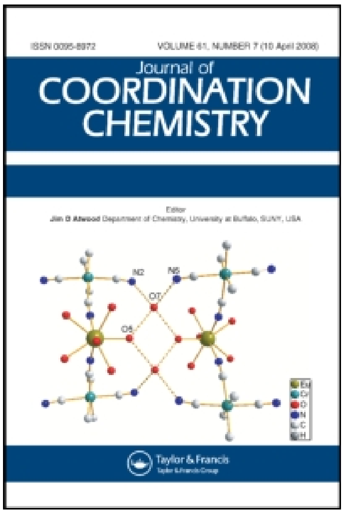

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SYNTHESIS AND ANTICARCINOGENIC ACTIVITY OF 5-FLUOROURACIL-1-ACETIC ACID COMPLEXES WITH RARE EARTHS

Wang Liu-Fang[a]; Yang Zheng-Yin[a]; Peng Zhou-Ren[a]; Cheng Guo-Quan[b]; Guo Hong-Ying[b]; Sun Al-Li[b]; Wang Qi[c]; He Feng Ying[c]
[a] Department of Chemistry, Lanzhou University, Lanzhou, P.R.C. [b] Tumor institute of Gansu Province, P.R.C. [c] Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, P.R.C.

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NOTE

SYNTHESIS AND ANTICARCINOGENIC ACTIVITY OF 5-FLUOROURACIL-1-ACETIC ACID COMPLEXES WITH RARE EARTHS

WANG LIU-FANG,* YANG ZHENG-YIN, PENG ZHOU-REN

Department of Chemistry, Lanzhou University, Lanzhou 730000, P.R.C.

CHENG GUO-QUAN, GUO HONG-YING, SUN AL-LI

Tumor institute of Gansu Province, P.R.C.

WANG QI and HE FENG YING

Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, P.R.C.

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Thirteen new solid complexes of 5-fluorouracilacetic acid (FAA) with rare earth metals (RE) have been synthesized. Elemental analysis, IR, UV spectra, TG-DTA, conductance measurements and ^{1}H NMR spectra have been used to characterise them. The general formula of the complexes is $Ln(FAA)_3 \cdot 2H_2O$ ($Ln = La \rightarrow Yb$, Pm not included). The anticarcinogenic activity of $La(FAA)_3 \cdot 2H_2O$ was tested. The results obtained showed that the survival period of mice which had been transplanted with ascites carcinoma (HepA) and then treated with the La complex can be prolonged to 235% of the control but the ligand alone showed little anticarcinogenic activity. Some 42% of EC cancer cell growth can be inhibited by the La complex. The LD_{50} is 500 mg kg^{-1}.

Keywords: Anticarcinogenic activity, rare earth metals, 5-fluorouracil-1-acetic acid, ascites carcinoma

INTRODUCTION

FAA is a commonly used clinical anticarcinogenic agent, but its application is limited due to its toxicity. On the other hand, it has been reported some time ago that pituitary gland-related tumors can be cured by administration of rare earth elements.[1] In order to study the effect of substituent groups and the rare earth ion on the anticarcinogenic activity of 5-fluorouracil, corresponding rare earth complexes of a ligand derivative have been synthesized. Structure and properties were characterized and anticarcinogenic activity tested. The results obtained showed that these complexes possess favourable anticarcinogenic activity.

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EXPERIMENTAL

Apparatus and Reagents

The apparatus used for this study included a 1106 elemental analyzer (Carlo Erba, Italy), a DDS-12 digital conductometer (Zhejiang Xaoshan Instrument Standard Spares Plant, China), a 170 SX Fourier IR spectrophotometer (Nicolet, USA), a UV-240 spectrophotometer (Shimadzu, Japan), a PCT-2 thermal balance (Beijing Analytical Instrument Plant, China) and an FT-80A nuclear magnetic resonance instrument (Varian, USA). The chemicals used included rare earth oxides (99.99%, Yaolong Chemical Works, Shanghai, China) which were transformed into carbonates, $Ln_2(CO_3)_3$, and FAA which was synthesized[2] using analytical grade 5-fluorouracil and chloroacetic acid.

Synthesis of the Complexes

$Ln_2(CO_3)_3$ (1.09 mmol) was added to 40 cm^3 of an aqueous solution containing FAA (2.66 mmol). The mixture was warmed and stirred for 15 hrs keeping the temperature below 80°C. The pH of the solution was finally about 7. Excess Ln salt was filtered off and the filtrate was concentrated on a water bath to separate the complex, which was then filtered, washed with absolute ethanol, dried under an infrared lamp and then in a vacuum desiccator. The final powdered products were colourless. C, H, N contents were determined as indicated above and Ln by EDTA titration. Ce content was obtained by weighing the CeO_2 residue after calcinating the Ce complex at 800°C.

RESULTS AND DISCUSSION

Composition and Properties of the Complexes

Elemental compositions, molar conductances and molecular formulae of the complexes are listed in Table I. The complexes are stable in air and very soluble in water. They are also soluble in $(CH_3)_2SO$, slightly soluble in CH_3OH and EtOH, but not in acetone and $CHCl_3$. As seen in Table I, the molar conductances of the complexes in $(CH_3)_2SO$ vary from 36 to 74.5 S cm^2 mol^{-1}.

Thermal Stability of the Complexes

The thermal behaviour of the complexes was similar. They all have a fixed m.p. over a narrow range. Two endothermic peaks on the DTA curve (94 ~ 204°C) were seen. The complexes lose two molecules of H_2O in this range. The temperature corresponding to water loss indicates that the water molecules are bound, this being also confirmed by IR studies. There is an absorption peak at 244 ~ 265°C coinciding with the m.p. All complexes have two exothermic peaks (300 ~ 600°C) corresponding to 70% weight loss. Thermal data are listed in Table II.

TABLE I
Analyses and molar conductances for the complexes

Complex	N%		C%		H%		RE%		Conductance in $(CH_3)_2SO$, S cm^3 mol^{-1}
	Calc	Found	Calc	Found	Calc	Found	Calc	Found	
$La(FAA)_3 \cdot 2H_2O$	11.14	10.89	29.35	28.94	2.17	2.09	18.87	19.11	47.4
$Ce(FAA)_3 \cdot 2H_2O$	11.34	10.91	29.30	29.60	2.17	1.99	19.01	19.16	45.6
$Pr(FAA)_3 \cdot 2H_2O$	11.38	11.34	29.27	29.71	2.17	2.21	19.10	18.91	59.3
$Nd(FAA)_3 \cdot 2H_2O$	11.33	11.45	29.14	29.64	2.16	2.20	19.45	19.55	59.5
$Sm(FAA)_3 \cdot 2H_2O$	11.24	10.78	28.90	28.36	2.14	1.98	20.12	19.96	36.6
$Eu(FAA)_3 \cdot 2H_2O$	11.22	10.78	28.84	28.61	2.14	1.94	20.89	20.74	51.0
$Gd(FAA)_3 \cdot 2H_2O$	11.4	11.23	28.64	29.05	2.12	2.08	20.84	20.47	57.5
$Tb(FAA)_3 \cdot 2H_2O$	11.1	10.87	28.57	28.51	2.12	2.21	21.02	21.04	57.1
$Dy(FAA)_3 \cdot 2H_2O$	11.06	11.10	28.44	28.60	2.11	1.99	21.40	20.99	57.6
$Ho(FAA)_3 \cdot 2H_2O$	11.02	11.31	28.35	28.70	2.10	1.96	21.65	21.67	68.1
$Er(FAA)_3 \cdot 2H_2O$	10.99	11.26	28.26	28.39	2.09	2.12	21.89	21.87	53.6
$Tm(FAA)_3 \cdot 2H_2O$	10.97	11.39	28.20	28.08	2.09	1.93	22.06	21.93	54.0
$Tb(FAA)_3 \cdot 2H_2O$	10.91	11.01	28.05	28.16	2.07	1.96	22.34	22.01	74.3

TABLE II
Thermal data for the complexes

		H_2O loss temp., °C*			Phase transition temp., °C (T_3)	Decomposition temp., °C		Total wt loss, %
	m.p.	T_1	T_2	%		T_4	T_5	
Ligand	250	108	204	4.89	248	321	574	72.4
La**	250	146	200	4.92	246	331	583	72.0
Ce	244	102	121	4.88	244	311	487	72.3
Pr	246	101	192	4.86	246	293	559	72.7
Nd	251	120	185	4.82	249	374	504	71.5
Sm	249	147	192	4.82	249	365	555	72.0
Eu	243	119	192	4.77	248	334	548	70.8
Gd	242	147	188	4.76	243	339	556	70.6
Tb	260	102	195	4.76	261	333	540	70.6
Dy	256	155	188	4.72	257	339	569	70.4
Ho	260	113	157	4.71	269	331	550	70.7
Er	260	115	162	4.70	262	332	597	69.6
Tm	265	94	147	2.68	264	320	555	69.2

* H_2O lost corresponds to two molecules of water. Residue after decomposition corresponds to Ln_2O_3.
** Metal complexes as listed in Table I.

TABLE III
UV data for ligand and complexes

	λ_{max} (nm)	10^{-3} ε, mol l^{-1} cm^{-1}	λ_{max} (nm)	10^{-3} ε mol l^{-1} cm^{-1}
FAA	272	4.02	205	3.97
$La(FAA)_3 \cdot 2H_2O$	272	24.8	212	21.8
$Ce(FAA)_3 \cdot 2H_2O$	272	25.4	210	22.8
$Pr(FAA)_3 \cdot 2H_2O$	272	23.5	210	21.5
$Nd(FAA)_3 \cdot 2H_2O$	272	25.3	207	24.7
$Sm(FAA)_3 \cdot 2H_2O$	272	24.0	209	22.0
$Eu(FAA)_3 \cdot 2H_2O$	272	25.5	207	24.5
$Gd(FAA)_3 \cdot 2H_2O$	272	25.2	209	23.3
$Tb(FAA)_3 \cdot 2H_2O$	273	23.8	207	24.1
$Dy(FAA)_3 \cdot 2H_2O$	272	26.3	210	22.9
$Ho(FAA)_3 \cdot 2H_2O$	273	24.3	209	22.1
$Er(FAA)_3 \cdot 2H_2O$	273	24.7	207	23.4
$Tm(FAA)_3 \cdot 2H_2O$	273	24.7	207	23.4
$Yb(FAA)_3 \cdot 2H_2O$	273	27.5	210	24.8

Electronic Spectra

The UV absorption of aqueous solutions of the complexes was measured. As seen in Table III, the molar extinction coefficients of the complexes are about six times larger than the free ligand. The values should be about three times as large if the addition rule could be applied. This abnormal result is probably due to special steric properties of the complexes.

IR Studies

The IR spectra of the thirteen complexes are similar; ν_{OH} and δ_{H-OH} peaks appear at 3396–3481 and 1627–1640 cm^{-1}, respectively; the ligand gave no such bands. This proves the existence of coordinated water in the complexes and coincides with the results of thermal analysis. The characteristic $\nu_{C=O}$ mode of the ligand carboxy group (1703 cm^{-1}) disappeared upon complexation. Instead, the complexes displayed both symmetric and unsymmetric stretching vibrations of COO^- (1571 ~ 1604, 1401 ~ 1407 cm^{-1}). This fact strongly suggests the coordination of the ligand carboxy group with the Ln(III) ions. The $C^2 = 0$ stretch of the pyrimidine ring shifted from 1744 cm^{-1} (ligand) to 1687 ~ 1701 cm^{-1} in the complexes, this being due to weakening of C=O bond strength on coordination. By comparison with the free ligand, the appearance of ν_{Ln-O} at 365–375 cm^{-1} in the complexes further proves the coordination of the ligand with the rare earths.

^1H NMR of $La(FAA)_3 \cdot 2H_2O$

The ^1H NMR spectra of the La complexes were studied using DMSO as solvent and reference. FAA: δ 12.0 (1H, COOH); δ 11.5 (1H, NH); δ 8.2 (1H, J = 7.1 Hz, C^6–H); δ 4.1 (2H, CH_2). $La(FAA)_3 \cdot 2H_2O$: δ 11.5 (1H, NH); δ 7.9 (1H, J = 7.1 Hz, C^6–H); δ 4.1 (2H, CH_2); δ 3.0–3.7 (broad peak, H_2O). It is apparent that, after coordination, the COOH hydrogen peak disappears. The displacement of C^6–H to high field (0.3 ppm) is due to the transfer of electron density at C^2=O to La^{3+} after coordination; this in turn causes an increase of electron density at C^6–H. This fact also proves the coordination of C^2=O with the La^{3+} ion.

Anticarcinogenic Activity

Table IV summarizes results concerning mice which were transplanted with hepatic carcinoma cell (HepA) and intraperitoneally injected with $La(FAA)_3 \cdot 2H_2O$ or FAA. The number of mice was ten in each group tested and that in control group was fifteen. The results shown in Table IV indicate that the La complexes possess certain

TABLE IV
Results of tests against Hep A*

	Dosage ID_{50}	Average life (days) Test group		Control		Life prolongation, %	P value
Ligand	1/12.5	11.1	1.5	12.5	3.1	−11.2	
	1/15	11.1	2.9	12.5	2.9	−11.2	
	1/20	11.3	2.2	12.5	3.1	−9.6	
La complex	1/10	25.1	16.5	10.6	1.7	136.7	0.01
	1/15	35.5	17.6	10.6	1.7	234.9	0.001
	1/15	39.4	16.8	12.2	2.4	222.9	0.001
	1/20	29.4	17.8	12.2	2.4	140.9	0.01
	1/25	20.5	4.0	12.2	2.4	68	0.5

* 10 doses, one dose per day, intraperitoneally administered. The mice used were healthy Kunming species supplied by the Lanzhou Institute of Bioproducts (originally from the Kunming Institute of Zoology).

inhibitory effects on the growth of HepA cell. The life duration of mice transplanted with HepA cells can be prolonged by 2.35 times over the control if the optimum dosage of the La complex was intraperitoneally administered (10 doses, one dose every day). The ligand itself had no such effect. In addition, we have tested the inhibitory effects of the La complexes on the growth of EC and C_{27} cells. The inhibitory rates were 41.8 and 16.8%, respectively. The LD_{50} of the La complexes is 500 mg kg^{-1}.

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