Synthesis, Characterization, and Antibacterial Activity of Lanthanide(III) Complexes of Thiosemicarbazone Derived from 8-Acetyl-4-methylumbelliferone

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Seven new lanthanide complexes of thiosemicarbazone derived from 8-acetyl-4-methylumbelliferone (H_2L) have been prepared and characterized by elemental analysis, molar conductivity, IR, XPS, TG-DTA, UV, and ^{1}H NMR. The general formula of the complexes is $Ln(HL)_3$ where Ln = La, Ce, Pr, Nd, Sm, Eu, and Gd. The antibacterial activity of the metal complexes in which the effect of the ligand was not lost by entering the complex, increases in the order Gd, Eu, La, Pr, Sm, Nd, Ce.

Thiosemicarbazones have evoked considerable interest due to their broad spectrum of biological activities, which includes antibacterial, antifungal, antiviral, antitumour, and anticarcinogenic properties [1, 2]. It is well known that some thiosemicarbazones have increased activity when administered as metal complexes [3—5]. Further, it is becoming increasingly clear that some lanthanide elements have antibacterial activity [6].

In this present investigation, we have synthesized seven lanthanide complexes of thiosemicarbazone derived from 8-acetyl-4-methylumbelliferone which have significant antibiotic and antifungal activity, with a view to studying the effect of the coordination of lanthanide ions on the activity of the ligand and to exploring the possibility of their use as potential biocidal agents against some microorganisms.

EXPERIMENTAL

The ligand 8-acetyl-4-methylumbelliferone thiosemicarbazone (I) was prepared according to the literature method [7], lanthanide tris-perchlorates were prepared from their oxides and perchloric acid.

All the solvents and reagents used were of anal. grade.

Elemental analyses were carried out on a Vario EL apparatus and metal contents were determined volumetrically by EDTA titration. IR spectra were obtained in KBr disc on a Nicolet FTIR 170SX spectrophotometer. MS were taken on a VG.ZAB-HS instrument (FAB). ^{1}H NMR spectra were recorded on a Bruker AM400 spectrometer using DMSO-d_6 as solvent and TMS as internal reference. Electronic spectra were taken on a Shimadzu UV-240 spectrometer. TG-DTA measurements were made in a nitrogen atmosphere between room temperature and 800 ℃ using a Du Pont 1090-B thermal analyzer. Molar conductivity in DMF at 10^{-3} mol dm^{-3} concentration was measured on a DDS-11A molar conductometer from Shanghai Analytical Equipment Factory.

In vitro antibacterial activity of the complexes along with the ligand has been screened against *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Bacillus subtilis* (*B. subtilis*) by paper disc method at 200 μg cm^{-3} in DMSO. The solution (10 mm^3) was poured into the disc that had a diameter of 6 mm. Then, all discs were placed on the appropri-

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Table 1. Characterization of the Complexes

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%				M.p.	Molar conductivity
			Ln	C	H	N	°C	Ω^{-1} cm^2 mol^{-1}
II	$(C_{13}H_{12}N_3O_3S)_3La$	1009.85	13.75	46.38	3.59	12.49	252 (dec.)	8.52
			13.98	46.74	3.48	12.52		
III	$(C_{13}H_{12}N_3O_3S)_3Ce$	1011.05	13.86	46.33	3.59	12.47	258 (dec.)	7.96
			13.71	46.58	3.69	12.71		
IV	$(C_{13}H_{12}N_3O_3S)_3Pr$	1011.85	13.92	46.29	3.59	12.46	260 (dec.)	8.73
			13.87	46.14	3.38	12.36		
V	$(C_{13}H_{12}N_3O_3S)_3Nd$	1015.15	14.20	46.14	3.57	12.42	263 (dec.)	8.19
			14.03	46.35	3.42	12.59		
VI	$(C_{13}H_{12}N_3O_3S)_3Sm$	1021.35	14.72	45.86	3.55	12.34	260 (dec.)	6.93
			14.58	45.97	3.62	12.17		
VII	$(C_{13}H_{12}N_3O_3S)_3Eu$	1022.95	14.86	45.79	3.55	12.33	265 (dec.)	7.84
			15.06	45.52	3.79	12.24		
VIII	$(C_{13}H_{12}N_3O_3S)_3Gd$	1028.25	15.30	45.55	3.53	12.26	268 (dec.)	8.58
			15.57	45.37	3.28	12.41		

Table 2. IR Spectra of the Ligand and its Complexes

Compound	$\tilde{\nu}$/cm^{-1}								
	ν(OH)	ν_{as}(NH$_2$)	ν_s(NH$_2$)	ν(C═O)	ν(C═N)	ν(C═S)	ν(Ln—S)	ν(Ln—N)	ν(Ln—O)
I	3382	3281	3180	1690	1600	1170			
II		3283	3183	1688	1582	1168, 1085	352	420	432
III		3280	3180	1692	1585	1168, 1092	348	414	447
IV		3280	3182	1689	1580	1168, 1089	340	400	430
V		3283	3180	1690	1579	1168, 1095	357	420	450
VI		3281	3182	1692	1584	1170, 1090	346	411	438
VII		3283	3182	1690	1580	1168, 1085	351	420	442
VIII		3283	3182	1688	1579	1168, 1092	342	417	437

ate medium previously seeded with organisms in Petri dishes and stored in an incubator at 37 °C. The inhibition zone (mm) around each disc was measured after 24 h.

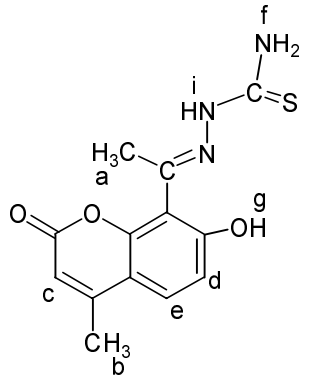
Complexes

A solution of lanthanide(III) perchlorate (1 mmol) in EtOH (5 cm^3) was added to 10 cm^3 of ethanolic solution of the ligand (3 mmol) and NaOH (3 mmol). The mixture was stirred under reflux for 6 h and then filtered. The complexes thus obtained were washed successively with ethanol and diethyl ether and dried *in vacuo* over P_4O_{10}.

RESULTS AND DISCUSSION

The analytical data of the complexes are given in Table 1. The elemental analyses data show that the seven complexes (*II*—*VIII*) have the general formula $Ln(HL)_3$ (where Ln = La, Ce, Pr, Nd, Sm, Eu, and Gd). They are air-stable, soluble in DMSO and DMF, but insoluble in the most known solvents: alcohol, ether, benzene, acetone, and water. The molar conductivity values of the complexes fall in the range for nonelectrolytes [8].

The main IR data of the ligand and the complexes are listed in Table 2. In the spectrum of the ligand wavenumbers of various intensities are exhibited at 3382 cm^{-1}, 3281 cm^{-1}, 3180 cm^{-1}, and 1690 cm^{-1} being assignable to ν(OH), ν_{as}(NH$_2$), ν_s(NH$_2$), and ν(C═O), respectively. The disappearance of the band due to ν(OH) in the complexes suggests deprotonation of phenolic group and subsequent bonding through this oxygen. The ν(C═O) is not shifted because it is not involved in bonding. In the spectra of all the complexes, the ν(C═N) band appears to shift from 1600 cm^{-1} to *ca.* 1582 cm^{-1}. This shift to lower frequency indicates the involvement of the azomethine nitrogen in bonding to the Ln^{3+} ion [9, 10]. The ν(C═S) band is observed at 1170 cm^{-1} in the spectrum of the free ligand, and new bands are observed in 1085—1095 cm^{-1} range together with a broad band of very weak intensity at 1168 cm^{-1} in the complexes. These changes in the ν(C═S) vibrations are suggestive of the participation of thioketosulfur in



Formula 1. Structure of H_2L.

chelation [11]. In addition, the new bands which appeared in the spectra of the complexes in the regions 340—357 cm^{-1}, 400—420 cm^{-1}, and 430—450 cm^{-1} may be assigned to ν(Ln—S), ν(Ln—N) (azomethine) and ν(Ln—O), respectively [12].

The mode of coordination discussed above receives further support from the ^1H NMR spectra of the ligand H_2L and the complex $La(HL)_3$ in DMSO-d_6. The structure of H_2L and the labeled H atom are shown in Formula 1. The chemical shifts for H_2L δ: 2.20 (s, 3H, H_a), 2.35 (s, 3H, H_b), 6.17 (s, 1H, H_c), 6.91—7.66 (m, 2H, $H_{d,e}$), 7.81 (bs, 2H, H_f), 8.19 (bs, 1H, H_g), 10.57 (bs, 1H, H_i); and for $La(HL)_3$ δ: 2.27 (s, 3H, H_a), 2.38 (s, 3H, H_b), 6.19 (s, 1H, H_c), 7.10—7.73 (m, 2H, $H_{d,e}$), 7.89 (bs, 1H, H_f), 10.64 (bs, 1H, H_i). The broad signal peak due to the hydroxyl proton of the free ligand disappeared in the La(III) complex, confirming the coordination of the La^{3+} ion with the oxygen atom of the hydroxyl group by deprotonation. The —NH proton signal shifts downfield in the complex, which suggests that the ligand is coordinating through the sulfur atom of the NH—C═S group without enolization and the —NH proton undergoes dishielding [13, 14]. The methyl proton signal adjacent to the azomethine group shows downfield shift due to the involvement of the N in bonding with the La^{3+} ion.

The electronic spectra in the visible region of the solid Pr(III), Nd(III), Sm(III), and Eu(III) complexes exhibit changes in the intensity and shifts in position of the absorption bands relative to the respective aquoions salts. The red shift of bands is related to covalence in the metal—ligand bond. Calculated values for the bonding parameters β, δ, and $b^{1/2}$ are presented in Table 3 [15]. The values of the nephelauxetic ratio (β) are smaller than 1 and the positive values of the bonding parameter ($b^{1/2}$) and Sinha's parameter (δ) indicate the occurrence of some covalent character in the metal—ligand bond [16]. The comparatively smaller magnitude of the $b^{1/2}$ values also shows the involvement of the $4f$-orbital in the metal—ligand bond to a very small degree [17]. The $b^{1/2}$ and δ in these complexes increase in the order $Pr(HL)_3$, $Nd(HL)_3$, $Sm(HL)_3$, $Eu(HL)_3$ which reveals that for the same ligand covalence increases with the increasing number of the lanthanide.

In order to obtain further insight into the nature of bonding, XPS spectra of the complexes and the ligand were recorded in the powder form at room temperature. We found only one symmetric sulfur $2p$ peak, at *ca.* 161.8 eV, for the complexes similar to the ligand but *ca.* 0.8 eV higher, the higher BE value of the complexes suggesting thioketosulfur participation in coordination with the lanthanide metal. The N (C═N) $1s$ binding energy in the complexes shifts to higher energy by 1.27 eV, thus confirming the coordination of the azomethine nitrogen [18].

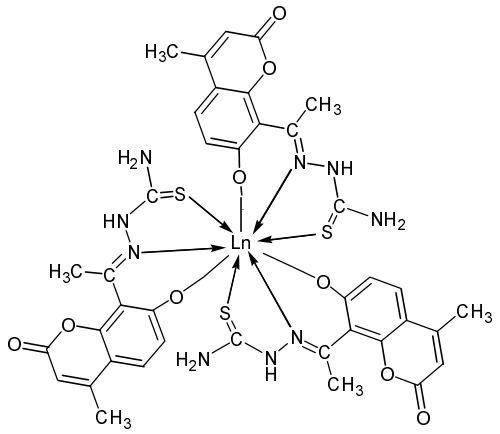
The thermal properties of the ligand and the complexes were measured by the TG and DTA methods. The thermographs of all the complexes are quite similar, but all differ obviously from H_2L. The TG-DTA diagram of the ligand shows that the ligand melts at 197 ℃ and begins to decompose at 210 ℃, which is

Table 3. Electronic Spectra of the Pr(III), Nd(III), Sm(III), and Eu(III) Complexes

Compound	$\tilde{\nu}$/cm^{-1}	Assignment	Covalent parameters
IV	22470	$^3H_4 \rightarrow {}^3P_2$	$\beta = 0.9961$
	21210	$\rightarrow {}^3P_1$	$\delta = 0.3915$
	20607	$\rightarrow {}^3P_0$	$b^{1/2} = 0.044$
	16804	$\rightarrow {}^1D_2$	
V	19500	$^4I_{9/2} \rightarrow {}^2G_{9/2}$	$\beta = 0.9947$
	17260	$\rightarrow {}^4G_{5/2}, {}^2G_{7/2}$	$\delta = 0.5328$
	13426	$\rightarrow {}^2S_{3/2}, {}^4F_{7/2}$	$b^{1/2} = 0.051$
	12420	$\rightarrow {}^4F_{5/2}, {}^4H_{9/2}$	
VI	24510	$^6H_{5/2} \rightarrow {}^4F_{7/2}$	$\beta = 0.9914$
	23700	$\rightarrow {}^6P_{5/2}$	$\delta = 0.8675$
	21500	$\rightarrow {}^4I_{13/2}$	$b^{1/2} = 0.065$
VII	24190	$^7F_0 \rightarrow {}^5D_3$	$\beta = 0.9904$
	21286	$\rightarrow {}^5D_2$	$\delta = 0.9693$
	18854	$\rightarrow {}^7D_1$	$b^{1/2} = 0.141$

Table 4. Antibacterial Activity Data of the Ligand and its Complexes

Compound	Concentration μg/disc area	Diameter of the inhibition zone/mm		
		S. aureus	*E. coli*	*B. subtilis*
I	2	12.3	10.2	11.6
II	2	15.6	11.4	12.0
III	2	18.2	13.2	14.5
IV	2	16.0	12.0	13.5
V	2	17.6	12.5	13.8
VI	2	17.4	12.3	13.6
VII	2	15.1	11.0	11.7
VIII	2	14.3	10.7	10.6
Penicillin	2	23.0	0	20.0
Streptomycin	10	0	15.0	0



Formula 2. Suggested structure of the complexes.

accompanied by the release of heat. The complexes are more thermally stable than the ligand, decompose exothermically through more than one stage and start around 252—268 °C, which is accompanied by a considerable mass loss in the TG curves. Finally, stable lanthanide oxides are formed at *ca.* 800 °C.

Based on the aforementioned data, a proposed structure of the title lanthanide(III) complexes is shown in Formula 2.

The data listed in Table 4 clearly illustrate that the free ligand H_2L and its complexes have antibacterial potency against all tested organisms, whereas the antibacterial activity of the seven complexes is higher than that of the ligand. It is thought that the increase in activity may be due to the chelation of lanthanide(III) ions and the presence of sulfur atoms [19]. The antibacterial activity of the complexes $La(HL)_3$ increases in the order of elements Gd, Eu, La, Pr, Sm, Nd, Ce. A comparison of the ligand and complexes with penicillin and streptomycin reveals that the present compounds are less toxic than penicillin, but are more potent than streptomycin against *E. coli*. In order to obtain a more complete understanding of the complexes and possible wider application, their antibacterial activity against other strains is being tested.

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