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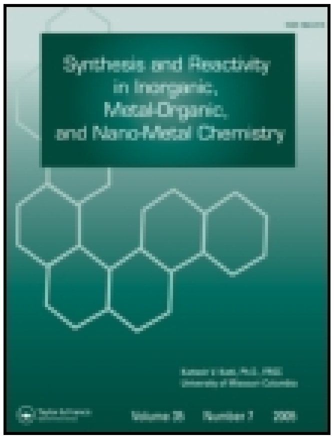

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SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF RARE EARTH COMPLEXES OF 1-PHENYL-3-METHYL-4-BENZOYL-5-PYRAZOLONE BENZOYLHYDRAZONE

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SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF RARE EARTH COMPLEXES OF 1-PHENYL-3-METHYL-4-BENZOYL-5-PYRAZOLONE BENZOYLHYDRAZONE

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ABSTRACT

1-Phenyl-3-methyl-4-benzyol-5-pyrazolone benzoylhydrazone (H_2L) was prepared by condensation of 1-phenyl-3-methyl-4-benzyol-5-pyrazolone with benzoylhdrazine. Six rare earth complexes of H_2L have been synthesized and characterized on the basis of elemental analyses, IR, UV, ^{1}H NMR spectra and thermal analyses. The general formula of the complexes is $Ln(HL)_3 \cdot 3H_2O$ (where Ln(III) = La, Pr, Nd, Eu, Gd and Er). In addition, the suppression ratio (η_r) for $O_2^{-\bullet}$ radicals as well as the inhibitory ratio (η_1) for lipid peroxidation were determined by an UV spectral method. The results show that η_r and η_1 of the complexes are around 39–51% and 20–39% respectively. For the ligand, $\eta_r = 36\%$ $\eta_1 = 18\%$.

INTRODUCTION

The surplus free radicals in the body are often scavenged by superoxide dismutase (SOD), which makes the free radical density in the body to be held at a normal level. SOD is a natural scavenger for $O_2^{-\bullet}$ radicals. However, SOD is expensive and unstable, so it is very important to devise metal complexes that can replace SOD. Our previous work showed that the rare earth complexes of the hydrazone derived from 1-phenyl-3-methyl-4-benzyol-5-pyrazolone (PMBP) with isoniazid have certain scavenger effects on $O_2^{-\bullet}$ radicals.[1,3] 1-Phenyl-3-methyl-5-hydrody-4-pyrazolone benzyolhydrazone (H_2L) and its rare earth complexes have been synthesized with a view to further investigating the biological activities of some similar hydrazone complexes with rare earths and both their scavenger effects on $O_2^{-\bullet}$ radicals and inhibitory effects on lipid peroxidation as determined by UV spectra.

EXPERIMENTAL

Materials

Nitrobluetetrazolium (NBT), methionine (MET), vitamin B_2 ($VitB_2$), tris(hydroxymethyl)aminomethane (Tris), thiobarbituric acid (TBA) and ascorbic acid were purchased from Sigma Chemical Co. Trichloroacetic acid (TCA), 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone (PMBP), benzoyl hydrazine and Ln_2O_3 (where Ln = La, Pr, Nd, Eu, Gd and Er) were produced in China. All chemicals used were of analytical grade. Tris-HCl buffers were prepared in deionized distilled H_2O. The hydrated rare earth(III) chlorides were prepared by dissolving Ln_2O_3 in concentrated HCl, and then crystallizing the products.

Physical Measurements

Carbon, hydrogen and nitrogen were analyzed on a VarioEL elemental analyzer. The rare earth contents of the complexes were determined by titration with EDTA. The infrared spectra (IR, $\nu = 4{,}000\text{–}300\,\text{cm}^{-1}$) were determined by the KBr pressed disc method on a Nicolet-170SX FT-IR spectrophotometer. The ultraviolet spectra (UV, $\lambda_{max} = 190\text{–}400\,\text{nm}$) of the complexes were recorded on a Shimadzu UV-240 spectrophotometer and distilled H_2O was used as a reference and solvent. The *f-f* transitions of the electronic spectra ($\lambda_{max} = 380\text{–}600\,\text{nm}$) of the central ions in solid complexes were measured by reflectance spectroscopy; the samples were pressed into discs of 1 mm thickness. $BaSO_4$ was used as a reference, and pure $LnCl_3 \cdot 6H_2$ as a control. The thermal behavior was monitored on a PCT-2 differential thermal analyzer, where α-Al_2O_3 was used as a reference in static air. ^1H NMR spectra were measured on a Nicolet FT-80A NMR spectrometer, using TMS as a reference in $CDCl_3$. The molar conductance values were determined in anhydrous ethanol on a model DSS-11A conductivity meter.

Scavenger Test of $O_2^{-\bullet}$ Radicals

The $O_2^{-\bullet}$ radicals were produced by the system of MET/VitB_2/NBT.[4] Solutions of MET (9 mM), VitB_2 (0.054 mM) and NBT (0.67 mM) were prepared with 0.01 M Tris-HCl buffer (pH = 8) avoiding light. The reaction mixture (4.5 mL) included MET (1.5 mL), NBT (1.5 mL), VitB_2 (1.5 mL) and the compound to be tested (0.3–1.0 mg). After illuminating with a fluorescent lamp at room temperature for 10 min the absorbance (A_s) of the mixture was measured at 560 nm on an UV-240 spectrophotometer. The sample without the tested compound was used as the control, its absorbance is A_0. The suppression ratio was calculated on the basis of $(A_0-A_s)/A_0$.

Inhibitory Action for Lipid Peroxidation

1 g of fresh rabbit liver was weighed into a glass homogenizer, 10 mL of physiological saline solution was added, and the mixture was homogenized in an ice bath. The sample (4 mL) containing the tested compound (0.3 μM) and a control without the tested compound were vibrated at constant 37 °C for 2 h, then a 20% aqueous solution of TCA (3 mL) was immediately added to every sample and the control, respectively. After 15 min the reaction mixtures were centrifuged at 4000 cycles per min for 10 min. The clear solution of the samples (3 mL) was mixed in a screw-capped tube with 3 mL of TBA reagent, and heated in a boiling water bath for 30 min, then cooled in tap water. The absorbances (A_s,A_0) were measured at 532 nm, using 20% TCA as a reference. The inhibitory ratio was calculated on the basis of $(A_0-A_s)/A_0$.

Preparation of the Ligand

PMBP (2.224 g, 8 mol) and benzoyl hydrazine (1.088 g, 8 mmol) were dissolved in anhydrous ethanol (50 mL) and refluxed on a water bath for 2 h. From the light yellow solution eventually precipitated a great deal of yellow solid. The product was purified by recrystallizing it in anhydrous ethanol;

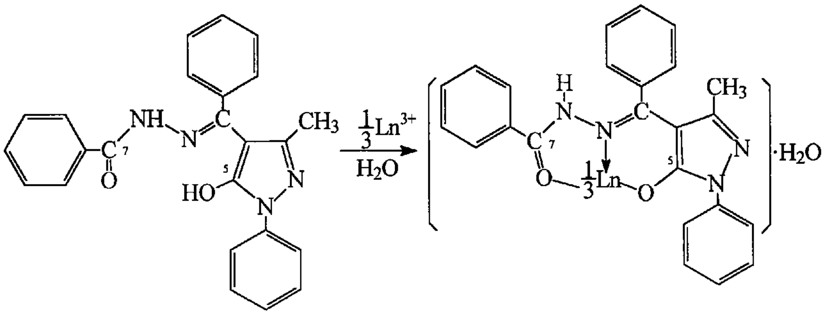
yield, 2.94 g (92%); m.p. 198–199 °C. Anal. Found: C, 72.63; H, 4.89; N, 14.08. Calc. for $C_{24}H_{19}N_4O_2$ (395.44): C, 72.90; H, 4.84; N, 14.17%. ^1H NMR ($CDCl_3$), δ (ppm): 1.53 (3H, singlet, CH_3); 7.20–8.10 (17H, multiplet, 3 phenyl, -NH-, OH).

Preparation of the Complexes

The ligand (0.38 g, 1 mmol) was added to water (50 mL) and heated at 50 °C with stirring, and the pH was adjusted to 7 by the addition of an aqueous solution of NaOH (10%). After all of the ligand was dissolved, a solution of $LaCl_3 \cdot 6H_2O$ (0.35 g, 1 mmol) in water (10 mL) was added dropwise to the system. After stirring at 50 °C for 0.5 h, a yellow precipitate formed. The product was separated by suction filtration, and purified by washing three times with water, and dried in a vacuum. The yield was 0.31 g (72%). The Pr, Nd, Eu, Gd and Er complexes were synthesized by the same method. All of the complexes are yellow powders, with the yields being 0.33 g (73%), 0.36 g (78%), 0.30 g (65%), 0.37 g (79%), 0.31 g (67%), respectively.

RESULTS AND DISCUSSION

All of the complexes are yellow and soluble in polar organic solvents such as anhydrous ethanol, dimethyl sulfoxide and trichloromethane, slightly soluble in water, and may be kept in air for one year. The molar conductivities of the complexes are around 2.56–5.01 $ohm^{-1} \cdot cm^2 \cdot mol^{-1}$ in anhydrous ethanol, showing that the complexes are non-electrolytes in anhydrous ethanol. Elemental analyses and molar conductivity data are listed in Table I. The elemental analyses show that the formulas of the complexes are $Ln(HL)_3 \cdot 3H_2O$ [Ln(III) = La, Pr, Nd, Eu, Gd and Er)] [see Eq. (1)].



(1)

Table I. Elemental Analysis and Molar Conductivity

Formula	M.w.	D.p.[a] (°C)	Color	Yield (%)	Elemental Analysis (Calc.) % C	H	N	Ln	Λ_M[b] (u)
$La(HL)_3 \cdot 3H_2O$	1376.3	411	Yellow	72	62.59	4.63	12.28	10.32	2.56
$LaC_{72}H_{60}N_{12}O_9$					(62.70)	(4.61)	(12.20)	(10.08)	
$Pr(HL)_3 \cdot 3H_2O$	1378.3	400	Yellow	73	62.52	4.53	12.09	10.51	3.48
$PrC_{72}H_{60}N_{12}O_9$					(62.61)	(4.60)	(12.18)	(10.21)	
$Nd(HL)_3 \cdot 3H_2O$	1381.6	432	Yellow	78	62.38	4.47	12.17	10.63	3.96
$NdC_{72}H_{60}N_{12}O_9$					(62.46)	(4.59)	(12.15)	(10.43)	
$Eu(HL)_3 \cdot 3H_2O$	1389.3	389	Yellow	65	62.09	4.48	11.98	11.01	2.77
$EuC_{72}H_{60}N_{12}O_9$					(62.11)	(4.56)	(12.08)	(10.92)	
$Gd(HL)_3 \cdot 3H_2O$	1394.6	410	Yellow	79	61.98	4.47	12.01	11.26	3.23
$GdC_{72}H_{60}N_{12}O_9$					(61.88)	(4.55)	(12.04)	(11.26)	
$Er(HL)_3 \cdot 3H_2O$	1404.6	395	Yellow	67	61.35	4.39	12.03	11.89	5.01
$ErC_{72}H_{60}N_{12}O_9$					(61.44)	(4.51)	(11.95)	(11.98)	

[a] D.p. is the decomposition point.
[b] $u = ohm^{-1} \cdot cm^2 \cdot mol^{-1}$.

Infrared Spectra

The main stretching frequencies of the IR spectra of the ligand and its complexes are tabulated in Table II. The aqueous ν(OH) and δ(HOH) bands of the complexes appear at 3367 and 1600 cm^{-1} or so, showing that there is some crystal water in the complexes.[3] The $\nu(C_7{=}O)$ and $\nu(C_5{=}O)$ vibrations of the free ligand are at 1645 and 1541 cm^{-1}, respectively. For the complexes these peaks shift to 1630 and 1435 cm^{-1} or so. Δν is equal to 13–16 or 105–107 cm^{-1}. The new bands around 454–458 cm^{-1} of the complexes are assigned to ν(M-O).[3] All of these prove that both of the carbonyl oxygens have formed a coordination bond with the rare earth ions, one of which ($C_5{=}O$) is in the enolic form. The band at 1593 cm^{-1} of the free ligand is assigned to the ν(C=N) stretching vibration; it shifts to 1569 cm^{-1} in its complexes. The new band around 348–351 cm^{-1} for the complexes is assigned to ν(M-N).[5] The new band further confirms that the nitrogen of the imino group bonds to the rare earth ions. For the ligand, ν(NH) and δ(NNH) appear at 3055 and 1521 cm^{-1}; these two bands for the complexes shift to 3058 and 1540 cm^{-1}, respectively, which demonstrates that there is one hydrogen of the -NHN= group in the complexes. All of these data confirm the fact that a conjugate chelate ring formed by ligand enolization exists in the complexes.

Table II. Main IR Data Ligand and Its Complexes (cm^{-1})

Complexes	ν(OH)	ν(NH)	$\nu(C_7{=}O)$	ν(C=N)	$\nu(C_5{=}O)$	δ(HOH)	δ(NNH)	ν(M-O)	ν(M-N)
H_2L		3055 w	1645 m	1593 m	1541 m		1521 w		
$La(HL)_3{\cdot}3H_2O$	3363 m	3058 m	1629 m	1567 m	1434 m	1599 m	1539 m	458 w	351 m
$Pr(HL)_3{\cdot}3H_2O$	3363 m	3058 m	1629 m	1569 m	1435 m	1599 m	1540 m	455 w	349 m
$Nd(HL)_3{\cdot}3H_2O$	3367 m	3057 m	1630 m	1569 m	1436 m	1600 m	1540 m	454 w	350 m
$Eu(HL)_3{\cdot}3H_2O$	3367 m	3057 m	1630 m	1569 m	1436 m	1599 m	1540 m	455 w	349 m
$Gd(HL)_3{\cdot}3H_2O$	3367 m	3058 m	1632 m	1570 m	1436 m	1602 m	1541 m	455 w	349 m
$Er(HL)_3{\cdot}3H_2O$	3367 m	3058 m	1630 m	1571 m	1435 m	1601 m	1541 m	457 w	348 m

Electronic Spectra

UV spectra data of complexes are listed in Table III. The free ligand exhibits three absorption bands at 251, 300 and 354 nm, respectively. The complexes also yield three bands at 244, 320 and 364 nm in the UV region. It is clear that a blue-shift of the first band has occurred to a certain extent, which shows that the phenyl ring and the conjugate chelate ring in the complexes are not co-planar because of their repulsion from each other. The red-shift of next two bands further proves that there is a conjugate chelate ring formed by ligand enolization in the complexes.[3] The *f-f* transition absorption for the Pr(III) and Nd(III) complexes in the solid have been determined, as shown in Table IV. The results show that all of the absorption peaks of the complexes are somewhat different from those of the aqua ions (Pr(III), Nd(III)), due to the nephelauxetic effect.[6] The values of β and δ indicate that although bonding in the complexes has a slightly covalent character, they are mainly bonded by the bonding which is typical for lanthanide complexes. The fact that a series of complexes have similar UV spectra shows that the 4*f*-electrons of the central ions impose a very limited effect on the ligand.

^{1}H NMR Spectra

The ^{1}H NMR Spectra of the ligand and its complexes are assigned as follows: H_2L, δ (ppm), 1.53 (3H, singlet, CH_3), 7.20–8.10 (17H, multiplet, 3Ph-, NH, OH); $La(HL)_3{\cdot}3H_2O$, δ (ppm), 1.31 (3H, singlet, -CH_3), 6.80–8.16 (15H, broad peak, 3Ph-), 8.80 (1H, singlet, -NH-). The OH and -NH- in the free ligand appear at 7.20–8.10 ppm. In the complexes, the

Table III. UV Data of the Ligand and Its Complexes

	λ_{max} (nm)			$\varepsilon \times 10^{-4}$ (L/mol·cm)		
Compounds	λ_1	λ_2	λ_3	ε_1	ε_2	ε_3
H_2L	251	300	354	2.777	1.288	1.006
$La(HL)_3{\cdot}3H_2O$	244	320	364	6.852	2.717	4.198
$Pr(HL)_3{\cdot}3H_2O$	244	320	364	6.852	2.359	4.451
$Nd(HL)_3{\cdot}3H_2O$	244	320	364	5.443	2.370	4.355
$Eu(HL)_3{\cdot}3H_2O$	244	320	364	7.079	2.401	4.193
$Gd(HL)_3{\cdot}3H_2O$	244	320	364	7.090	2.291	3.927
$Er(HL)_3{\cdot}3H_2O$	246	320	364	7.324	2.417	4.285

Table IV. *f-f* Transition Data and Energy Levels of Central Ions

Complexes	$\nu_{com}(cm^{-1})$	$\nu_{quo}(cm^{-1})$	Energy level	Parameter
$Pr(HL)_3{\cdot}3H_2O$	16,949	16,807	${}^3H_4 \rightarrow {}^1D_2$	$\beta = 0.9993$
	17,182	17,153	${}^3H_4 \rightarrow {}^3P_0$	$\delta = 0.271$
	20,325	20,704	${}^3H_4 \rightarrow {}^3P_1$	$b^{1/2} = 0.019$
$Nd(HL)_3{\cdot}3H_2O$	17,007	17,182	${}^4I_{9/2} \rightarrow {}^4G_{5/2}{}^2G_{7/2}$	$\beta = 0.9966$
	18,939	19,011	${}^4I_{9/2} \rightarrow {}^4G_{7/2}$	$\delta = 0.341$
	23,095	23,095	${}^4I_{9/2} \rightarrow {}^1P_{1/2}$	$b^{1/2} = 0.041$

hydrogen of the -OH group is replaced by metal. The -NH- group of the complexes shifts downfield (8.80 ppm) compared to that of the free ligand. All of these observations prove that the complexes have formed.[1] The hydrogen of the =NNH- group still exists in the complexes. This conclusion is also supported by the IR spectra.

Thermal Analysis

Thermal analysis data of the ligand and its complexes are listed in Table V. The DTA curves of the ligand have an endothermic peak at 201 °C, but there is no weight lost on the corresponding TG curves, showing that this is a phase transition process which is the same as the melting point of the ligand. In addition, there are three exothermic peaks for the ligand between 283 and 547 °C. The complexes have their first endothermic peak

Table V. Thermal Analysis Data of Ligand and Complexes

Complexes	Dehydration t_1 (°C)	Water loss[a] (%)	M.p. t_2 (°C)	Decomp. (°C) t_3	t_4	t_5	t_6	Residue[a] (%)
H_2L			201	283	454	547		
$La(HL)_3{\cdot}3H_2O$	118	4.40 (3.92)		411	498	531	689	12.6 (11.8)
$Pr(HL)_3{\cdot}3H_2O$	121	4.10 (3.92)		400	474	529	701	13.2 (12.3)
$Nd(HL)_3{\cdot}3H_2O$	103	4.01 (3.91)		432	510	538	726	12.5 (12.2)
$Eu(HL)_3{\cdot}3H_2O$	112	4.18 (3.89)		389	476	521	693	12.8 (12.7)
$Gd(HL)_3{\cdot}3H_2O$	109	3.92 (3.87)		410	508	541	756	13.5 (13.0)
$Er(HL)_3{\cdot}3H_2O$	121	4.30 (3.84)		395	500	529	743	13.5 (13.6)

[a]Data in parentheses are calculation.

Table VI. Biological Activity Data

Complexes	Dose (mg/L)	Average suppression ratio (%) for $O_2^{-\bullet}$	Average inhibitory ratio (%) for lipid peroxidation
Control (SOD)	8.5	97	93
H_2L	78.4	36	18
$La(HL)_3 \cdot 3H_2O$	188	42	35
$Pr(HL)_3 \cdot 3H_2O$	125	48	23
$Nd(HL)_3 \cdot 3H_2O$	118	51	20
$Eu(HL)_3 \cdot 3H_2O$	216	51	39
$Gd(HL)_3 \cdot 3H_2O$	162	42	34
$Er(HL)_3 \cdot 3H_2O$	174	39	31

between 109 and 121 °C, with a weight loss around 3.92–4.40%. This is the peak corresponding to dehydration of the complexes. Between 389 and 756 °C, there are four exothermic peaks; the initial temperature of decomposition is greater than 389 °C which indicates that the thermal stability of the complexes is higher than that of the free ligand which decomposed at 283 °C, showing that there may be extensive conjugation in the chelate ring in the complexes.

Biological Activity

The biological activity data are listed in Table VI. The results show that H_2L and its rare earth complexes act as scavengers for $O_2^{-\bullet}$ radicals and possess some inhibitory affect on lipid peroxidation. In comparison with the rare earth complexes of PMBP-isonicotinoyl hydrazone,[1] the biological activity of $Ln(HL)_3 \cdot 3H_2O$ and of the ligand is inferior. The difference between the PMBP-isonicotinoyl hydrazone rare earth complexes and $Ln(HL)_3 \cdot 3H_2O$ is that the former has a 4-pyridyl group and the latter has a phenyl group. Compared with the control SOD, the average suppression rate for $O_2^{-\bullet}$ radicals and average inhibitory rate for lipid peroxidation are far less than these of SOD, which proves that the rare earth complexes have biological activity.

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