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Synthesis, Spectral and Fungicidal Studies on Dioxobridged Binuclear Niobium(V) and Tantalum(V) Complexes of N-Alkylphenothiazines

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Six new dioxobridged binuclear complexes of the type $[MO(L)Z]_2Z$, where M=niobium(V) or tantalum(V), L=N-alkylphenothiazines (NAPs) and Z=tartrate and oxalate for niobium and tantalum respectively, were synthesized. The stoichiometry of the complexes was proposed on the basis of elemental analyses, molar conductance, magnetic and thermal data. The coordination behaviour of the ligands was determined with the help of spectroscopic studies. The fungicidal activity of the complexes was evaluated.

Introduction

Metal ion interactions with phenothiazines have been extensively studied both *in vivo* and *in vitro*. N-alkylphenothiazines are used in psychiatry¹ and chemotherapy². These biologically active compounds find extensive applications in the field of medicine³. In the pharmaceutical industry they are used as anticholinergic, antiemetic and antihistaminic drugs^{1,2}. They are excellent electron donors⁴ and exhibit low ionization potentials. Complexes of NAPs with copper(II)⁵, dioxouranium(VI)⁶ and lanthanides^{7,8} have been synthesized. In this continuation of our work, we report the synthesis, characterization and fungicidal studies of dioxobridged binuclear niobium(V) and tantalum(V) complexes of N-alkylphenothiazines, the structures of which are shown in Figure 1.

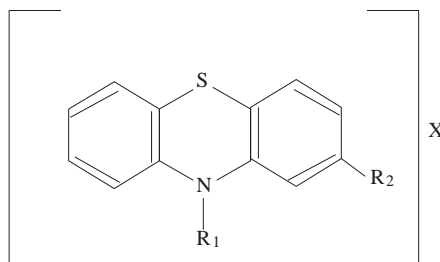


Figure 1. General structure of the N-alkylphenothiazines

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Methoxypromazine maleate (MPM)	:	$R_1 = (\text{CH}_2)_3\text{N}(\text{CH}_3)_2$; $R_2 = \text{OCH}_3$; $X = \text{C}_4\text{H}_4\text{O}_4$
Prochlorperazine dimaleate (PCPD)	:	$R_1 = (\text{CH}_2)_3\text{NC}_4\text{H}_8\text{NCH}_3$; $R_2 = \text{Cl}$; $X = 2\text{C}_4\text{H}_4\text{O}_4$
Butaperazine dimaleate (BPD)	:	$R_1 = (\text{CH}_2)_3\text{NC}_4\text{H}_8\text{NCH}_3$; $R_2 = \text{CO}(\text{CH}_2)_2\text{CH}_3$; $X = 2\text{C}_4\text{H}_4\text{O}_4$

Experimental

Starting Materials

The methoxypromazine maleate, prochlorperazine dimaleate and butaperazine dimaleate (Rhone poulenc, Paris, France, and A.G. Bayers, Leverkusen, Germany) were used as received. Niobium pentoxide, tantalum pentoxide, potassium pyrosulphate, tartaric acid, ammonium oxalate, ethanol, ether, dimethyl formamide (DMF) and dimethyl sulphoxide (DMSO) used were of AnalaR grade.

Analytical Procedures

The elemental analyses were determined with a Carlo-Erba 1106 analyser. Niobium and tantalum were estimated gravimetrically by direct ignition to M_2O_5 where M=niobium(V) or tantalum(V).

Physical Measurements

Molar conductance of the complexes was measured in 10^{-3} M DMF solutions using an Elico CM-82T conductivity bridge. The i.r. spectra of the samples in KBr pellets were recorded on a Shimadzu FTIR-470 spectrometer. ^1H -nmr spectra on a Hitachi R-600 spectrometer in deuterated DMSO using TMS as an internal standard and electronic spectra on a JASCO-UVIDEC-610 double beam spectrophotometer were recorded. The magnetic susceptibilities were determined by the Gouy method at room temperature using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as calibrant. Thermal analyses were carried out on a RIGAKU-TAS 100 electrobalance with a linear heating rate of $10^\circ\text{C min}^{-1}$ in static air.

Synthesis of the Complexes

Niobium(V) solution was prepared⁹ by the fusion of 0.126 g of niobium pentoxide with 5 g of potassium pyrosulphate and leaching the mass with 10% tartaric acid solution (30 ml). The solution was then diluted to 250 ml. Tantalum(V) solution was prepared⁹ by the fusion of 0.2580 g of tantalum pentoxide with 3 g of potassium pyrosulphate and dissolving the mass in 3% hot ammonium oxalate solution (25 ml). The solution was diluted to 250 ml. All the complexes were prepared according to the following general method. An ethanolic solution of NAP (4 m.mol) was added to an aqueous solution of niobium(V) (3 m.mol) with constant stirring. The complex precipitate was set aside for 1 hour, filtered, washed several times with ethanol followed by ether and dried under reduced pressure over fused CaCl_2 . In a similar way, tantalum(V) complexes were prepared by adding ethanolic solutions of NAPs (4 m.mol) to aqueous solutions of tantalum(V) (2.3 m.mol).

Fungicidal Studies

The fungicidal activity of the NAPs and the complexes was assayed against three different fungi namely, *Botryodiplodia theobromae*, *ceratocystis paradoxa* and *Lenzites trabea* at different concentrations by the poisoned food technique¹⁰. Experiments were conducted by using potato dextrose agar (PDA) and solutions of the NAPs and complexes prepared in 10% DMF were poured into petri plates containing PDA after solidification. The test fungi were taken as 2 mm dishes from a seven days old culture and were placed at the centre of the petri plates. The experiment was carried out with four replicates per treatment and incubation was conducted at $22 \pm 2^\circ\text{C}$ for eight days. The radial growth of the colony was recorded on the completion of the incubation and the mean diameter for each concentration was recorded. The average percentage inhibition of the fungicidal growth medium compared to the respective controls was calculated using the Vincent equation¹¹: $I=100 (C-T)/C$, where I=percentage inhibition, T=average diameter of the fungal growth on the tested plates and C=average diameter of the fungal growth on the control plates.

Results and Discussion

The interaction of aqueous niobium(V) or tantalum(V) solution with ethanolic solution of NAPs in the form of maleate or dimaleate yields the complexes. The maleate or dimaleate ion of the ligands go into solution during the reaction and do not participate in coordination with metal ions.

The analytical data of the complexes given in Table 1 suggest a general formula $[\text{MO}(\text{L})\text{Z}]_2\text{Z}$, where M= Nb(V) or Ta(V), L=NAP and Z=tartrate or oxalate. The complexes are non-hygroscopic and stable at room temperature. They are soluble in DMF and DMSO and insoluble in water and common organic solvents. They do not possess sharp melting points. The molar conductances in DMF are in the range of 65-90 $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$ for Nb-NAP complexes and 60-100 $\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$ for Ta-NAP complexes at 10^{-3}M concentration indicating the 1:1 electrolytic, nature of the complexes. The magnetic susceptibility values at room temperature indicate that the complexes are diamagnetic as expected for Nb(V) and Ta(V) complexes. These results are in consistent with the stoichiometry proposed for the complexes on the basis of analytical data.

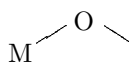
Table 1. Analytical data and molar conductance of the complexes

Complex	Colour	Found (calcd) %				Λ_M ($\text{ohm}^{-1} \text{cm}^2 \text{mol}^{-1}$)
		C	H	N	M	
$[\text{NbO}(\text{MP})\text{C}_4\text{H}_4\text{O}_6]_2 \text{C}_4\text{H}_4\text{O}_6$	Pale	44.04	4.33	4.32	14.34	65
	Yellow	(44.66)	(4.34)	(4.34)	(14.40)	
$[\text{NbO}(\text{PCP})\text{C}_4\text{H}_4\text{O}_6]_2 \text{C}_4\text{H}_4\text{O}_6$	Pink	43.78	4.24	5.94	13.16	72
		(44.29)	(4.26)	(5.96)	(13.19)	
$[\text{NbO}(\text{BP})\text{C}_4\text{H}_4\text{O}_6]_2 \text{C}_4\text{H}_4\text{O}_6$	Yellow	48.15	4.96	5.65	12.52	90
		(48.65)	(5.00)	(5.68)	(12.56)	
$[\text{TaO}(\text{MP})\text{C}_2\text{O}_4]_2 \text{C}_2\text{O}_4$	Pale	38.76	3.40	4.32	28.10	100
	Yellow	(39.19)	(3.42)	(4.35)	(28.14)	
$[\text{TaO}(\text{PCP})\text{C}_2\text{O}_4]_2 \text{C}_2\text{O}_4$	Pink	38.90	3.39	5.96	25.72	80
		(39.29)	(3.42)	(5.98)	(25.76)	
$[\text{TaO}(\text{BP})\text{C}_2\text{O}_4]_2 \text{C}_2\text{O}_4$	Yellow	43.64	4.12	5.67	24.48	60
		(43.90)	(4.20)	(5.69)	(24.52)	

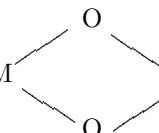
The electronic spectra of all the complexes in DMF show no absorption peaks in the visible region

since the intensities of their DMF solutions decrease continuously, probably owing to the interaction of the solvent with complexes. The electronic spectra of the ligands and the corresponding complexes show absorption bands in the 262-282 nm region attributable to the $\pi \rightarrow \pi^*$ transition. Bands in the 304-314 nm region in NAP may be assigned to the $n \rightarrow \pi^*$ transition. This band is slightly shifted towards the higher energy region in the spectra of the niobium(V) and tantalum(V)-NAP complexes evidently owing to coordination.

It was reported² that the ions R_3N^+H combined with Cl^- ion present in the molecules of NAP gives rise to a broad band at the 2500-2300 cm^{-1} region. A broad band observed at 2600-2350 cm^{-1} in the i.r. spectra of the free NAP corresponds to $-(CH_2)_3N^+H(CH_3)_2$ in MPM and $-(CH_2)_3HN^+C_4H_8NCH_3$ in PCPD and BPD combined with X^- anion (X^- =maleate or dimaleate). In the i.r. spectra of the corresponding niobium(V) and tantalum(V) complexes this band is absent indicating that the tertiary nitrogen atom of the side chain is a site of coordination. The selected i.r. frequencies are given in Table 2. It was pointed out that the heterocyclic nitrogen atom attached to the alkyl side chain gives rise to a characteristic broad band in the 2860-2825 cm^{-1} region¹². In the i.r. spectra of the corresponding complexes these bands are either absent or shifted to a higher frequency by 10-30 cm^{-1} in niobium complexes and 10-20 cm^{-1} in tantalum complexes, indicating that the heterocyclic nitrogen atom is another site of coordination. The new bands that appeared in the 395-375 cm^{-1} and 455-440 cm^{-1} regions may be assigned to $\nu(Nb-N)$ and $\nu(Ta-N)$ respectively. In aromatic derivatives, the $\nu(CSC)$ generally appears as a band of weak or moderate intensity in the 705-670 cm^{-1} region¹³. However, some difficulty was experienced in recognizing the $\nu(CSC)$ mode in NAPs due to the presence of the intense CH out-of-plane deformation band in this region¹⁴. In all the complexes it has been found that there is no change in $\nu(CSC)$, supporting the non-coordination of the heterocyclic sulphur atom. Thus i.r. spectra showed that NAPs act as bidentate ligands, coordinating to the metal through the heterocyclic and tertiary nitrogen atoms. The coordination of bidentate tartrate or oxalate is confirmed by the bands at 1710-1675 cm^{-1} (asymmetric COO vibration) and 1410-1375 cm^{-1} (symmetric COO vibration)¹⁵. Bands observed in the region 490-470 cm^{-1} correspond to

 M-O-M moiety. Presence of $\nu(M-O)$ modes has been excluded because of the absence of peaks in the

560-520 cm^{-1} region¹⁶. The complexes also exhibit two bands at 625-615 cm^{-1} and 480-465 cm^{-1} (when M = Nb) and 630-620 cm^{-1} and 430-415 cm^{-1} (when M=Ta) due to antisymmetric and symmetric vibrations

of the M  M bridge bond.

The ¹H-nmr spectra of both niobium(V) and tantalum(V) complexes exhibit chemical shifts at lower fields for N-CH₂ protons which appear at $\delta=2.75 - 2.90$ ppm and $\delta = 2.80 - 2.95$ ppm for niobium(V) and tantalum(V) complexes respectively when compared to that in the free NAPs $\delta=2.55 - 2.70$ ppm. This down-field shift in the signal of the complexes may be attributed to the coordinating effect of the nitrogen atom of the alkyl side chain, which results in a deshielding of the protons attached to it.

Table 2. Selected i.r. data (cm⁻¹) of M(V)- NAP complexes

Complex	$\nu_a(\text{OCO})$	$\nu_s(\text{OCO})$	$\nu_a(\text{M-O}_b)$	$\nu_s(\text{M-O})$	$\nu(\text{M-N})$
[NbO(MP)C ₄ H ₄ O ₆] ₂ C ₄ H ₄ O ₆	1705	1380	625	470	375
[NbO(PCP)C ₄ H ₄ O ₆] ₂ C ₄ H ₄ O ₆	1710	1405	620	480	385
[NbO(BP)C ₄ H ₄ O ₆] ₂ C ₄ H ₄ O ₆	1680	1410	615	465	395
[TaO(MP)C ₂ O ₄] ₂ C ₂ O ₄	1685	1385	625	415	450
[TaO(PCP)C ₂ O ₄] ₂ C ₂ O ₄	1675	1380	630	420	455
[TaO(BP)C ₂ O ₄] ₂ C ₂ O ₄	1710	1375	620	430	440

Thermogravimetric studies indicate that all the niobium(V)-NAP complexes are thermally stable up to 140°C and tantalum(V)-NAP complexes up to 150°C. The decomposition takes place in two steps, namely the decomposition of organic moiety and the loss of tartrate or oxalate followed by the formation of M₂O₅ in the temperature ranges of 260-310°C and 350-520°C respectively in niobium complexes and 170-390°C and 510-630°C respectively in tantalum complexes. The weight loss became constant at 670°C in both complexes. The weight loss observed in each case was in good agreement with the weight loss calculated on the basis of the stoichiometry proposed for the complexes in static air.

The screening data of average percentage inhibition of the fungi at 0.01, 0.25 and 0.5% concentrations for the complexes, metal ion solutions and NAPs are given in Table 3. The data reveals that the complexes display greater fungitoxicity compared to the free NAPs. The possible explanation for the toxicity of the complexes can be explained by chelation theory¹⁷. It was suggested that chelation reduces the polarity of the metal ion considerably mainly because its positive charge is partially shared with donor atoms and π -electron delocalization over the whole chelating ring is feasible. This increases the lipophilic character of the metal chelates, which favours its permeation through lipid layers of the fungus membranes.

Table 3. Screening data of M(V)-NAP complexes

Compound	Average % inhibition								
	Botryodiplodia theobromae			Ceratocystis paradoxa			Lenzites trabea		
	0.01	0.25	0.5	0.01	0.25	0.5	0.01	0.25	0.5
[NbO(MP)C ₄ H ₄ O ₆] ₂ C ₄ H ₄ O ₆	9.8	26.3	61.2	10.2	22.5	62.8	10.5	23.2	61.6
[NbO(PCP)C ₄ H ₄ O ₆] ₂ C ₄ H ₄ O ₆	10.6	30.3	62.6	12.2	25.8	62.0	10.1	22.4	64.3
[NbO(BP)C ₄ H ₄ O ₆] ₂ C ₄ H ₄ O ₆	10.3	28.6	61.8	11.3	24.2	61.4	9.6	21.8	63.8
[TaO(MP)C ₂ O ₄] ₂ C ₂ O ₄	11.2	29.2	63.0	9.9	31.8	63.8	10.8	32.7	62.8
[TaO(PCP)C ₂ O ₄] ₂ C ₂ O ₄	9.8	30.1	64.4	12.4	31.5	63.2	9.8	30.8	63.7
[TaO(BP)C ₂ O ₄] ₂ C ₂ O ₄	9.7	29.3	64.1	12.1	32.0	63.6	11.8	31.8	62.9
Niobium(V) solution	3-4	7-9	19-21	3-4	7-8	21-22	3-5	8-9	21-23
Tantalum(V) solution	3-5	10-12	20-22	4-6	11-13	23-24	4-5	10-12	23-25
N-alkylphenothiazines	2-3	5-6	9-11	3-4	6-7	8-9	2-3	5-6	9-11

Conclusion

None of the complexes gave crystals of sufficient quality to permit X-ray crystallographic analyses. Based on the above discussion, we propose a tentative six coordinated dioxobridged binuclear structure for both niobium(V) and tantalum(V)- NAP complexes. A general structure of the complexes is given in Figure 2 with PCPD as the ligand.

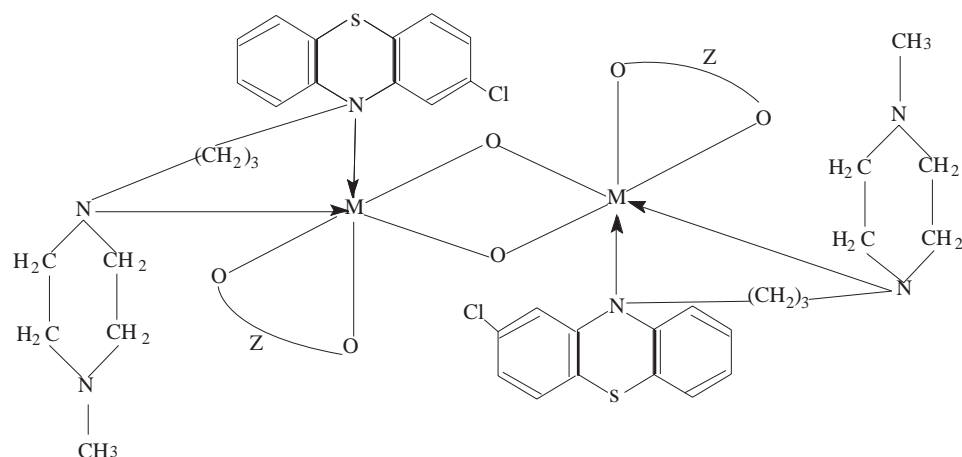


Figure 2: Structure of M(V) - PCP complex. M=Nb(V) or Ta (V) and Z = tartrate for Nb(V) and oxalate for Ta(V), PCP = prochlorperazine

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