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Investigations on Biologically Active Complexes of Thorium(IV) with N-alkylphenothiazines

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Eight coordinated complexes of thorium(IV) with six N-alkylphenothiazines (NAP) have been synthesized and characterized by spectral, analytical, conductometric and thermogravimetric studies. The empirical formula of the complexes corresponds to $[Th(L)_2(NO_3)_2](NO_3)_2$ (where L = NAP). The IR spectra suggest coordination of both the phenothiazine and nitrate groups in a bidentate fashion. The antibacterial screenings of all the complexes were studied against several bacteriae.

INTRODUCTION

Metal ion interactions with phenothiazines have been extensively studied both *in vivo* and *in vitro*. N-alkylphenothiazines (NAP) are biologically active compounds which find extensive applications in the fields of medicine[1] and chemical analysis.[2] In the pharmaceutical industry they are used as psychotherapeutic, antiemetic and antihistaminic drugs.[3] The study of metal-phenothiazine complexes has gained much importance in recent years due to their potential pharmacological activities.[4] The possible use of metal-phenothiazine complexes as fungicides and a considerable increase in the fungicidal activity by complexation of phenothiazines with tungsten(IV) and dioxouranium(VI) has been investigated.[5, 6] As the chemistry of thorium provides a potential for studying with high coordination numbers, it has been extensively studied.[7, 8] Thorium(IV) with an ionic radius of 0.99 Å and four positive charges fulfills the optimum conditions required for high coordination. In view of the above, it was considered worthwhile to isolate, characterize and investigate the antibacterial activities of thorium(IV) complexes with N-alkylphenothiazines.

EXPERIMENTAL

Elemental analyses were performed at the Regional Sophisticated Instrumentation Centre, Madras. Thorium content of the complexes was determined gravimetrically by oxalate-oxide method[9] and ionic nitrate was estimated gravimetrically using nitron.[9]

IR spectra were recorded on a Biorad SPC 3200 IR spectrometer using KBr pellet and far IR spectra on Bruker IFS 66V spectrometer using polyethylene pellets technique. UV spectra were recorded on a JASCO UVIDEC 610 double beam spectrophotometer. ^1H NMR spectral data were obtained on FT NMR R 600 HITACHI spectrometer in DMSO-d_6 using TMS as internal standard. Conductivity measurements were made with 10^{-3}M solution on a digital Equiuptronics conductivity bridge using DMF as solvent. Magnetic susceptibilities were determined by Gouy method at room temperature using $Hg[Co(SCN)_4]$ as calibrant. Thermal analysis was carried out on Rigaku-TGA electrobalance with linear heating rate of 10°C min^{-1} in static air.

Preparation of complexes

A concentrated solution of (6 mmole) chloropromazine hydrochloride (CPH), promethazine hydrochloride (PMH) and trifluoperazine hydrochloride (TFPH) in minimum amount of ethanol was added slowly, with vigorous stirring, to ethanolic solution of thorium nitrate (2.5 m mole). The solid complexes formed immediately were filtered, washed several times with ethanol followed by diethyl ether and dried in vacuum over fused $CaCl_2$.

Complexes of perazine (PZ) and propericiazine (PPC) were prepared by refluxing methanolic solution of thorium nitrate and N-alkylphenothiazines for 4 h in 1 : 2 molar ratio.

In a similar way, by refluxing aqueous solution of thorium nitrate and butaperazine dimaleinate (BPD) with equal volume of benzene for 2 h, the corresponding complex of thorium was prepared.

RESULTS AND DISCUSSION

The interaction of thorium nitrate with NAP results in the formation of thorium(IV)-NAP complexes with an empirical formula $[Th(L)_2(NO_3)_2](NO_3)_2$, (L = NAP) which corresponds to the analytical data presented in Table 1. The complexes are coloured, non-hygroscopic and stable at room temperature for long periods. They are insoluble in water and other common organic solvents, but are soluble in DMF and DMSO. They do not possess sharp melting points. The molar conductance values fall in the range 130–170 ohm^{-1} mol^{-1} cm^2 at 10^{-3} M concentration suggesting the 1 : 2 electrolytic behaviour of the complexes (Table-1). Magnetic susceptibility measurements proved that the complexes are diamagnetic as expected for thorium(IV) complexes. The results are consistent with the stoichiometry proposed for the complexes on the basis of analytical data.

Electronic spectra: The electronic spectra of all the complexes in DMF show no absorption peaks in visible region. The free NAP ligands show a sharp band in the 254–270 nm and a weak broad band in the 306–316 nm regions, while their corresponding complexes exhibit peaks in 265–280 nm and 304–312 nm region, which are attributable to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions respectively. These shifts may be evidently due to coordination effect.

Infrared spectra: The relevant IR absorption frequencies of thorium(IV)-NAP complexes are given in Table-1. Broad bands in the range 2600–2350 cm^{-1} in the free NAP ligands[3] due to the interaction of $—CH_2NR_2H^+$ (R = methyl or pentyl) with X^- (X = chloride or maleinate) are found to either disappear or reduce to a small hump in the corresponding complexes showing that a tertiary nitrogen atom of the alkyl side chain is involved in coordination to the metal. Presence of bands in the region 2860–2826 cm^{-1} assigned to the heterocyclic nitrogen atom attached to alkyl group in the IR spectra of the free NAP ligands, suffered a significant positive shift in their corresponding complexes suggesting the participation of the heterocyclic nitrogen atom in coordination. Thus the IR

TABLE-1

ANALYTICAL, MOLAR CONDUCTANCE AND MAIN IR SPECTRAL DATA (cm^{-1}) OF THORIUM(IV)-NAP COMPLEXES

Complex	Elemental analysis, Found (Calcd.) %				NO_3 (ionic)*	Λ_M (ohm^{-1} $mole^{-1}$ cm^2)	NO_3 (ionic)	(NO_3) (coordinated)				ν(Th—N)
	C	H	N	Th								
$[Th(CP)_2(NO_3)_2](NO_3)_2$	36.28 (36.49)	3.62 (3.57)	9.98 (10.01)	21.05 (20.75)	0.1110 (0.1100)	147	1380, 830	1490	1280	1040	810	515
$[Th(PM)_2(NO_3)_2](NO_3)_2$	38.76 (38.94)	3.92 (3.81)	10.56 (10.68)	22.15 (22.13)	0.1183 (0.1188)	170	1382, 825	1494	1284	1036	812	480
$[Th(TFP)_2(NO_3)_2](NO_3)_2$	39.22 (38.94)	3.68 (3.70)	10.76 (10.81)	17.81 (17.92)	0.0958 (0.0962)	130	1388, 828	1496	1288	1038	808	520
$[Th(BP)_2(NO_3)_2](NO_3)_2$	44.68 (44.37)	4.64 (4.77)	10.84 (10.78)	18.02 (17.87)	0.0955 (0.0948)	135	1375, 820	1488	1290	1035	815	460
$[Th(PZ)_2(NO_3)_2](NO_3)_2$	41.05 (41.45)	4.40 (4.31)	11.98 (12.08)	21.96 (20.03)	0.1070 (0.1062)	140	1382, 825	1492	1286	1042	810	490
$[Th(PPC)_2(NO_3)_2](NO_3)_2$	41.32 (41.72)	3.52 (3.64)	11.46 (11.58)	18.98 (19.20)	0.1026 (0.1034)	148	1378, 830	1494	1288	1038	805	485

*Sample taken for nitrate estimation = 1.0 g spectral studies suggest that N-alkylphenothiazines act as bidentate chelates. The sharp band around 750 cm^{-1} observed in the spectra of NAP assignable to ν(CSC) stretching frequency[10] remains unaffected in the spectra of the corresponding complexes supporting the non-coordination of heterocyclic sulphur atom. IR spectra of the nitrate complexes exhibit four bands at 1496 (ν_4), 1285 (ν_1), 1038 (ν_5) and 810 (ν_3) cm^{-1} which can be assigned to the vibrational modes of the coordinated (C_{2v}) nitrate groups. The magnitude of splitting of the two bands at higher energies of about 208 cm^{-1} suggest that nitrate groups are present as bidentate ligands.[11] The bands observed at about 1380 cm^{-1} and 830 cm^{-1} region indicate the presence of ionic nitrate groups[12]. This shows that these complexes have both ionic and coordinate nitrate groups. The new bands recorded at 520–450 cm^{-1} in the far IR region are due to the stretching mode of the metal-nitrogen bands[13].

^1H NMR spectra: The ^1H NMR spectra of the ligands BPD and PZ and their corresponding complexes are recorded in DMSO-d_6. A multiplet found at 0.98 ppm in the spectra of BPD and thorium(IV)-BP complex is due to methyl protons of $CO(CH_2)_3CH_3$ group. The methylene protons of the above group give rise to a multiplet structure at 1.74 ppm. A broad multiplet appearing in the spectra of BPD and its thorium(IV) complex at 2.60 and 3.02 ppm respectively correspond to the methyl protons of N—CH_3 and N—CH_2 protons of the piperazine ring. These peaks are found to be shifted to lower frequency region ($\delta = 2.9$ and 3.12 ppm respectively) in the complex. In the spectra of BPD, a sharp signal at 6.15 ppm is due to —CH proton of the maleinate ion, which disappears in the spectra of the complexes indicating the absence of maleinate in the complex.

In the spectra of perazine and its complex, the N—CH_3 protons are the highly shielded ones followed by the methylene protons of the alkyl side chain (N—CH_3). The methylene protons of the piperazine ring and methylene protons of the alkyl side chain absorb at approximately the same field and hence a triplet is obtained in the spectra of PZ and its complex. A multiplet appearing in the region 6.8–7.1 ppm in BPD and its complex and 7.0–8.0 ppm in PZ and its complex may be assigned to the —CH protons of the benzene rings. The absorption peaks associated with the groups attached to nitrogen observed in the spectra of N-alkylphenothiazines are found to be shifted downfield in the spectra of the corresponding thorium(IV) complexes, probably due to coordinating effect of the nitrogen atom which results in the deshielding of the protons attached to it.

Thermogravimetric studies: Thermogravimetric results indicate that all thorium(IV)-NAP complexes are stable up to 250°C which shows that there are no coordinated solvent molecules. The pyrolysis data suggest that the complexes undergo two-stage decomposition in the temperature ranges 260–330°C and 360–640°C due to the loss of organic moiety and nitrate followed by the formation of ThO_2. The weight loss became constant around 700°C. The experimental results are in good agreement with the calculated values on the basis of stoichiometry proposed for the complexes.

Antibacterial activity: The antibacterial activities of the ligands and their complexes at 0.1, 0.2 and 0.3% concentrations were tested against three bacteria namely, *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* and the results are given in Table-2. The results show that NAP and thorium nitrate solutions are less active against bacteria. The activity is found to be enhanced on complexation. Thus antibacterial activity of thorium(IV)-phenothiazine complexes is greater than the free N-alkylphenothiazines. This is due to complexation which reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with donor group and possible π-electron delocalization over the whole complex molecule.

TABLE-2
ANTIBACTERIAL SCREENING DATA OF THORIUM(IV)-NAP COMPLEXES

Complex	Average inhibition zone (in mm)								
	E. coli (%)			*S. aureus* sp. (%)			*B. subtilis* (%)		
	0.1	0.2	0.3	0.1	0.2	0.3	0.1	0.2	0.3
$[Th(CP)_2(NO_3)_2](NO_3)_2$	1.0	2.5	4.0	1.0	2.0	4.5	1.5	3.0	4.5
$[Th(PM)_2(NO_3)_2](NO_3)_2$	1.0	2.0	3.5	1.0	2.5	4.5	2.0	3.5	5.0
$[Th(TFP)_2(NO_3)_2](NO_3)_2$	1.0	2.0	3.5	1.5	3.0	4.5	2.0	3.0	4.5
$[Th(BP)_2(NO_3)_2](NO_3)_2$	0.5	2.0	3.0	1.5	2.5	4.0	1.5	3.5	5.0
$[Th(PZ)_2(NO_3)_2](NO_3)_2$	1.0	2.5	4.0	1.0	2.5	4.0	1.5	3.0	4.5
$[Th(PPC)_2(NO_3)_2](NO_3)_2$	1.5	3.5	5.0	1.5	3.0	4.5	1.5	3.5	5.0
N-alkylphenothiazines	—	—	0.5	—	—	0.5	—	—	0.5
Thorium nitrate	—	—	0.5	—	—	0.5	—	—	0.5

In conclusion, the work presented shows that in all thorium(IV)-NAP complexes thorium is surrounded by four oxygen atoms from two nitrate groups and four nitrogen atoms from two N-alkylphenothiazines showing a coordination number of eight.

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