	7	4	6	5	6
2-Acpyd.BztH	5	7	3	5	4	6
[Mn(CH_3COO)(2-Acpyd.Bzt)H_2O]	6	9	5	7	4	6
[Mn(2-Acpyd.Bzt)$_2$]	7	10	6	8	5	7

TABLE III

Fungicidal screening data of ligands and their complexes. Inhibition (%) after 96 hours (conc. in ppm).

Compound	Macrophomina phaseolina			Fusarium oxysporum			Aspergillus niger		
	50	100	200	50	100	200	50	100	200
2-Acnaph.BztH	28	43	56	40	52	64	37	47	62
[Mn(CH_3COO)(2-Acnaph.Bzt)H_2O)]	30	47	60	48	62	72	48	59	72
[Mn(2-Acnaph.Bzt)$_2$]	34	54	65	55	68	80	59	70	84
2-Acthio.BztH	23	31	52	31	35	41	36	47	60
[Mn(CH_3COO)(2-Acthio.Bzt)H_2O]	26	37	60	37	45	50	45	58	70
[Mn(2-Acthio.Bzt)$_2$]	30	43	67	43	58	61	54	66	82
2-Acfur.BztH	15	24	40	17	27	52	32	40	55
[Mn(CH_3COO)(2-Acfur.Bzt)H_2O]	19	28	46	20	32	61	41	53	62
[Mn(2-Acfur.Bzt)$_2$]	22	31	48	27	40	75	52	60	74
2-Acpyd.BztH	28	27	52	24	35	58	34	45	58
[Mn(CH_3COO)(2-Acpyd.Bzt)H_2O]	33	45	61	29	41	69	43	57	62
[Mn(2-Acpyd.Bzt)$_2$]	49	58	78	35	50	80	51	64	74

of the metal complex, which subsequently favours its permeation through the lipoid layers of organism cell membrane and thereby normal cell process is impaired.

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