Synthesis and spectral characterisation of lanthanide(III) complexes of trimethoprim

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A new series of hepta coordinated lanthanide(III) complexes of the type [ML_2Cl_3] (where M = La^{III}, Pr^{III}, Nd^{III}, Sm^{III}, Gd^{III}, Tb^{III}, Dy^{III} or Y^{III}, L = trimethoprim) have been synthesised. The new complexes were characterised using various physico-chemical methods such as elemental analysis, spectral (IR, UV–VIS, ^{1}H NMR), magnetic and X-ray diffraction analysis. A monocapped trigonal prism structure has been tentatively proposed for the complexes.

Keywords: lanthanides, trimethoprim, synthesis, characterisation

Lanthanide(III) ions are known to exhibit interesting bonding possibilities with various types of ligands. Initially, coordination chemistry of lanthanides was limited to strong chelating ligands with oxygen as donor atoms.[1] However, with the development of new synthetic techniques, a good number of lanthanide(III) complexes with other ligating atoms were prepared and characterised.[2,3] Among the complexes with various types of ligands, lanthanide(III)–nitrogen donor complexes are not only interesting but they also find applications in organic synthesis and catalysis.[4] Extensive literature is available on lanthanide complexes with several polydentate ligands.[5-7] However, such complexes with biologically active ligands have received comparatively less attention. Lanthanide ions are often used as spectroscopic probe as a surrogates for Ca^{II} ion in studies of biological systems as well as promoters in the dyeing industry and a diagnostic agent in clinical medicine.[8-10] It is well known that when biologically active ligands are complexed with metal ions they exhibit enhanced microbiological activities. In this context, coordination compounds of trimethoprim, an antibacterial and antiprotozoal drug, with transition elements in their common oxidation states have been extensively investigated.[11-13] However, no work has been reported in the literature on the study of lanthanide(III) complexes with trimethoprim. Therefore, in continuation of our earlier reports on the study of lanthanide(III) complexes with biologically active ligands,[14,15] we report in this article the synthesis and spectral characterisation of selected lanthanide(III) complexes with trimethoprim as a ligand.

Experimental

Chlorides of lanthanum(III), praseodymium(III), neodymium(III), samarium(III), gadolinium(III), terbium(III), dysprosium(III) and yttrium(III) were obtained from Indian Rare Earths Limited, Alwaye, Kerala, S. India and all of them were used as received. The ligand, trimethoprim {5-[(3',4',5'-trimethoxyphenyl)methyl]-2,4-pyrimidine diamine, $C_{14}H_{18}N_4O_3$}, was obtained form Kerala State Drugs and Pharmaceuticals Ltd., Alleppy, Kerala, S. India in the pure form, it was certified as 100% pure and hence used as such. Solvents and other reagents were obtained from E.Merck and were purified using standard procedures.[16]

Preparation of the complexes: The lanthanide chelates were prepared by mixing together hot methanolic solutions of the appropriate lanthanide chloride (5 cm^3, 1 mmol) and trimethoprim (5 cm^3, 2 mmol) and refluxing the mixture for 6 h on a water bath. The reaction mixture was concentrated to 5 cm^3 and cooled for 12 h. The solid complex separated, in each case, was filtered, thoroughly washed with cold methanol, acetone and distilled water and dried *in vacuo*. The complexes were obtained in good yields (*ca*. 58%).

The elemental analyses (C, H, N, Cl and M) of all complexes were performed at the Central Drug Research Institute, Lucknow, India. The conductance data were obtained in 10^{-3} M DMF solution at room temperature using a Systronics conductivity meter-304. IR spectra were recorded in KBr pellets in the 4000–200 cm^{-1} region using a Perkin-Elmer 1600 FT-IR spectrometer. Electronic spectra were recorded with a Shimadzu UV-visible double beam spectrophotometer and related bonding parameters were calculated as reported elsewhere.[17,18] ^{1}H NMR spectra were recorded on a DPX 200 Varian Supercon instrument using DMSO-d_6 as solvent. The magnetic susceptibility measurements were made by the Gouy method using $Hg[Co(CNS)_4]$ as calebrant. Thermogravimetric analysis was carried out using a TG/DTA Sieko (Japan, model 320) instrument. The XRD patterns were recorded on a vertical type Phillips 1130/00 X-ray diffractometer.

Results and discussion

The new non electrolytic lanthanide(III) complexes, [ML_2Cl_3], where M = La^{III}, Pr^{III}, Nd^{III}, Sm^{III}, Gd^{III}, Tb^{III}, Dy^{III} or Y^{III}, containing trimethoprim ligand have been prepared. The molecular formula of the complexes have been assigned on the basis of the results of their elemental analysis (Table 1). The lanthanide(III) complexes were characterised by IR, UV-VIS, ^{1}H NMR, magnetic susceptibility measurements, TG/DTA and X-ray diffraction studies. All the complexes are colourless, microcrystalline and are stable in air. The molar conductance values of the complexes, ranging 8–13 mhos cm^2 mol^{-1}, reveal that the chelates have low conductivity, which indicates that the complexes are non electrolytic.

The IR spectrum of the ligand, trimethoprim, shows strong bands at 3470 cm^{-1} and 3300 cm^{-1} corresponding to asymmetric and symmetric stretching vibrational modes of N–H bonds of the primidine amino group.[19] In the spectra of complexes, a negative shift of the order of 130 to 150 cm^{-1} is observed with respect to these bands.The relatively large shift to lower frequencies is due to the weakening of N–H bonds resulting from the electron drainage from the nitrogen atom on account of coordination to the metal ion.[20] The broad bands, in the IR spectrum of the ligand, at 1250 cm^{-1} and 1035 cm^{-1} are assigned to asymmetric and symmetric stretching vibrational mode of C–O–C bonds of the methoxy groups. These bands remain unaffected in the spectra of complexes, which suggest that the methoxy groups of the ligand are not involved in coordination. In the spectra of complexes, the far IR spectral bands at 335 to 355 cm^{-1} and 275 to 300 cm^{-1} are assigned to M–N and M–Cl stretching vibrations respectively. The presence of these new bands confirms the bonding of the metal ion through pyrimidine amino-groups in these complexes.

The electronic spectrum of trimethoprim has two maxima at 33,380 cm^{-1} and 37,463 cm^{-1}, corresponding to $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions respectively. In complexes these maxima are shifted to high frequency regions. The shifts corresponding to $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ transitions are, respectively, in Pr^{III} complex 33,500 cm^{-1} and 37,840 cm^{-1}, in Nd^{III} complex 33,410 cm^{-1} and 37,520 cm^{-1} and in Sm^{III} complex 33,410 cm^{-1} and 37,597 cm^{-1}. The absorption bands of Pr^{III}, Nd^{III} and Sm^{III} in the UV and visible region appear due to transitions from the ground levels $^3H_4$, $^4I_{9/2}$ and $^6H_{5/2}$ respectively to the excited J-levels of 4f configuration.[21]

The shift of the maxima due to complexation from 22,471 to 22,314 cm^{-1}, 19,608 to 19,525 cm^{-1} and 26,667 to 26,548 cm^{-1} is observed for the complexes of Pr^{III}, Nd^{III} and Sm^{III} corresponding to the transitions $^3H_4\rightarrow{}^3P_2$, $^4I_{9/2}\rightarrow{}^4G_{9/2}$ and $^6H_{5/2}\rightarrow{}^6P_{3/2}$. This bathochromic shifts clearly indicate that the interaction of the metal ion with the ligand is due to the effect of crystal fields upon inter electronic repulsion among the 4f electrons. The values of the bonding parameter, $b^{1/2}$, (in the range of 0.036 – 0.066) lead to good

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Table 1 Analytical and magnetic susceptibility data for M^{III}-trimethoprim complexes.

Complex		Elemental analysis % Found (calculated) C	H	N	Cl	O	Metal	μ_{eff} (BM)
1	$[LaL_2Cl_3]$	40.7	4.4	13.6	12.9	11.6	16.8	Dia
		(40.7)	(4.5)	(13.4)	(12.8)	(11.7)	(16.9)	
2	$[PrL_2Cl_3]$	40.6	4.4	13.5	12.9	11.6	17.0	3.39
		(40.5)	(4.4)	(13.6)	(12.9)	(11.7)	(16.9)	3.68
3	$[NdL_2Cl_3]$	40.5	4.3	13.5	11.6	12.8	17.4	
		(40.5)	(4.1)	(13.4)	(11.6)	(12.6)	(17.7)	
4	$[SmL_2Cl_3]$	40.2	4.3	13.4	12.7	11.5	18.0	2.14
		(40.2)	(4.4)	(13.2)	(12.7)	(11.5)	(18.0)	
5	$[GdL_2Cl_3]$	39.8	4.3	13.3	12.6	11.4	18.6	7.76
		(40.0)	(4.2)	(13.4)	(12.8)	(11.2)	(18.5)	
6	$[TbL_2Cl_3]$	39.8	4.3	13.3	12.6	11.4	18.8	9.93
		(39.5)	(4.4)	(13.4)	(12.6)	(11.3)	(18.8)	
7	$[DyL_2Cl_3]$	39.6	4.2	13.3	12.5	11.3	19.1	10.47
		(39.7)	(4.1)	(13.2)	(12.6)	(11.4)	(18.9)	
8	$[YL_2Cl_3]$	43.3	4.6	14.4	13.7	12.4	11.5	Dia
		(43.4)	(4.6)	(14.5)	(13.7)	(12.3)	(11.5)	

agreement for the presence of the covalent nature of the metal-ligand bond,[22] which is supported by the values (in the range of 5.1×10^{-3} to 24.5×10^{-3}) of oscillator strength, *f*.

Magnetic susceptibility data of the M^{III} complexes of trimethoprim at room temperature are given in Table 1. The La^{III} and Y^{III} complexes are diamagnetic while all other complexes are paramagnetic. The magnetic susceptibility values of all the paramagnetic complexes, except for Sm^{III}, show slight deviation from van Vleck values,[23] indicating very little participation of the 4f electrons in bonding as these electrons are well shielded by the $5s^2$ $5p^6$ octet. The relatively high value obtained in the case of Sm^{III} complex is due to the fact that the energy difference between the ground state and the next higher level is of the order of *kT*, which leads to thermal population of high energy levels and show susceptibilities due to the first order Zeeman effect.[24]

In the ^1H NMR spectrum of the ligand trimethoprim, the sharp singlet (2H) at δ 3.36 is assigned to the protons of the $-NH_2$ group at C-4. The protons of the $-NH_2$ group at C-2 get deshielded due to the neighbouring nitrogen atoms at positions 1 and 3 and appear as a sharp singlet (2H) at δ 3.53. The singlets at δ 3.62 correspond to the methoxy protons at C-4 while the one at δ 3.72 may be due to the methoxy protons at C-3 and C-5. The singlet (2H) at δ 5.7 may be due to methylene protons.[25] The protons of the phenyl ring, at positions C-2 and C-6 appear as a singlets (1H) at δ 6.09 and δ 6.55. The proton in the pyrimidine ring appears as a sharp singlet at δ 7.52. In the ^1H NMR spectrum of the La^{III} complex, the signals due to amino protons at C-2 and C-4 exhibit characteristic downfield shifts by 0.26 to 0.21 ppm, indicating coordination through the two amino- nitrogen atoms. The proton at C-6 of the pyrimidine ring also shifts upfield. The signals support the observation that the metal-ligand interactions are very weak and do not alter the electronic environment around the protons which are only a few bonds away from the metal ion.

All these M^{III} complexes have a similar physicochemical environment. Therefore, it was considered that the thermal behavior of one of the complexes would resemble that of others and hence only one complex *viz.* the La^{III}-trimethoprim complex was selected for carrying out thermal studies. The TG and DTA curves of this complex are shown in Fig. 1. The results indicate that the complex is stable up to 286°C. The absence of endothermic peak(s), unlike in the cases of La^{III} complex of tetracycline[14] and sulphamethoxazole,[15] lead to the conclusion that there are no water or solvent molecules coordinated or uncoordinated in the trimethoprim complexes. The complex underwent a two stage decomposition, first in the range of 286–300°C with a weight loss of 28.4%. This weight loss is due to the loss of an organic moiety. The second stage of decomposition occurred in the range of 300–366°C with a weight loss of 57.9% and this is due to the loss of chloride ions.[26] The above changes are indicated by the exothermic DTA curve at 300 and 342°C. The residue obtained after heating at 573°C to a constant weight is very close to that expected for the La^{III} oxide.[27] This is represented by the sharp DTA exothermic curve at 541°C.

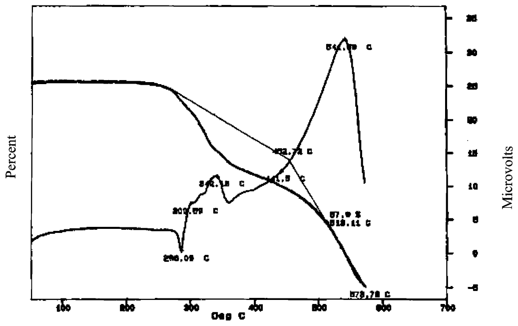

Fig. 1 Thermogram of Lanthanum-trimethoprim complex.

Our efforts to prepare single crystals of these complexes were unsuccessful. Therefore, powder X-ray diffraction pattern have been recorded. The diffraction pattern reveals the crystalline nature of the complex. Attempts to index the diffraction patterns using auto indexing computer programmes have failed to yield acceptable unit cell parameters in the crystal systems of the complexes.

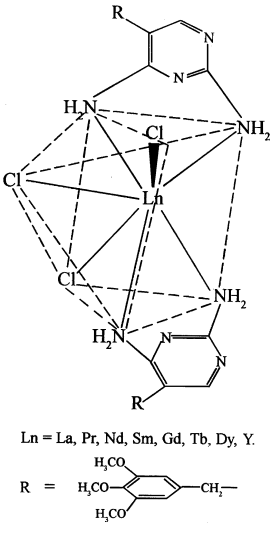

Fig. 2 Lanthanide-trimethoprim complex.

It is concluded from the above discussions that trimethoprim behaves as a bidentate ligand, chelating the M^{III} ions through the amino groups of the pyrimidine ring. On the basis of the physicochemical and spectral evidences, a coordination number of seven is proposed for the metal ions in these complexes. The most probable geometry of these complexes is a monocapped trigonal prism as shown in Fig. 2.

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