

Synthesis and structural investigation of biologically active complexes of lanthanide with chlorpromazine

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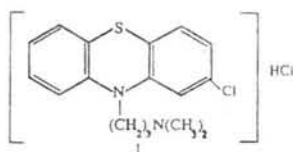
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Fourteen new complexes of lanthanide(III) nitrate with chlorpromazine as ligand have been synthesised with the general formula $[Ln(CP)_2(NO_3)_2]NO_3$ where Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu and CP = chlorpromazine. The complexes have been characterized on the basis of their elemental analysis, molar conductance, magnetic susceptibility, spectral, thermal and XRD data. Electronic spectral parameters (β , $b^{1/2}$, $\delta\%$, η) have been calculated for praseodymium(III), neodymium(III) and erbium(III) complexes. Probable structures for the complexes have been proposed on the basis of their physico-chemical studies. The fungicidal activity of the ligand and some of the isolated lanthanide(III) nitrate complexes have been tested.

During the last ten years lanthanide(III) chelates have gained considerable importance because of their numerous different uses. Due to their excellent luminescence properties, lanthanide(III) chelates are employed as markers in chemical and biological applications or *in situ* fluorescence imaging¹⁻⁴. On the other hand, they are utilized as paramagnetic shift reagents or relaxation agents in NMR spectroscopy and imaging^{5,6}. N-Alkylphenothiazines have been reported to be biologically versatile compounds possessing anticholinergic, antihistamine, antiamebic and fungicidal activities⁷. Recently, a considerable increase in the biological activity of phenothiazines on complexation with copper(II), molybdenum(IV), dioxouranium(VI), titanium(IV) and thorium(IV) have been reported⁸⁻¹². Hence it seemed worthwhile to study the complexes of phenothiazines with lanthanides. In the present paper, the authors report the isolation, structural investigation and fungicidal activities of complexes of lanthanide(III) nitrates with chlorpromazine. The chlorpromazine hydrochloride is shown in Structure I.

Materials and Methods

Chlorpromazine hydrochloride and the nitrates of



Ho, Er, Tm, Yb and Lu were received from Aldrich Chemical Company, Milwaukee, W.I., USA and of La, Ce, Pr, Nd, Sm, Eu, Gd, Tb and Dy were obtained from Indian Rare Earths Ltd., Trivandram, India.

Preparation of the complexes

An aqueous solution of chlorpromazine hydrochloride (30 ml, 3.93 mmol) was added with constant stirring to an aqueous solution of lanthanide(III) nitrate (30 ml, 1.10-1.15 mmol) at room temperature. The complexes separated were kept aside for 1h, filtered, washed several times with water followed by ethanol and dried *in vacuo* over fused $CaCl_2$. The yield varied from 60-75%.

The carbon, hydrogen and nitrogen contents were determined with a Carlo Erba 1106 elemental analyser. Metal content of the complexes was estimated by complexometric EDTA titration using xylenol orange as indicator¹³ and ionic nitrate content was estimated gravimetrically using nitron as nitron nitrate¹⁴ after dissolving in 2N sulphuric acid.

Molar conductance of the complexes were measured in 10^{-3} M DMF solutions using an ELICO model CM-82 T conductivity bridge. The magnetic measurements were recorded at room temperature by Gouy method using $Hg[Co(SCN)_4]$ as calibrant. The IR spectra of the ligand and the complexes were recorded on Shimadzu FT IR model 470 spectrometer using KBr disc technique. Electronic spectra in DMF were measured on a JASCO UVIDEDEC-610 double beam spectrophotometer. The ¹H NMR spectra were

Table 1—Characterization data of lanthanide(III) nitrate-CP complexes

	Found (Calcd.), %				NO ₃ ⁻ (ionic) ^a	Λ _M ^b	μ _{eff} B M
	Ln	C	H	N			
[La(CP) ₂ (NO ₃) ₂]NO ₃	14.40 (14.42)	42.40 (42.42)	3.97 (3.98)	10.16 (10.18)	0.0642 (0.0644)	85.34	Dia
[Ce(CP) ₂ (NO ₃) ₂]NO ₃	14.48 (14.53)	42.32 (42.36)	3.95 (3.97)	10.13 (10.17)	0.0642 (0.0643)	87.97	2.62
[Pr(CP) ₂ (NO ₃) ₂]NO ₃	14.55 (14.60)	42.30 (42.33)	3.96 (3.97)	10.15 (10.16)	0.0641 (0.0642)	90.78	3.56
[Nd(CP) ₂ (NO ₃) ₂]NO ₃	14.86 (14.90)	42.15 (42.18)	3.94 (3.95)	10.10 (10.12)	0.0638 (0.0640)	86.20	3.65
[Sm(CP) ₂ (NO ₃) ₂]NO ₃	15.38 (15.43)	41.90 (41.92)	3.91 (3.93)	10.02 (10.06)	0.0634 (0.0636)	70.64	1.83
[Eu(CP) ₂ (NO ₃) ₂]NO ₃	15.55 (15.57)	41.83 (41.85)	3.90 (3.92)	10.03 (10.04)	0.0635 (0.0635)	87.08	3.63
[Gd(CP) ₂ (NO ₃) ₂]NO ₃	16.00 (16.02)	41.58 (41.62)	3.88 (3.90)	9.95 (9.99)	0.0630 (0.0632)	88.89	7.57
[Tb(CP) ₂ (NO ₃) ₂]NO ₃	16.15 (16.17)	41.51 (41.55)	3.87 (3.89)	9.94 (9.97)	0.0628 (0.0630)	91.76	9.37
[Dy(CP) ₂ (NO ₃) ₂]NO ₃	16.43 (16.47)	41.38 (41.40)	3.87 (3.88)	9.93 (9.94)	0.0627 (0.0628)	87.97	10.58
[Ho(CP) ₂ (NO ₃) ₂]NO ₃	16.63 (16.68)	41.25 (41.30)	3.86 (3.87)	9.90 (9.91)	0.0625 (0.0627)	92.78	10.38
[Er(CP) ₂ (NO ₃) ₂]NO ₃	16.84 (16.87)	41.16 (41.20)	3.85 (3.86)	9.87 (9.89)	0.0623 (0.0625)	87.97	9.30
[Tm(CP) ₂ (NO ₃) ₂]NO ₃	16.98 (17.01)	41.12 (41.13)	3.83 (3.85)	9.85 (9.87)	0.0622 (0.0624)	87.08	7.68
[Yb(CP) ₂ (NO ₃) ₂]NO ₃	17.30 (17.35)	40.92 (40.96)	3.83 (3.84)	9.80 (9.83)	0.0620 (0.0622)	71.11	4.75
[Lu(CP) ₂ (NO ₃) ₂]NO ₃	17.47 (17.51)	40.85 (40.89)	3.82 (3.83)	9.76 (9.81)	0.0618 (0.0620)	92.76	Dia

^aSample taken for estimation of ionic nitrate=1.0g.

^b(Ohm⁻¹cm²mol⁻¹) in DMF as solvent

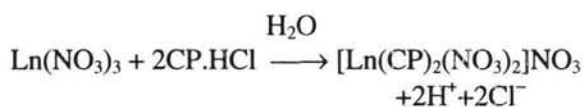
recorded on FT NMR R-600 HITACHI Spectrometer. Thermal analyses were carried out on RIGAKU-TGA instrument with a linear heating rate of 10°C min⁻¹ in static air. X-ray powder patterns were recorded on JEOL JDX-8P X-ray diffractometer using iron target.

Antifungal studies

Lanthanide nitrates, chlorpromazine hydrochloride and some of the corresponding lanthanide(III) complexes were tested against *Aspergillus niger*, *Aspergillus flavus* and *Trichoderma harzianum* at different concentrations by Batemann poisoned food technique¹⁵. The experiments were conducted using potato dextrose agar (PDA).

Results and Discussion

The reaction between aqueous solutions of lanthanide(III) nitrates and chlorpromazine hydrochloride results in the formation of complexes with the general formula [Ln(CP)₂(NO₃)₂]NO₃. The following general equation represents the stoichiometric reaction.



The complexes are non-hygroscopic and stable at room temperature for long periods. All the complexes are soluble in dil. sulphuric acid, DMF,

Table 2—Electronic spectral data of praseodymium(III), neodymium(III) and erbium(III) complexes

Ln(NO ₃) ₃	λ _{max} (cm ⁻¹) Complex	Assignment	Calculated parameter						
			ε	β	b ^{1/2}	δ%	η		
Pr(NO ₃) ₃	[Pr(CP) ₂ (NO ₃) ₂]NO ₃	³ H ₄ → ³ P ₁	22222	22062	991.3	0.9928	0.0600	0.7252	0.0036
			21276	21144	701.1	0.9938	0.0556	0.6238	0.0031
			20408	20228	412.2	0.9912	0.0663	0.8878	0.0044
			16949	16804	322.3	0.9915	0.0651	0.8572	0.0042
Nd(NO ₃) ₃	[Nd(CP) ₂ (NO ₃) ₂]NO ₃	⁴ I _{9/2} → ⁴ G _{9/2}	19607	19505	1001.3	0.9948	0.0509	0.5227	0.0026
			17241	17111	1522.8	0.9925	0.0612	0.7556	0.0037
			14705	14668	1468.5	0.9975	0.0353	0.2506	0.0012
			13513	13472	1408.9	0.9970	0.0387	0.0015	0.0009
			12500	12427	744.7	0.9942	0.0538	0.0029	0.0032
Er(NO ₃) ₃	[Er(CP) ₂ (NO ₃) ₂]NO ₃	⁴ I _{15/2} → ⁴ F _{7/2}	20408	20361	367.5	0.9954	0.0479	0.4621	0.0023
			19230	19160	653.6	0.9964	0.0424	0.3613	0.0018
			18867	18791	567.0	0.9920	0.0632	0.8391	0.0040
			15384	15282	353.5	0.9934	0.0574	0.6643	0.0033

Table 3—Antifungal screening data of lanthanide(III) nitrate-chlorpromazine complexes

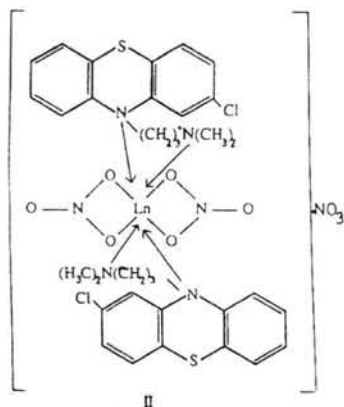
Compound	Average % Inhibition					
	<i>Aspergillus niger</i>		<i>Aspergillus flavus</i>		<i>Trichoderma harzianum</i>	
	0.01	0.25	0.01	0.25	0.01	0.25
[La(CP) ₂ (NO ₃) ₂]NO ₃	44.1	74.2	35.4	71.5	38.2	78.0
[Nd(CP) ₂ (NO ₃) ₂]NO ₃	35.2	70.0	33.5	64.7	42.7	74.2
[Sm(CP) ₂ (NO ₃) ₂]NO ₃	35.4	65.8	43.1	72.3	32.5	65.8
[HO(CP) ₂ (NO ₃) ₂]NO ₃	36.8	68.7	28.8	65.6	34.8	63.4
La(NO ₃) ₃	10.5	17.5	11.2	19.2	9.9	21.2
Nd(NO ₃) ₃	9.8	18.2	11.0	20.1	10.0	21.6
Sm(NO ₃) ₃	10.6	17.8	11.3	20.3	10.2	21.8
Ho(NO ₃) ₃	10.0	17.4	11.0	19.6	9.8	21.5
Chlorpromazine hydrochloride	8.2	16.0	10.4	18.6	9.7	20.9

DMSO and chloroform, sparingly soluble in acetonitrile and insoluble in water and other common organic solvents. They do not possess sharp melting points. The analytical data (Table 1) is in accordance with 1:2 metal-ligand stoichiometry. The molar conductances in DMF are in the range 70.64-92.78 Ohm⁻¹cm²mol⁻¹ (Table 1) indicating 1:1 electrolytic nature of the complexes.

The magnetic moment values indicate that lanthanum and lutetium complexes are diamagnetic whereas the remaining complexes are paramagnetic as expected for lanthanide(III) complexes. The measured values show a little deviation from the theoretical

values calculated from Van Vleck formula suggesting that 4f-electrons do not participate in bond formation. These data also suggest that there are no metal-metal interactions or spin-spin coupling.

The band observed at 2860 cm⁻¹ in the infrared spectrum of the ligand is attributed to the heterocyclic nitrogen atom carrying an alkyl group⁷. In the spectra of corresponding lanthanide(III) nitrate complexes, this band disappeared completely suggesting the coordination of heterocyclic nitrogen atom. The interaction of quarternary ammonium ion, R₃NH⁺ with chloride ion present in N-alkylphenothiazines leads to a broad band in 2500-2300 cm⁻¹ region⁷. A broad band



observed in the $2580\text{--}2465\text{ cm}^{-1}$ region of the ligand corresponds to $-\text{CH}_2\text{N}(\text{CH}_3)_2\text{H}^+$ combined with chloride ion. In the IR spectra of the corresponding lanthanide(III) complexes, this band either disappeared or reduced to a small hump showing that the tertiary nitrogen atom of the side chain is another site of coordination. This shows that chlorpromazine acts as a bidentate ligand with heterocyclic nitrogen atom and tertiary nitrogen atom as two coordination sites. The sharp band at 750 cm^{-1} observed in the spectrum of the ligand assignable to $\nu(\text{CSC})$ stretching frequency¹⁶ remains unaffected in the spectra of the corresponding lanthanide complexes suggesting the non-coordination of heterocyclic sulphur atom.

The nitrate complexes exhibit four bands at $1460\text{--}1450$, $1260\text{--}1250$, $1038\text{--}1031$ and $830\text{--}824\text{ cm}^{-1}$ which can be assigned to the vibrational modes of the coordinated (C_{2v}) nitrate groups¹⁷. The magnitude of splitting of the two bands at higher energies is $\sim 200\text{ cm}^{-1}$ indicating that nitrate groups are attached to the metal atom in a bidentate pattern. The band observed at $1384\text{--}1378\text{ cm}^{-1}$ is due to ionic nitrate present in the complexes. This shows that these complexes consist of both ionic and coordinated nitrate groups. The new bands observed in the region $450\text{--}443\text{ cm}^{-1}$ assignable to $\nu(\text{Ln-N})$ mode confirmed the participation of nitrogen atoms of chlorpromazine in coordination.

The proton NMR spectrum of chlorpromazine hydrochloride shows the resonance peaks corresponding to $-\text{N}-\text{CH}_2$, $-\text{N}-\text{CH}_3$ and the aromatic protons of the benzene ring in the region $\delta=3.00\text{--}3.25$ ppm (triplet), $\delta=2.65$ ppm (singlet) and $\delta=6.82\text{--}7.23$ ppm (multiplet) respectively with respect to TMS. In the spectra of corresponding lanthanum and lutetium complexes, the peaks corresponding to $-\text{N}-\text{CH}_2$ protons are found to be shifted to lower frequency

region ($\delta=3.08\text{--}3.35$ and $3.05\text{--}3.30$ ppm respectively) and the signal corresponding to $-\text{N}-\text{CH}_3$ protons are also found to be shifted to lower frequency region $\delta=2.72$ and 2.75 ppm respectively) indicating that heterocyclic nitrogen atom and the tertiary nitrogen atom are coordinated to the metal ion. The signal for aromatic protons of benzene ring in the complexes of lanthanum and lutetium are found to be in the region $\delta=6.8\text{--}7.5$ and $6.8\text{--}7.25$ ppm respectively. A downfield shift in the absorption peaks of the complexes with respect to $-\text{N}-\text{CH}_2$ and $-\text{N}-\text{CH}_3$ protons compared to their positions of the free ligand may be attributed to the corresponding effect of the nitrogen atoms, which results in deshielding of protons attached to it.

The electronic spectrum of chlorpromazine hydrochloride shows $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions at 32206 cm^{-1} and 36900 cm^{-1} respectively. In the spectra of corresponding lanthanide(III) complexes, the $n \rightarrow \pi^*$ bands are blue shifted to $32175\text{--}32010\text{ cm}^{-1}$ and $\pi \rightarrow \pi^*$ bands are red shifted to $37650\text{--}37537\text{ cm}^{-1}$. The $f\text{--}f$ bands for praseodymium(III), neodymium(III) and erbium(III) complexes in the visible region with various calculated parameters (β , $b^{1/2}$, $\delta\%$, η) in 10^{-3} M DMF solutions and their tentative assignments are given in Table 2. The values of nephelauxetic ratio ($\beta\phi$) are smaller than unity and the values of the bonding parameter ($b^{1/2}$) and the Sinha's parameter ($\delta\%$) are both positive suggesting the occurrence of covalent character in metal-ligand bonding. The shapes of the hypersensitive transition closely resembles with that of the eight coordinated complexes reported by Karraker. The electronic spectral parameters also suggest weak covalent nature¹⁸ of the metal-ligand bonds.

The TGA curves for the lanthanide(III) nitrate complexes have been recorded. The thermogravimetric results indicate that the complexes are stable upto 240°C showing the absence of water and other coordinated solvent molecules. The decomposition of the complexes occurs in two steps. The first step involves the decomposition of organic moiety in the temperature range $300\text{--}410^\circ\text{C}$. The second step consists of the loss of nitrate at $420\text{--}730^\circ\text{C}$ followed by the formation of lanthanide(III) oxide. The weight loss became constant at 750°C . The DTA studies show that both the decomposition of organic moiety and the formation of lanthanide(III) oxides are exothermic processes.

Antifungal activity

Lanthanide nitrates, chlorpromazine hydrochloride and the corresponding lanthanum(III), neodymium(III), samarium(III) and holmium(III) complexes were tested for their efficacy in controlling three fungi, namely *Aspergillus niger*, *Aspergillus flavus* and *Trichoderma harzianum* by the poisoned food technique. The screening data for the average percentage inhibition of the fungi at 0.01% (0.313 mM, 0.227 mM and 0.102 mM respectively for the ligand, lanthanide nitrates and their corresponding complexes) and 0.25% (7.84 mM, 5.69 mM and 2.56 mM respectively) concentrations are given in Table 3. The values obtained strongly support that the lanthanide nitrate complexes exhibit two to four times greater fungitoxicity than lanthanide nitrates and the free ligand. Further, the data also indicates that with the increase in concentration, the fungitoxicity also increases. A possible explanation for the greater toxicity of the complexes has been proposed¹⁹. It was suggested that in the chelated complex, the positive charge of the metal is partially shared with donor atoms and there is π -electron delocalisation over the whole chelate ring. This increases the lipophilic character of the metal chelate and favours its permeation through lipid layers of the fungus membranes.

On the basis of spectral studies, molar conductance values and thermal studies, it is concluded that two molecules of chlorpromazine and two nitrate groups are bound to lanthanide ion and another nitrate ion is in the outer coordination sphere exhibiting a coordination number of eight. None of the complexes gave single crystals of sufficient quality to conduct X-ray crystallographic analysis. However, X-ray powder diffraction analysis of the complexes were carried out. The intensity and d (nm) data of the complexes are different from that of the ligand. The occurrence of new phases shows that the formation of complexes of all lanthanide nitrates with chlorpromazine are isomorphous. The fluorescence spectrum of europium(III) nitrate-chlorpromazine complex in DMF

solution showed no characteristic peaks corresponding to $^5D_0 \rightarrow ^7F_n$ transitions.

In the light of the above discussions, the following general structure has been proposed for the lanthanide(III) nitrate-chlorpromazine complexes (Structure II).

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