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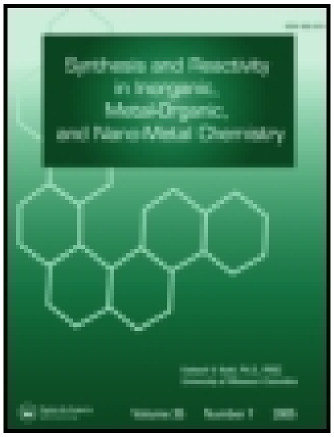

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry
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Synthesis, Characterization and Antibacterial Activity of the Transition Metal Complexes of (1-formylferrocene)-3,5-dibenzyloxybenzoyl hydrazone

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A new chelating ligand, (1-formylferrocene)-3,5-dibenzyloxybenzoyl hydrazone (HL) and three transition metal complexes, ML_2 [M = Cu(II), Ni(II), Zn(II)], have been synthesized and characterized on the basis of elemental analyses, molar conductivity, IR and 1H NMR spectra. The structure of the prepared complexes is suggested. The antibacterial activities of the prepared compounds have been evaluated. The ligand (HL) and its complexes showed selective antibacterial acitivity against *S. aureus*.

Keywords ferrocene, hydrazone, complexes, synthesis, antibacterial activity

INTRODUCTION

Ferrocene is either a stable inorganic compound or an aromatic molecule, to which the encapsulated iron provides attractive optical, structural, and electrochemical properties.[1] The ferrocene group was introduced into penicillins and cephalosphorins as an important moiety changing their antibiotic activities.[2]

The biological, chemical and industrial versatility of hydrazones and their complexes continues to attract considerable attention.[3,4] Especially, isonicotinhydrazide and its N-isopropyl acylhydrazone have been used as effective drugs in curing human tuberculosis in the past few years.[5] The copper salicylaldehyde benzoylhydrazone complex is a potent inhibitor of DNA synthesis and cell growth and is more effective than the free chelator.[6] It is assumed that their mode of biological action is attributed to the formation of stable chelates with transition metals present in the cell. Such a process inhibits many vital enzymatic reactions catalyzed by these transition metal ions.[7] The results of our previous studies showed that 3,5-dibenzyloxybenzoyl hydrazone and its complexes have antibacterial activities.[8,9]

Due to the biological importance of ferrocene group and acylhydrazones, we synthesized a new ligand, (1-formylferrocene) -3, 5-dibenzyloxybenzoyl hydrazone (HL), and prepared its complexes with nickel(II), copper(II), zinc(II). All of the compounds synthesized were tested for their antibacterial activities against *E. coli* and *S. aureus*. The test results were also evaluated. The structure of the ligand is shown as in Figure 1.

EXPERIMENTAL

Materials

All chemicals used in this work were of analytical reagent grade. 1-formylferrocene was prepared by a literature method.[10] 3,5-dibenzyloxybenzoichydrazide was also prepared according to the literature procedure.[11]

Measurements

The melting points of the compounds were determined on an X-4 microscopic melting point apparatus (made in China) and are uncorrected. Elemental analyses were carried out on a Vario EL elemental analyzer. IR spectra were obtained in KBr disc on a Nicolet FT-IR 5DX spectrometer in the 4000–400 cm^{-1} region. ^1H NMR spectra ($CHCl_3$-*d*) were recorded on a Bruker AC-80A instrument with TMS as an internal standard. Mass spectra were performed on a VG-7070E spectrometer (made in USA, EI at 70eV). All conductivity measurements were performed in DMF with a DDS-11A conductometer (made in Shanghai, China) at 25°C.

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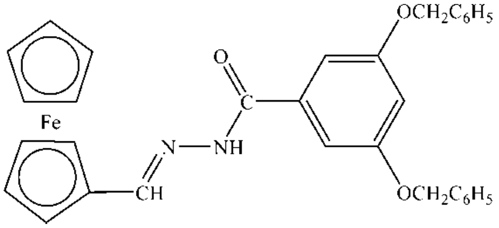

FIG. 1. The structure of the ligand.

Preparation of the Ligand (HL)

To an ethanol solution (30 mL) of 3, 5-dibenzyloxybenzoichydrazide (3.48 g, 10 mmol), an ethanol solution (15 mL) of 1-formylferrocene (1.23 g, 10 mmol) was added with stirring at room temperature. Then the mixture was refluxed in an oil bath for 4 hours. After cooling to room temperature, the precipitated solid was filtered, washed with ethanol and recrystallized from anhydrous ethanol to give the ligand (HL) in a yield of 45% (2.36 g), m. p. 198–199°C. ^{1}H NMR ($CHCl_3$-*d*, 80 MHz) δ: 10.05 (1H, s, NH), 7.90 (1H, s, CH), 7.41~ 6.90 (m, ArH), 5.09 (4H, s, -OCH_2), 4.31 (5H, s, C_5H_5), 4.83 ~ 4.64 (4H, m, C_5H_4). MS (FAB) m/z (%): 544.3 (M^+).

Preparation of the Complexes

A solution of $M(OAc)_2 \cdot 4H_2O$ (0.2 mmol) [M = Ni(II), Cu(II), Zn(II)] in methanol (10 mL) was added dropwise with stirring to a solution of the ligand (0.0916 g, 0.2 mmol) in ethanol. The reaction mixture was refluxed in an oil bath for 4 hours, then cooled and filtered. The filter cake was washed three times with water and anhydrous ethanol, and finally dried in vacuo at room temperature over three days.

Testing of the Antibacterial Activity

All of the compounds synthesized were tested for their antibacterial activities against *E. coli* and *S. aureus* at a concentration of 100 μg/mL in the nutrient agar media employing the cup-plate method.[12] The zone of the growth inhibition of the bacteria, produced by the diffusion of the compounds from the cup into the surrounding medium, was measured after 24 hours. Chloromycetin (a trademark used for an antibiotic preparation of chloramphenicol) was used as a standard.

RESULTS AND DISCUSSION

The elemental analyses and some physical properties of the ligand and its complexes are given in Table 1. The analytical results show that the composition of five complexes corresponds to ML_2 [M = Ni(II), Cu(II), Zn(II)].

The ligand is soluble in common organic solvents, such as ethanol, methanol, acetone and chloroform. The complexes are insoluble in water, partly soluble in chloroform, and are easily soluble in DMF and DMSO. The low molar conductance ($5.71-11.35\ S \cdot cm^2mol^{-1}$) of the complexes suggests that they are non-electrolytes in DMSO solution.[13]

IR Spectra

The IR spectral data of the compounds and their tentative assignments are shown in Table 2. It can be seen that the characteristic absorption peaks in the IR spectra of all of the complexes are similar, which indicate that the complexes have similar structures. The bonding of the ligand to the metal ions was investigated by comparing the infrared spectra of the free ligand with its metal complexes. The following conclusions in this regard can be drawn: (i) The IR spectra show that the ν(C=O) band at 1642 cm^{-1} and the ν(NH) band at 3193 cm^{-1} in the spectra of the ligand were absent in the complexes. These suggest the bonding of the ligand through the enolate oxygen in the enol form of the hydrazone group.[14] (ii) The IR spectra indicate that the ν(C=N) bands in the spectra of the ligand at 1588 cm^{-1} due to the azomethine linkage were shifted towards lower frequency by 41–58 cm^{-1} in the complexes, indicating that the ligand coordinates to the metal ions via the azomethine nitrogen.[15] (iii) Bonding through the azomethine nitrogen[16] is also indicated from the shift of ν (N-N) to higher frequencies by 14–16 cm^{-1}.

TABLE 1
Elemental analysis data and physical properties of the compounds

Compound (formula)	Color	Yield (%)	Found (Calcd.) (%) C	H	N	Λ_m ($S \cdot cm^2mol^{-1}$)[a]
HL $(C_{32}Fe\ H_{28}N_2O_3)_2$	Red brown	52	70.71(70.59)	5.52(5.15)	4.93(5.15)	
Ni L_2 $(C_{64}FeH_{56}NiN_4O_6)_2$	Brown	63	67.40(67.13)	4.95(4.72)	5.04(4.90)	5.71
Zn L_2 $(C_{64}FeH_{56}N_4O_6Zn)$	Yellow brown	80	66.64(66.72)	4.48(4.69)	5.10(4.86)	11.35
Cu L_2 $(C_{64}CuFeH_{56}N_4O_6)$	Brown	72	66.78(66.81)	4.82(4.70)	4.58(4.87)	6.82

[a] For the molar conductance, the concentration of the solution (in DMSO) was about 10^{-3} mol/dm^3.

TABLE 2
IR spectra data[a] of the ligand (HL) and its complexes (cm^{-1})

Compounds	Fc	ν_{NH}	$\nu_{C=O}$	$\nu_{C=N}$	$\nu_{N\text{-}N}$
HL	3062_m, 1454_w, 814_w	3193_m	1642_s	1588_s	840_w
NiL_2	3060_m, 1456_w, 814_w			1530_s	860_w
CuL_2	3063_m, 1455_w, 814_w			1531_s	869_w
ZnL_2	3063_m, 1454_w, 815_w			1547_s	847_w

[a] w = weak, s = strong, m = medium.

^1H NMR Spectra

Since the majority of the coordination compounds are paramagnetic, only the ^1H NMR spectra of the ligand (HL) and ZnL_2 were obtained. The ligand (HL) exhibits signals at δ (ppm) 10.05 (1H, s, NH), 7.90 (1H, s, CH), 7.41–6.90 (m, ArH), 5.09 (4H, s, $-OCH_2$), 4.83 ~ 4.64 (4H, m, C_5H_4), 4.31 (5H, s, C_5H_5), while in the ZnL_2 complex signals are at δ (ppm) 7.56 (1H, s, CH), 7.44 ~ 6.99 (m, ArH), 5.14 (4H, s, $-OCH_2$), 4.57 (4H, m, C_5H_4), 4.29 (5H, s, C_5H_5). The disappearance of the signal at 10.05 (s, NH) in the complex proves that the hydrazone group coordinates to the metal ions through enolate form. The downfield shift of the CH signals suggests bonding of the ligand through the azomethine nitrogen of the hydrazone group. Thus, the ^1H NMR studies reinforce the conclusions drawn from the IR spectra.

Antibacterial Activity

The antibacterial activity test results of the ligand and its complexes are shown in Table 3. Preliminary bioassays indicate that the ligand and its three complexes were active against *S. aureus*, although they did not have the effectiveness against *E. coli*. It is manifested that the Ni(II), Cu(II) and Zn(II) complexes showed almost the same antibacterial activity against *S. aureus* compared with the ligand, although they did not reach the effectiveness of the bacteriostatic activity of chloromycetin taken as standard drug at the concentration of 100 μg/mL.

TABLE 3
Antibacterial activities of the ligand (HL) and its complexes

Compd.	*S. aureus*	*E. coli*
HL	+	—
NiL_2	+	—
CuL_2	+	—
ZnL_2	+	—
DMSO	—	—
Chloromycetin	+++	+++

Zone diameter of growth inhibition: <10 mm (—), 10–12mm (+), 13–15 mm (++), >16 mm (+++). The diameter of the cup is 8 mm.

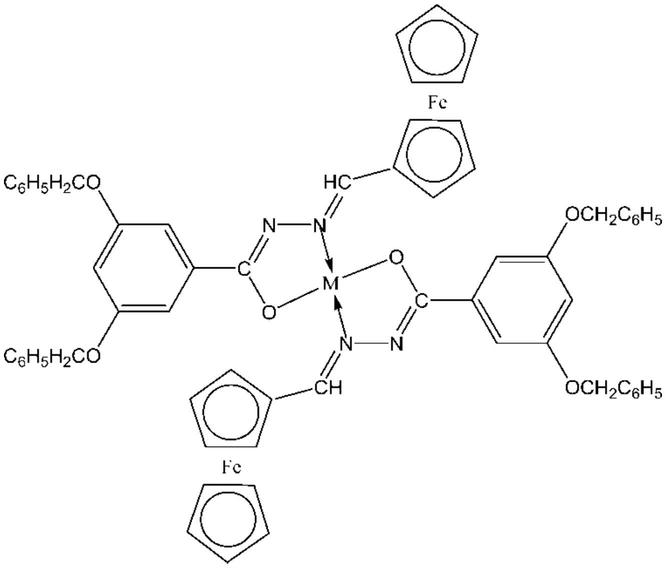

FIG. 2. The supposed structure of the complexes.

CONCLUSIONS

The following conclusion can be drawn:

(1) The metal ions are coordinated by the ligand with O and N donors from the enol oxygen of the hydrazone group (-N=C-O) and the azomethine (CH=N) group, respectively. The suggested structure of the complexes is shown in Figure 2.

(2) The ligand and its three complexes showed selective antibacterial acitivity against *S. aureus*. The formations of the complexes have little effect in the antibacterial activity of the ligand HL.

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