

Table 4 Physicochemical data for oxadiazoles

Compound	n	Yield (%)	m.p.* (°C)	Mol. formula	Analysis (%)	
					N Found (Requires)	S Found (Requires)
Va	5	68	240(d)	C ₉ H ₁₂ O ₂ N ₄ S ₂	20.60 (20.58)	22.90 (23.52)
Vb	6	65	233-35	C ₁₀ H ₁₄ O ₂ N ₄ S ₂	19.38 (19.58)	22.30 (22.37)
Vc	7	58	180	C ₁₁ H ₁₆ O ₂ N ₄ S ₂	18.45 (18.66)	21.25 (21.33)
Vd	8	60	112-13	C ₁₂ H ₁₈ O ₂ N ₄ S ₂	17.63 (17.83)	20.20 (20.38)

*Compounds crystallized from EtOH.

IR (KBr): 3150-3100 (-NH), 1510-1500 (-C=N), 1175-1170 (C=S) cm⁻¹.

mixture was then concentrated and cooled, and the solid which separated was filtered, dried and crystallized. The data are given in table 4.

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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF THIOMALATES OF Ag(I), Hg(II) AND Cd(II)

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THIOMALIC acid (TMA) is a versatile ligand with a 'soft' sulphur of a sulphhydryl group and 'hard' oxygens of two carboxylate groups. Its complexes with many metal ions have been reported in solution¹⁻⁶, though only a few of them have been isolated and characterized⁷⁻¹⁰. TMA is also a biologically important compound which has been shown to serve as an antidote against cadmium, mercury and arsenic poisoning¹¹; its complexes with some metal ions have been recommended in the treatment of various disorders¹²⁻¹⁴. In this context it was thought desirable to synthesize and characterize some more complexes and also determine their antimicrobial activity. In this paper such studies on metal thiomalates of Ag(I), Hg(II) and Cd(II) are reported.

Metal acetates and nitrates and thiomalic acid used were of analytical reagent grade. IR spectra (4000-200 cm⁻¹) were recorded on a NICOLET-DX in KBr-CsI pellet/nujol mull. ¹H NMR spectra were recorded in a JEOL FT NMR Fx 90Q spectrometer in DMSO-d₆.

Thermogravimetric analysis was carried out on a fabricated instrument. Heating rate was maintained at 10°C/minute.

Preparation of metal thiomalates

Ag₂[C₄H₄O₄S]: Isolation of this 2:1 Ag(I)-TMA complex has been reported by Ellis *et al.*⁷ However, a different method was employed to obtain better yield. Methanolic solution of TMA (0.01 mol) was added to methanolic solution of AgNO₃ (0.02 mol) dropwise with constant stirring. This resulted in the precipitation of an amorphous white powder. It was filtered, washed with methanol and then with ether, and dried over CaCl₂ *in vacuo*. The yield was 83%. The compound decomposes without melting at ~140°C.

Ag[C₄H₅O₄S]: 1:1 Ag(I)-TMA complex, hitherto reported only in solution phase⁷, was isolated as follows: AgNO₃ (0.02 mol) and TMA (0.02 mol) were dissolved in 100 ml and 10 ml of methanol respectively. TMA solution was added to AgNO₃ solution dropwise with constant stirring. A white precipitate appeared first, which dissolved afterwards, yielding a yellow solution. This solution was concentrated to ~30 ml in vacuum over P₂O₅. Petroleum ether was added dropwise with stirring. A light yellow solid separated. The material was filtered, washed with a mixture of acetone and petroleum ether (1:9), and dried over CaCl₂ *in vacuo*. The yield was 60%. The compound decomposes without melting at ~115°C.

Cd(II) thiomalate and Hg(II) thiomalates: Complexes of 1:1 stoichiometry were prepared by the method of Patil and Krishnan⁸. Another Hg(II) complex, of 1:2 stoichiometry, reported in solution only^{1, 15, 16} was isolated as follows: 0.01 mol of Hg(CH₃COO)₂ and 0.02 mol of TMA were dissolved in 10 ml and 50 ml of methanol respectively. The mercuric acetate solution was added to TMA solution with constant stirring. The clear solution that resulted was concentrated to about 25 ml *in vacuo*. Benzene (about 15 ml) was added with constant stirring to separate a white product. This was filtered, washed with a mixture of benzene and methanol (80:20), and dried *in vacuo* over P₂O₅. The yield was 70%. The compound decomposes without melting at ~170°C.

Analysis

Ag(I) was determined volumetrically by Volhard's method^{17a}, and Hg(II) gravimetrically as sulphide^{17b} after decomposing the complexes with concentrated HNO₃. Sulphur was estimated^{17c} as BaSO₄ after decomposing the complex with Na₂CO₃ and

Na₂O₂. Carbon and hydrogen contents were estimated microanalytically on a CARLO ERBA model 1106 at RSIC, Chandigarh. The analytical data are given in table 1.

IR and ¹H NMR spectroscopic studies

The S-H stretching mode of TMA occurring near 2560 cm⁻¹ disappears in all the thiomalates, indicating the linkage of Ag(I) or Hg(II) with S of the sulphhydryl group. This is supported by C-S stretching frequencies of these complexes, which are shifted towards lower frequency (i.e. <660 cm⁻¹). The thiomalates show a strong band at 1680 cm⁻¹ which is due to free -COOH indicating the presence of at least one such -COOH group in all the compounds. Actually, in the case of Ag[C₄H₅O₄S], both the carboxylic groups appear to be free on the basis of ¹H NMR. The ¹H NMR spectrum of this complex clearly shows the presence of two carboxylic protons centred at δ 9.7 ppm. The -CH- proton appears as a triplet at δ 3.9 ppm, and two -CH₂- protons as a multiplet overlapping with peaks of impurity in DMSO-d₆ at δ 2.8 ppm.

However, in Ag₂[C₄H₄O₄S], the second silver atom may be coordinated to one of the carboxylate groups. A strong band around 1560 cm⁻¹ reflects the coordination of this group⁸ to Ag(I). Thus, in this complex, the TMA moiety acts as a bridge between two silver atoms. ¹H NMR spectra of this compound and Hg[C₄H₅O₄S]₂ could not be recorded because of their insolubility in common solvents. However, the presence of all the four -COOH groups in the free state was inferred by titrating this compound against NaOH; four moles of alkali were consumed when one mole of aqueous suspension of the complex was titrated against NaOH. This confirmed that mercury is bonded to both the S atoms of the sulphhydryl groups of two TMA molecules. The ν_{M-S} in these complexes is observed in the range 350-200 cm⁻¹ as a rather weak and broad band.

Table 1 Analytical data for TMA complexes

Complex	% Found (% calc.)			Metal
	Carbon	Hydrogen	Sulphur	
Ag ₂ [C ₄ H ₄ O ₄ S]	14.23 (13.19)	1.19 (1.10)	14.78 (13.73)	59.29 (59.29)
Ag[C ₄ H ₅ O ₄ S]	18.35 (18.68)	1.94 (1.95)	12.23 (12.45)	41.14 (41.97)
Hg[C ₄ H ₅ O ₄ S] ₂	19.32 (19.32)	2.01 (2.01)	11.73 (12.90)	41.67 (40.37)

Table 2 Antimicrobial activity of TMA and metal thiomalates

Compound	MIC ($\mu\text{g/ml}$)			
	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>C. albicans</i>
TMA	1000	500	500	*
$\text{Ag}_2[\text{C}_4\text{H}_4\text{O}_4\text{S}]$	250	250	250	500
$\text{Ag}[\text{C}_4\text{H}_5\text{O}_4\text{S}]$	*	*	*	*
$\text{Cd}[\text{C}_4\text{H}_4\text{O}_4\text{S}]$	250	250	250	500
$\text{Hg}[\text{C}_4\text{H}_4\text{O}_4\text{S}]$	**	**	**	**
$\text{Hg}[\text{C}_4\text{H}_5\text{O}_4\text{S}]_2$	**	**	125	250

*Active as neat samples only.

**Inactive.

A broad absorption ($3480\text{--}2600\text{ cm}^{-1}$) due to OH stretching and the presence of submaxima of varying intensity suggest polymeric nature for the compounds due to hydrogen bonding between free --COOH groups of neighbouring molecules^{18,19}. However, the asymmetric and symmetric C–H stretch vibrations ($\sim 2900\text{ cm}^{-1}$) of methylene and methine groups are also expected to overlap in this very region.

Formation of Ag_2S and HgS was found in thermogravimetric analysis of Ag(I) and Hg(II) thiomalate respectively. This supports the conclusion drawn from IR studies that the metal atoms are linked to the S atom of the sulphhydryl group.

Molecular weight and conductance measurements could not be carried out because of the low solubility of the complexes in common solvents.

Antimicrobial activity

TMA and its complexes were tested²⁰ for antimicrobial activity against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria and a fungus (*Candida albicans*). The minimum inhibitory concentrations (MIC) are listed in table 2. The data give a clear indication that antimicrobial activity of TMA is appreciably enhanced after complexation with metal ions.

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