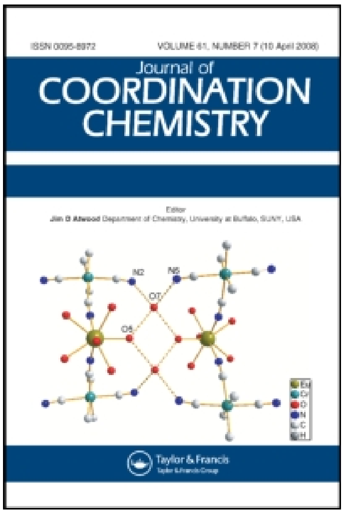

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Synthesis, characterization and antioxidative activity of new rare earth complexes of 6-hydroxy chromone-3-carbaldehyde-(4'-hydroxy)benzoyl hydrazone

Tian-Rong Li[a]; Zheng-Yin Yang[a]; Bao-Dui Wang[a]
[a] College of Chemistry and Chemical Engineering and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

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Synthesis, characterization and antioxidative activity of new rare earth complexes of 6-hydroxy chromone-3-carbaldehyde-(4′-hydroxy)benzoyl hydrazone

TIAN-RONG LI, ZHENG-YIN YANG* and BAO-DUI WANG

College of Chemistry and Chemical Engineering and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R. China

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A new ligand, 6-hydroxy chromone-3-carbaldehyde-(4′-hydroxy)benzoyl hydrazone (H_3L), was prepared by condensation of 6-hydroxy-3-carbaldehyde chromone with 4-hydroxy benzoyl hydrazine. Four rare earth complexes of formula $[Ln(H_3L)_2(NO_3)_2] \cdot NO_3$ [where Ln(III) = La (**1**), Sm (**2**), Eu (**3**) and Dy (**4**)] have been synthesized and characterized on the basis of IR spectra, UV spectra, elemental analyses, molar conductivity, and thermal analyses. Suppression ratios for $O_2^{-\bullet}$ (**a**) and $OH^\bullet$ (**b**) of the ligand and its complexes were studied by spectrophotometric methods. The experiments show that IC_{50} (**a**) and IC_{50} (**b**) of the complexes are 24.07–57.32 and 6.97–14.08 µM, respectively. For the ligand, IC_{50} (**a**) and IC_{50} (**b**) are 148.29 and 15.67 µM, respectively. The La (**1**), Sm (**2**), Eu (**3**) complexes are better effective inhibitors for $OH^\bullet$ than mannitol, indicating that the complexes suppress $O_2^{-\bullet}$ and $OH^\bullet$ and are more effective antioxidants than the ligand.

Keywords: 6-Hydroxy chromone-3-carbaldehyde-(4′-hydroxy)benzoyl hydrazone; Rare earth complexes; Antioxidative activities

1. Introduction

Superoxide radical ($O_2^{-\bullet}$) and hydroxyl radical ($OH^\bullet$) are produced in most organ systems and participate in various physiological and pathophysiological processes such as carcinogenesis, aging, viral infection, inflammation, and others [1]. They damage cellular function and are involved with diseases such as atherosclerosis, arthritis, muscular dystrophy and, very likely, cancer [2]. Superoxide dismutase (SOD) is a natural scavenger for $O_2^{-\bullet}$. It often can scavenge the surplus free radicals in the body and hold the free radical density in the body at a normal level. However, the use of the SOD protein as a therapeutic is confined by its price, size, charge and rapid clearance [3]. Likewise, a variety of $OH^\bullet$ scavengers are known, but their applications were also limited [4]. Many researchers have been working to develop metal complexes as efficient scavengers.

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*Corresponding author. Email: yangzy@lzu.edu.cn

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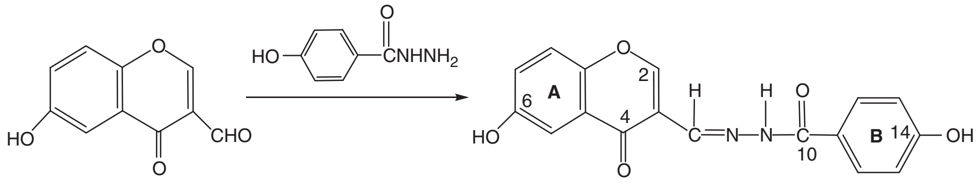

Figure 1. Preparation route of the ligand.

Hydrazones and their complexes have provoked wide interest for their diverse biological and pharmaceutical activities, such as anticancer, antitumor and anti-oxidative activities, as well as inhibition of lipid peroxidation etc. [5–12]. Our previous work showed that rare earth complexes of 4,5,7-trihydroxy-flavanone benzoyl hydrazone have certain antioxidative and cytotoxic activities [12, 13]. As a continuation of the study of flavone benzoyl hydrazone and its complexes, a ligand, 6-hydroxy chromone-3-carbaldehyde-(4′-hydroxy)benzoyl hydrazone (figure 1), and its rare earth complexes have been synthesized and characterized on the basis of elemental analyses, molar conductivity, IR and UV spectra, and thermal analyses. Their antioxidative activities (scavenger effects on $O_2^{-\bullet}$ and $OH^{\bullet}$) are also reported in this article. Information obtained form this study will help to develop new therapeutic reagents for some diseases.

2. Experimental

2.1. *Materials*

Nitroblue tetrazolium (NBT), methionine (MET), vitamin B_2 ($VitB_2$) were purchased from Sigma Chemical Co. 4-hydroxy benzoyl hydrazine and safranin, EDTA were purchased from the Beijing Chemical Co. (P.R. China). 6-Hydroxy-3-carbaldehyde chromone was prepared according to the literature method [14]. All materials and solvents were of analytical grade. The rare earth(III) nitrates were prepared form their oxides (99.9%) acquired form Nong Hua (P.R. China). EDTA-Fe(II) and KH_2PO_4-K_2HPO_4 buffers were prepared with deionized and distilled water.

2.2. *Physical measurements*

Melting points of the compounds were determined on an XT4-100× microscopic melting point apparatus (Beijing Electrooptical Instrument Factory, China). Carbon, hydrogen, and nitrogen were analyzed on an Elemental Vario EL analyzer. The metal contents of the complexes were determined by titration with EDTA. Infrared spectra (4000–400 cm^{-1}) were determined with KBr disks on a Thermo Nicolet FT-IR spectrometer. The ultraviolet spectra (270–450 nm) of the ligand and its complexes were recorded on a Varian Cary 100 Conc spectrophotometer and DMF was used as a reference and solvent. The thermal behavior was monitored on a WCT-2A differential thermal analyzer (Beijing Optics Instrument Factory, China). The molar conductance values were determined in DMF on a DDS-11C conductivity meter (Shanghai Leici Factory, China). ^1H NMR spectra were recorded on a Varian VR 300 MHz spectrometer with $(CD_3)_2SO$ as solvent and $SiMe_4$ as an internal standard. The antioxidative activity was performed in DMF with a 72 spectrophotometer (Shanghai Analytical Instrument Factory, China).

2.3. *Preparation of the ligand*

6-Hydroxy-3-carbaldehyde chromone (1.90 g, 10 mmol) and 4-hydroxy benzoyl hydrazine (1.52 g, 10 mmol) were dissolved in ethanol (40 cm^3). The mixture was then stirred for two hours at room temperature and a white precipitate formed (figure 1). The precipitate was filtered and washed with ethanol. Finally, the product was purified by recrystallizing in DMF/H_2O ($v/v = 1:1$) and dried in vacuum. Yield, 2.90 g (90%); m.p. 256–258°C. Anal. Found (%): C, 62.71; H, 3.78; N, 8.90. Calcd for $C_{17}H_{12}N_2O_5$: C, 62.96; H, 3.70; N, 8.64. ^1H NMR (DMSO-d_6), δ (ppm): 11.68 (1H, br, NH), 10.14 (1H, s, 6-OH), 10.09 (1H, s, 14-OH), 8.72 (1H, s, 2-H), 8.56 (1H, s, CH=N), 7.81–6.82 (7H, m, Ph–H).

2.4. *Preparation of the complexes*

The ligand (0.324 g, 1 mmol) and the La(III) nitrate (0.217 g, 0.5 mmol) were dissolved in methanol (10 cm^3). The solution was stirred and heated to 60°C. After 5 min, the solution was filtered to remove residue and continued stirring for 24 h at room temperature. Finally, there was a white precipitate, the La(III) complex (**1**), which was separated by suction filtration, purified by washing several times with ethanol, and dried in vacuum. Sm (**2**), Eu (**3**) and Dy (**4**) complexes were prepared in the same way.

2.5. *Scavenger measurement of $O_2^{-\bullet}$*

The superoxide radicals ($O_2^{-\bullet}$) were produced by the system of MET/VitB_2/NBT [15]. The amount of $O_2^{-\bullet}$ and suppression ratio for $O_2^{-\bullet}$ can be calculated by measuring the absorbance at 560 nm. Solutions of MET, VitB_2, and NBT were prepared with 0.067 M phosphate buffer (pH = 7.8) avoiding light. The tested compounds were dissolved in DMF. The 10 cm^3 reaction mixture contained MET (0.01 M), NBT (4.6×10^{-5} M), VitB_2 (3.3×10^{-6} M), and the tested compound (the final concentration: $C_{i(i=1\text{–}4)} =$ 11.5, 23, 46, 92 μM). After illuminating with a fluorescent lamp at 30°C for 10 min, the absorbances of the samples (A_i) were measured at 560 nm. The sample without the tested compound was used as the control and its absorbance was A_0. The suppression ratio for $O_2^{-\bullet}$ was calculated from the following expression:

$$\text{Suppression ratio} = 100\frac{A_0 - A_i}{A_0} \tag{1}$$

where A_i = the absorbance in the presence of the ligand or its complexes and
A_0 = the absorbance in the absence of the ligand or its complexes.

2.6. *Scavenger measurement of OH•*

The hydroxyl radical (OH•) in aqueous media was generated through the Fenton reaction [16]. The solution of the compound to be tested was prepared with DMF. The sample contained $1\,\mathrm{cm}^3$ of 0.15 M phosphate buffer (pH = 7.4), $1\,\mathrm{cm}^3$ of $40\,\mu\mathrm{g\,cm}^{-3}$ safranin, $1\,\mathrm{cm}^3$ of 0.945 mM EDTA-Fe(II), $1\,\mathrm{cm}^3$ of 3% H_2O_2, and $0.5\,\mathrm{cm}^3$ of the solution of the compound to be tested (the final concentration: $C_{i(i=1\text{–}4)} = 11.5$, 23, 46, 92 µM). The sample without the tested compound and EDTA-Fe(II) was used as the control. The reaction mixtures were incubated at 37°C for 30 min in a water-bath. The absorbances of the samples (A_i) and the control (A_0) were measured at 520 nm. The suppression ratio for OH• was calculated from the following expression:

$$\text{Suppression ratio} = 100\frac{A_i}{A_0} \tag{2}$$

where A_i = the absorbance in the presence of the ligand or its complexes and
A_0 = the absorbance in the absence of the tested compound and EDTA-Fe(II).

3. Results and discussion

All of the complexes are air stable for extended periods and soluble in DMSO, DMF and methanol, slightly soluble in ethanol and water and insoluble in chloroform, ethyl acetate and diethyl ether. The molar conductivities of the complexes are around $100\text{–}107\,\mathrm{Ohm}^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$ in DMF, showing that all complexes are 1 : 1 electrolytes [17]. The elemental analyses and molar conductivities (table 1) show that formulas of the complexes conform to $[\mathrm{Ln(H_3L)_2(NO_3)_2}]\cdot\mathrm{NO_3}$ [where Ln(III) = La (**1**), Sm (**2**), Eu (**3**) and Dy (**4**)].

3.1. *IR spectra*

The main stretching frequencies of ligand and its complexes are listed in table 2; the IR spectra of the complexes are similar. The ν (C_4=O) and ν (C_{10}=O) vibrations of the free ligand are at 1632 and $1649\,\mathrm{cm}^{-1}$, respectively; for the complexes these peaks shift to 1606 and $1624\,\mathrm{cm}^{-1}$. $\Delta\nu_{(\text{ligand–complexes})}$ is equal to 23–27 and $21\text{–}25\,\mathrm{cm}^{-1}$. The band at $590\,\mathrm{cm}^{-1}$ is assigned to ν (M–O). These demonstrate that the oxygen of carbonyl has formed a coordinative bond with the rare earth ions. The band at $1598\,\mathrm{cm}^{-1}$ for the free ligand is assigned to the ν (C=N) stretch. It shifts to $1574\,\mathrm{cm}^{-1}$ for its complexes.

Table 1. Elemental analyses and molar conductivities of the free ligand and its complexes.

Compounds	H_3L	**1**	**2**	**3**	**4**
C% found (Calcd)	62.71 (62.96)	41.45 (41.94)	41.56 (41.45)	41.67 (41.38)	40.20 (40.94)
H% found (Calcd)	3.78 (3.70)	2.23 (2.46)	2.35 (2.44)	2.35 (2.43)	2.32 (2.41)
N% found (Calcd)	8.90 (8.64)	10.02 (10.07)	10.08 (9.96)	9.79 (9.94)	10.09 (9.83)
Ln% found (Calcd)		14.35 (14.27)	15.52 (15.27)	16.14 (15.41)	16.85 (16.31)
Λ_M ($\mathrm{Ohm}^{-1}\,\mathrm{cm}^2\,\mathrm{mol}^{-1}$)		100	102	107	105

Table 2. IR spectral data of the free ligand and its complexes (cm^{-1}).

Compounds	H_3L	**1**	**2**	**3**	**4**
ν (C_4=O)	1632s	1606s	1605s	1609s	1606s
ν (C_{10}=O)	1649s	1624s	1628s	1628s	1624s
ν (C=N)	1598s	1572s	1574s	1574s	1573s
ν_1 (NO_3)		1478m	1479m	1478m	1480m
ν_2 (NO_3)		1174m	1176m	1176m	1176m
ν_3 (NO_3)		841m	839m	839m	837m
ν_4 (NO_3)		1322s	1323s	1322s	1323s
ν_0 (NO_3)		1383s	1382s	1382s	1383s
ν (M–O)		593w	590w	590w	589w
ν (M–N)		439w	437w	437w	435w

s = strong; m = medium; w = weak.

Table 3. UV spectral data of the free ligand and its complexes.

Compounds	H_3L	**1**	**2**	**3**	**4**
λ_{max} (nm)	287, 377	291, 328	289, 325	294, 318	294, 326
$\varepsilon_{max} \times 10^{-5}$ ($L\,mol^{-1}\,cm^{-1}$)	0.13, 0.04	1.5, 1.7	1.1, 1.2	0.97, 0.91	1.2, 1.1

Weak bands at 437 cm^{-1} are assigned to ν (M–N), further confirming that the nitrogen of the imino-group bonds to the rare earth ions [18–21].

The absorption bands assigned to the coordinated nitrates are observed about at 1480 (ν_{as}) and 839 (ν_s) cm^{-1}. The separation of the two highest frequency bands $|\nu_4 - \nu_1|$ is approximately 156 cm^{-1}, indicating that the coordinated nitrates in the complexes are bidentate. The free nitrates (ν_0) appear at 1384 cm^{-1} in the spectra of the complexes [20, 21]. This conclusion is also supported by the result of the conductivity experiments.

3.2. *UV spectra*

The UV spectral data of the compounds in DMF are listed in table 3. The free ligand has a strong absorption band at 287 nm and a weak absorption band at 377 nm (figure 2). The bands at 287 nm and 377 nm are related to the absorption of **A** ring and **B** ring, respectively (figure 1). The spectra of the complexes are similar to the free ligand, except for the peak at 377 nm, which shifts to 325 nm. The blue-shift shows that the **B** ring plane with the conjugate chelate ring plane are noncoplanar because of repulsive interactions [22].

3.3. *Thermal analyses*

The thermal analysis data are listed in table 4. The complexes begin to decompose at 251°C or so and there are three exothermic peaks around 251–447°C. The corresponding TG curves show a series of weight loss. Under 200°C, there are no endothermic peaks and no weight loss on corresponding TG curves, indicating that

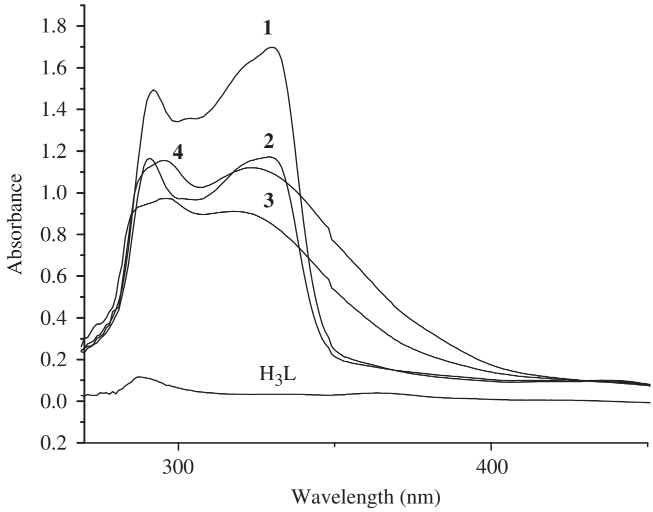

Figure 2. The UV spectra of the compounds.

Table 4. Thermal analyses of the complexes.

	Decomp.			
Complexes	t_1 (°C)	t_2 (°C)	t_3 (°C)	Residue[a] (%)
1	247	379	444	15.89 (16.74)
2	252	367	447	17.00 (17.71)
3	256	379	450	17.35 (17.84)
4	251	386	438	18.24 (18.71)

[a] Data in parentheses are the calculated values.

there are no crystal or coordinate solvent molecules. While being heated to 800°C, the complexes become their corresponding oxides. The residues are in agreement with calculated values.

On the basis of above evidence and analyses, the possible structure of the complexes is shown in figure 3.

3.4. *Suppression ratio for $O_2^{-\bullet}$ and $OH^{\bullet}$*

The data of the suppression ratio for $O_2^{-\bullet}$ are listed in table 5. We find that the inhibitory effect of the tested compounds on $O_2^{-\bullet}$ are concentration related and the suppression ratio increases with the increasing sample concentration in the range of the tested concentration (figure 4). The suppression ratio of the ligand ($IC_{50} = 148.29\,\mu M$) for $O_2^{-\bullet}$ is the least while Sm(III) complex (**2**) ($IC_{50} = 24.07\,\mu M$) is the most effective. It is clear that the scavenger effect on $O_2^{-\bullet}$ can be enhanced by formation of metal-ligand coordination complexes and the nature of the rare earth ions also affects the ability.

Comparison of the inhibitory effect on $OH^{\bullet}$ is shown in table 6. All compounds scavenge $OH^{\bullet}$ also in a concentration-dependent manner (figure 5). The order of the

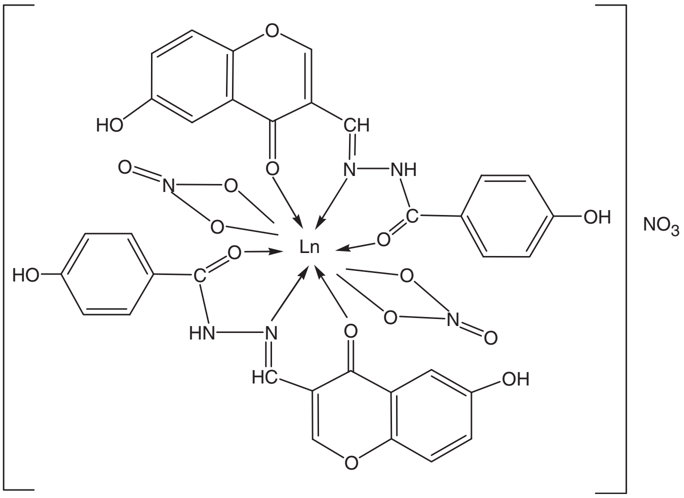

Figure 3. The possible structure of the complexes.

Table 5. The influence of investigated compounds for $O_2^{-\bullet}$.

Compounds	Suppression ratio (%) for $O_2^{-\bullet}$ 11.5 μM	23 μM	46 μM	92 μM	Equation	IC$_{50}$[a] μM	*r*
H_3L	33.84	43.21	53.87	57.25	$y = 0.263x - 0.071$	148.29	0.958
1	33.80	43.83	63.66	66.34	$y = 0.489x - 0.343$	52.96	0.969
2	12.52	32.13	46.66	55.62	$y = 0.527x - 0.228$	24.07	0.992
3	25.32	32.86	50.81	56.10	$y = 0.360x - 0.133$	57.32	0.952
4	32.93	47.61	67.47	80.14	$y = 0.438x - 0.166$	33.15	0.998

[a] IC$_{50}$ values were calculated from regression lines where *x* was log of the tested compound concentration and *y* was percent inhibition of the tested compounds. When the percent inhibition was 50%, the corresponding concentration of the tested compound was the half inhibitory concentration IC$_{50}$.

r = correlation coefficient.

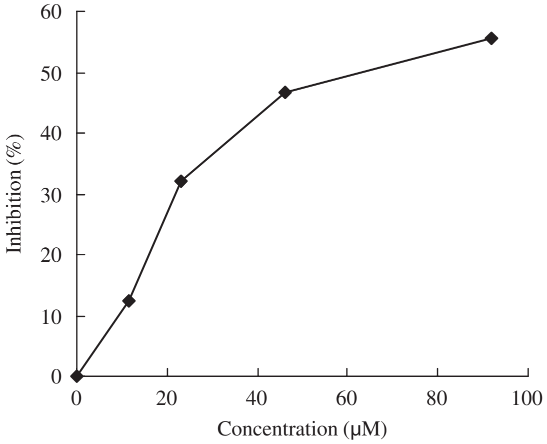

Figure 4. Suppression ratio for $O_2^{-\bullet}$ of **2**.

Table 6. The influence of investigated compounds for $OH^\bullet$.

Compounds	Suppression ratio (%) for $OH^\bullet$ 11.5 μM	23 μM	46 μM	92 μM	Equation	IC_{50} μM	*r*
H_3L	42.50	58.23	70.50	79.20	$y=0.400x+0.022$	15.67	0.979
1	52.10	72.40	89.50	96.50	$y=0.489x+0.035$	8.93	0.954
2	53.91	65.13	83.70	92.76	$y=0.441x+0.071$	9.39	0.980
3	55.51	65.60	76.30	82.50	$y=0.300x+0.247$	6.97	0.984
4	45.25	58.87	77.53	86.49	$y=0.464x-0.033$	14.08	0.980
Mannitol	49.00	72.40	90.49	98.90	$y=0.559x-0.068$	10.38	0.980

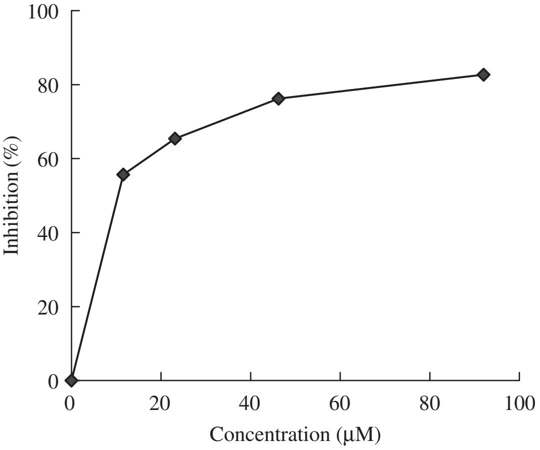

Figure 5. Suppression ratio for $OH^\bullet$ of **3**.

suppression ratio of compounds tested for $OH^\bullet$ is **3** > **1** > **2** > mannitol > **4** > H_3L. It is clearly shown that metal complexes exhibit considerable scavenging activity and that La (**1**), Sm (**2**), Eu (**3**) complexes are more effective inhibitors for $OH^\bullet$ than mannitol which is usually used as special scavenger for $OH^\bullet$. Therefore, the antioxidative activities of the complexes studied in this article should be further examined.

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