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Synthesis and Structural Investigation of Biologically Active Complexes of *N*-Alkylphenothiazines with Dioxouranium(VI)

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Abstract

Six *N*-alkylphenothiazines (NAP) have been used to synthesize the complexes of the general formula $[UO_2(OAc)_2L(H_2O)_2]$ where L = NAP. The complexes have been characterised on the basis of their elemental analysis, molar conductance, magnetic susceptibility, spectral and thermal data. Probable structures for the complexes have been proposed on the basis of their physico-chemical properties. The fungicidal activity of NAP and the isolated dioxouranium(VI) complexes has been tested.

Introduction

N-alkylphenothiazines have been reported to be biologically versatile compounds, possessing anticholinergic, antihistamine, antiamoebic and fungicidal activities [1, 2]. The importance of the toxicity in the compounds containing nitrogen and sulphur have been well established in many fungicides [3]. It is known that the metal complexes have greater activity than the ligands themselves. Furthermore, NAP are widely used in the treatment of mental retardation [2]. Formation of complexes or cation radicals between platinum metals and phenothiazines in aqueous medium has provided a basis for the spectrophotometric determination of platinum metals [4–7]. Hence it seemed worthwhile to study the complexes of NAP with dioxouranium(VI). In the present paper, the authors report the isolation and characterisation of dioxouranium(VI) complexes with *N*-alkylphenothiazines.

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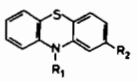
Experimental

Uranylacetate dihydrate, chlorpromazine hydrochloride (CPH), promethazine hydrochloride (PMH), mepazine hydrochloride (MH), perazine dimalonate (PDM), propionyl promazine phosphate (PPP) and propericiazine (PPC) were used as received. The trivial and systematic names of the above NAP are given in Table I.

TABLE I. *N*-Alkylphenothiazines



Trivial and systematic names of the ligand	R_1	R_2
Chlorpromazine hydrochloride (CPH) 2-Chloro-10(γ-dimethyl amino-propyl)phenothiazine	$-(CH_2)_3NMe_2$	–Cl
Promethazine hydrochloride (PMH) 10-(2-Dimethylamino-1-propyl)phenothiazine	$-CH_2CHMeNMe_2$	
Mepazine hydrochloride (MH) 10-[(1-Methyl-3-piperidyl)methyl]phenothiazine	$-CH_2CH(CH_2)_4NMe$	
Perazine dimalonate (PDM) 10-[3-(4-Methyl-1-piperazinyl)propyl]phenothiazine	$-(CH_2)_3(CH_2)_4NMe$	
Propionylpromazine phosphate (PPP) 1-10[3-Dimethylamino)propyl]phenothiazine-2-yl-propanone	$-(CH_2)_3NMe_2$	$-COCH_2Me$
Propericiazine (PPC) 2-Cyano-10-[3-(4-hydroxypiperidino)propyl]phenothiazine	$-(CH_2)_3NC_5H_9OH$	–CN

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TABLE II. Analytical and Conductance Data for the NAP Complexes of Dioxouranium(VI)

Complex	Elemental analysis (%)[a]				Ω
	C	H	N	U	
$[UO_2(OAc)_2CP(H_2O)_2]$	34.0 (33.9)	3.8 (3.9)	3.7 (3.8)	31.4 (32.0)	44.0
$[UO_2(OAc)_2PM(H_2O)_2]$	35.9 (35.6)	4.5 (4.2)	3.5 (3.9)	33.2 (33.6)	48.5
$[UO_2(OAc)_2M(H_2O)_2]$	37.1 (37.6)	4.7 (4.4)	3.7 (3.8)	32.9 (32.4)	45.8
$[UO_2(OAc)_2P(H_2O)_2]$	37.5 (37.7)	4.3 (4.6)	5.5 (5.6)	31.8 (31.2)	49.5
$[UO_2(OAc)_2PP(H_2O)_2]$	38.6 (38.7)	4.8 (4.4)	3.8 (3.6)	30.9 (30.7)	48.6
$[UO_2(OAc)_2PPC(H_2O)_2]$	38.6 (38.0)	4.3 (4.2)	5.1 (5.3)	30.5 (30.2)	50.0

[a]Calculated values are given in parentheses.

Synthesis of the Complexes

An aqueous solution of PPP or PDM (0.5 g in 100 cm^3) was added with constant stirring to an aqueous solution of uranyl acetate dihydrate (0.42 g in 100 cm^3) at room temperature. The complexes formed instantaneously were filtered and dried *in vacuo* with 60% yield.

The complexes of CPH, PH, MH and PPC were prepared by refluxing aqueous solutions of the ligands (1.0 g in 90 cm^3) with uranyl acetate dihydrate (0.50 g in 100 cm^3) for six hours and cooling under ice-cold water for four days. The complexes separated were filtered and dried *in vacuo* with 50% yield.

Analyses

Analyses for carbon, hydrogen and nitrogen were performed at Bio-organic Chemistry Division, Bhaba Atomic Research Centre, Bombay, India. Uranium was estimated gravimetrically by direct ignition to U_3O_8.

Physical Measurements

The magnetic susceptibilities were determined by the Gouy method at room temperature using Hg-$[Co(SCN)_4]$ as calibrant. The IR spectra of samples in KBr pellets were recorded on a Perkin-Elmer spectrophotometer model 781. Far IR spectra were recorded using polythene discs on a polytech far IR spectrophotometer model 30. The visible and UV spectra of the complexes in dimethylformamide (DMF) were measured on a Beckman spectrophotometer model DB. The molar conductance of the complexes was measured on 10^{-3} M DMF solutions using Philips PR 9500 conductivity bridge. Thermal analysis was carried out on a Stanton Redcraft TG 750/770 electrobalance with a heating rate 6 °C min^{-1} in air. X-ray diffraction data was obtained with a Jeol X-ray diffractometer model JDX 8 P.

The antifungal activity of the ligands and the complexes was assayed against three different fungi namely Batryodiphodia (Sp.), Schizophyllum (Sp.) and Penicillium (Sp.). The solutions of the ligands and the complexes were prepared in 10% DMF solution and the nutritive medium for the growth of the algae consisted of 2% malt and 2% Agar Agar in distilled water. The growth inhibition percentage was calculated on the basis of the average diameter of the fungal colony.

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

where C = diameter of the fungus colony in the control plates after 7 days and T = diameter of the fungus colony in the treated plates after 7 days.

Results and Discussion

The interaction of dioxouranium(VI) acetate dihydrate with NAP results in the formation of the complexes with the formula $[UO_2(OAc)_2L(H_2O)_2]$ where L = NAP, which correspond to the analytical data presented in Table II. The complexes are stable, non hygroscopic and yellow or orange yellow coloured solids. They are insoluble in water and common organic solvents but are soluble in DMF and dimethyl sulphoxide. The complexes do not possess sharp melting points. The molar conductance, in DMF are in the range 44–50 ohm^{-1} cm^2 mol^{-1} (Table II) indicating the non-electrolytic nature [8] of the complexes. The magnetic susceptibility measurements at room temperature indicate that the complexes are diamagnetic as expected for dioxouranium(VI) complexes. The results are consistent with the stoichiometry proposed on the basis of analytical data.

Infrared Spectra

The selected IR frequencies of the dioxouranium-(VI) complexes are given in Table III. All the complexes exhibit a strong band at 940–910 cm^{-1} characteristic of the asymmetric frequency ν_3 of the dioxouranium ion [9]. The sharp band at 1650–1605 cm^{-1} confirms the $\nu_{asym}(COO)$ of acetate indicating

TABLE III. Selected IR Spectral Data (cm^{-1}) for the NAP Complexes of Dioxouranium(VI)

Complex	ν_{asym}(O=U=O)	ν(U–N)	ν_{asym}(COO)
$[UO_2(OAc)_2CP(H_2O)_2]$	940	440	1610
$[UO_2(OAc)_2PM(H_2O)_2]$	915	462	1625
$[UO_2(OAc)_2M(H_2O)_2]$	935	434	1640
$[UO_2(OAc)_2P(H_2O)_2]$	910	436	1645
$[UO_2(OAc)_2PP(H_2O)_2]$	920	450	1630
$[UO_2(OAc)_2PPC(H_2O)_2]$	925	460	1650

thereby the unidentate coordination of acetate ion [10]. The presence of a strong and broad band around 3540–3350 cm^{-1} may be due to coordinated water molecules. Bands observed in the 2860–2825 cm^{-1} region in the IR spectra of NAP may be due to the heterocyclic nitrogen atom attached to an alkyl group [2]. In the IR spectra of the corresponding complexes this band had disappeared completely suggesting the coordination of heterocyclic nitrogen atom.

In the *N*-alkylphenothiazine drugs, $-R_3NH^+$ interaction with Cl^- gives rise to a broad band in the 2500–2300 cm^{-1} region [2]. A broad band observed in the 2610–2335 cm^{-1} region in the IR spectra of the ligands corresponds to the $-CH_2NR_2H^+$ together with X^- (X = Cl, PO_4 or malonate). In the IR spectra of the corresponding complexes of dioxouranium(VI), this band had totally disappeared indicating that the tertiary nitrogen atom of the side chain is the another site of coordination. The medium intense bands at 465–435 cm^{-1} may be assigned to ν(U–N) [11] modes. Thus NAP acts as bidentate ligand.

Electronic Spectra

The electronic spectra of all dioxouranium(VI) complexes exhibit a band at 410–435 nm which is assigned to the $^1E_g \rightarrow {}^3\pi_u$ transition [11, 12] typical of the UO_2^{2+} moiety. The band at 248–262 nm region found in the NAP and their corresponding complexes may be assigned to $\pi \rightarrow \pi^*$ transition. The band found in the 300–320 nm region in the NAP may be attributed to the $n \rightarrow \pi^*$ transition. This band is found slightly shifted towards higher energy region in the spectra of the complexes, evidently due to coordination.

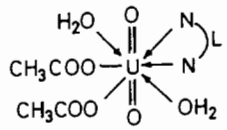
Thermogravimetry (TG) and Differential Thermal Analysis (DTA)

TG studies indicate the coordination of water molecules in the complexes and that the decomposition occurs in two steps. The first step consists of the loss of coordinated water molecules in the temperature range *ca.* 110–240 °C. The second step involves the decomposition of the organic moiety and oxidation ultimately to form U_3O_8. The weight loss became constant at *ca.* 640 °C and the weight loss agreed with that calculated on the basis of the stoichiometry proposed for the complexes. The final product U_3O_8, was identified by X-ray diffraction data. The DTA studies show that the loss of water molecules was accompanied by an endothermic peak at *ca.* 150–200 °C and the formation of U_3O_8 resulting in the exothermic peak at *ca.* 520–550 °C.

Antifungal Activity

It was found that the maximum concentrations of *N*-alkylphenothiazines, $UO_2(OAc)_2 \cdot 2H_2O$ and their corresponding complexes required to inhibit the complete growth of the three fungi are 20–25, 2–5 and 0.25–0.85% respectively.

In the light of foregoing discussion, the following structure has been proposed for the dioxouranium(VI)–NAP complexes:



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