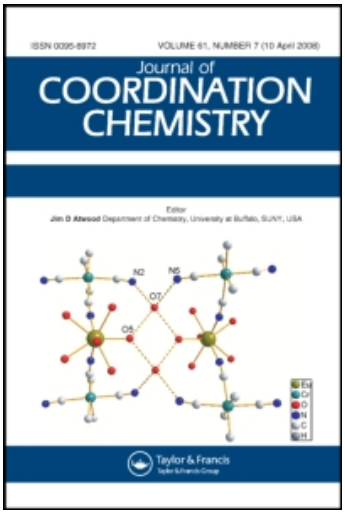

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

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To cite this Article Li, Ming-Xue , Zhou, Jing , Zhao, Hong , Chen, Chun-Ling and Wang, Jing-Ping(2009) 'Iron(III) complex of 2-acetylpyrazine thiosemicarbazone: synthesis, spectral characterization, structural studies and antitumoral activity', Journal of Coordination Chemistry, 62: 9, 1423 — 1429
To link to this Article: DOI: 10.1080/00958970802626529
URL: http://dx.doi.org/10.1080/00958970802626529

Journal of Coordination Chemistry
Vol. 62, No. 9, 10 May 2009, 1423–1429

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Iron(III) complex of 2-acetylpyrazine thiosemicarbazone: synthesis, spectral characterization, structural studies and antitumoral activity

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(*Received 2 July 2008; in final form 5 August 2008*)

$[Fe(HL)_2]Cl_3 \cdot 1.5H_2O$ (**1**), where $HL = C_7H_9N_5S$, 2-acetylpyrazine thiosemicarbazone, was obtained and fully characterized. X-ray diffraction studies show that complex **1** crystallizes in monoclinic lattice, space group $P2_1/n$, with $a = 11.342(6)$, $b = 12.547(6)$, $c = 17.056(9)$ Å, $\beta = 103.551(7)^\circ$, $V = 2360(2)$ Å^3, $Z = 2$, $M_r = 1159.46$, $D_{Calcd} = 1.632\,g\,cm^{-3}$, μ(Mo-Kα) = $1.188\,mm^{-1}$, $F(000) = 1184$, the final $R_1 = 0.0955$ and $wR_2 = 0.2626$. The 2-acetylpyrazine thiosemicarbazone is a tridentate ligand and binds to the metal through the pyrazine nitrogen, the imine nitrogen and the sulfur in the neutral thione form yielding an octahedral geometry. The title iron complex showed significant antitumor activity against the Ec9706 human esophagus cancer cell line with an IC_{50} value (10.50 μM) in a micromolar range similar to cisplatin.

Keywords: Thiosemicarbazone; Iron complex; Crystal structure; Cytotoxic activity

1. Introduction

Thiosemicarbazones and their metal complexes have variable bonding properties, structural diversity, and a broad spectrum of biological properties such as antiviral, antibacterial, antimalarial, antifungal, and antitumoral activities [1, 2]. Triapin has been tested in phase I trial for patients with advanced cancer [3]. The biological activity of thiosemicarbazones is attributed to their chelating ability with transition metal ions bonding through sulfur and two nitrogen atoms [4]. Thiosemicarbazones containing a pyridine ring give rise to NNS tridentate systems and their metal complexes have stimulated widespread interest in biological activities [5–7]. To our knowledge, there is comparatively little biological research about metal complexes with 2-acetylpyrazine thiosemicarbazone. Because of that, we previously synthesized 2-acetylpyrazine thiosemicarbazone and its complexes [8, 9], finding that

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Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online © 2009 Taylor & Francis
DOI: 10.1080/00958970802626529

2-acetylpyrazine thiosemicarbazone and its cobalt(II) complex have antitumor activities against lung cancer A549 cell lines [9].

Many studies have suggested that iron complexes have significantly greater antitumor activity than the free ligand [10–12]. The cytotoxicity and antitumoral activity of thiosemicarbazone–iron(III) complexes may be related to the reaction of complexes with cell thiols or thiol containing proteins [13]. Continuing our research concerning biological properties of thiosemicarbazones [9, 14, 15], we report here the synthesis and spectral properties of iron(III) complex with 2-acetylpyrazine thiosemicarbazone (HL, in scheme 1). In addition, the antitumor activity of the title complex was investigated against Ec9706 esophagus cancer cell line, and it shows significant antitumor activity.

2. Experimental

2.1. *General procedures*

All solvents and reagents are commercially available and used without further purification. 2-Acetylpyrazine thiosemicarbazone was prepared according to the literature method [16].

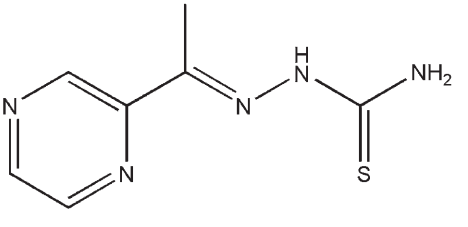
Elemental analyses (C, H, and N) were performed on a Perkin–Elmer 240 analyzer. Infrared spectra were recorded as KBr discs on a Nicolet 170 FT infrared spectrophotometer. Crystal structure determination was carried out on a Siemens SMART-CCD X-ray diffractometer.

2.2. *Synthesis of* $[Fe(C_7H_9N_5S)_2]Cl_3 \cdot 1.5H_2O$

The title complex was synthesized by addition of $FeCl_3 \cdot 6H_2O$ (0.125 m mol, 0.034 g) to an ethanol solution (30 mL) of 2-acetylpyrazine thiosemicarbazone (0.25 m mol, 0.049 g). After refluxing for 2 h with stirring, the dark-red precipitate was filtered. Crystals suitable for X-ray studies were obtained by slow evaporation of the filtrate. Elemental analysis, found (%): C, 29.03; H, 3.55; N, 24.12. Calcd: C, 28.99; H, 3.62; N, 24.16.

2.3. *Crystal structure determination*

A summary of the crystal data and refinement results of the iron complex are listed in table 1. Intensities were collected on a Siemens SMART-CCD diffractometer equipped



Scheme 1.

with a graphite-monochromated Mo-Kα ($\lambda = 0.71073$ Å) radiation using the SMART and SAINT programs [17]. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques with SHELXTL version 5.1 [17]. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. The hydrogen atoms were positioned according to theoretical models.

2.4. In vitro *cytotoxicity study*

Cytotoxic effects of the iron complex were evaluated by MTT test for Ec9706 human esophagus cancer cell line.

Ec9706, human esophagus cancer cell line were cultured in RPMI-1640 medium supplemented with 10% FBS, 100 U mL^{-1} of penicillin, 100 μg mL^{-1} of streptomycin at 37°C in humidified air with 5% CO_2. Then the cultured cells were plated into 96-well-plates (5×10^3 cells per well). The next day compounds at various concentrations diluted in culture medium were added (200 μL per well) to the wells, 48 h later 20 μL of MTT (0.5 mg mL^{-1} MTT in PBS) were added and cells were incubated for a further 4 h. Two hundred microliters of DMSO were added to each culture to dissolve the reduced MTT crystals. The MTT-formazan product dissolved in DMSO was estimated by measuring absorbance at 570 nm with a micro plate reader. Then the inhibitory percentage of each compound at various concentrations was calculated, and the IC_{50} value was determined.

Table 1. Summary of crystal data and refinement results for the complex.

Empirical formula	$C_{28}H_{42}N_{20}O_3S_4Fe_2Cl_6$
Formula weight	1159.46
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions (Å, °)	
a	11.342(6)
b	12.547(6)
c	17.056(9)
β	103.551(7)
Volume (Å^3)	2360(2)
Z	2
D_{Calcd} (Mg m^{-3})	1.632
Absorption coefficient (mm^{-1})	1.188
$F(000)$	1184
Crystal size (mm^3)	$0.20 \times 0.18 \times 0.16$
θ range for data collection (°)	2.04–25.00
Limiting indices	$-13 \le h \le 13$, $-14 \le k \le 13$, $-20 \le l \le 15$
Reflections collected	4141
Independent reflections	2677
Completeness to $\theta = 25.00°$ (%)	99.7
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4141/30/295
Maximum and minimum transmission	0.8327, 0.7971
Goodness-of-fit on F^2	0.954
Final R indices [$I \ge 2\sigma(I)$]	$R_1 = 0.0955$, $wR_2 = 0.2626$
Largest diffraction peak and hole (e Å^{-3})	1.733 and −1.262

Table 2. Selected bond lengths (Å) and angles (°) of the iron complex.

S(1)–C(1)	1.698(5)	S(2)–C(8)	1.687(5)
C(1)–N(1)	1.316(6)	C(8)–N(6)	1.355(7)
C(1)–N(2)	1.354(6)	C(8)–N(7)	1.346(6)
N(2)–N(3)	1.366(5)	N(7)–N(8)	1.380(6)
N(3)–C(2)	1.311(6)	N(8)–C(9)	1.279(6)
C(2)–C(3)	1.489(7)	C(9)–C(10)	1.467(7)
C(2)–C(4)	1.453(6)	C(9)–C(11)	1.475(7)
Fe(1)–N(3)	1.904(4)	Fe(1)–N(8)	1.904(4)
Fe(1)–N(4)	1.922(4)	Fe(1)–N(9)	1.963(4)
Fe(1)–S(1)	2.294(1)	Fe(1)–S(2)	2.303(1)
C(4)–C(2)–N(3)	112.0(4)	C(2)–N(3)–N(2)	120.0(4)
N(3)–N(2)–C(1)	117.5(4)	N(2)–C(1)–S(1)	120.4(3)
N(1)–C(1)–S(1)	122.2(4)	C(11)–C(9)–N(8)	111.2(4)
C(9)–N(8)–N(7)	120.4(4)	N(8)–N(7)–C(8)	117.6(4)
N(7)–C(8)–S(2)	121.9(4)	N(6)–C(8)–S(2)	122.2(4)
N(3)–Fe(1)–N(8)	178.5(1)	N(4)–Fe(1)–S(1)	166.4(1)
N(9)–Fe(1)–S(2)	166.0(1)	S(1)–Fe(1)–S(2)	93.5(1)
N(8)–Fe(1)–N(9)	80.3(1)	N(8)–Fe(1)–S(1)	95.1(1)
N(3)–Fe(1)–N(4)	81.2 (1)	N(3)–Fe(1)–S(2)	95.5(1)
S(1)–Fe(1)–N(3)	85.2(1)	S(2)–Fe(1)–N(8)	86.0(1)

Table 3. Hydrogen bond lengths (Å) and angles (°) of the iron complex.

D–H···A	d(H···A)	d(D···A)	∠(DHA)
N(1)–H(1A)···Cl(3)	2.44	3.146(6)	140.1
N(1)–H(1A)···Cl(2)	2.60	3.134(4)	121.1
N(2)–H(2A)···Cl(3)	1.95	2.768(5)	158.1
O(2W)–H(2WA)···Cl(1)	2.47(1)	3.215(4)	152(2)
O(2W)–H(2WB)···Cl(1)	2.53(1)	3.234(5)	145(2)
N(6)–H(6B)···Cl(2)	2.60	3.318(5)	141.3
N(6)–H(6C)···Cl(1)	2.88	3.564(5)	138.0
N(7)–H(7A)···Cl(2)	2.33	3.089(4)	147.0

3. Results and discussion

Selected bond distances and angles of the iron(III) complex are shown in table 2, hydrogen bond lengths and angles in table 3. Figure 1 shows the molecular structure of the iron complex along with the atom numbering scheme; the unit cell packing is depicted in figure 2.

3.1. *Crystal structure of the iron complex*

The two ligand molecules coordinate to iron as neutral tridentate species via the thione sulfur, imine nitrogen, and pyrazine nitrogen, resulting in distorted octahedral geometry. The two thiosemicarbazone ligands have slightly different Fe–N (pyrazine) bond distances, both longer than the Fe–N (azomethine) distances; this may be attributed to the fact that the azomethine nitrogen is a stronger base than the pyrazine nitrogen [18]. The distances of Fe1–S1 [2.294(1) Å] and Fe1–S2 [2.303(1) Å] are longer than those in iron(III) complexes with 2-benzoylpyridine-*N*(4)-(butane-1, 4-diyl) thiosemicarbazone [18] and 2-pyridineformamide-N(4)-methylthiosemicarbazone [19].

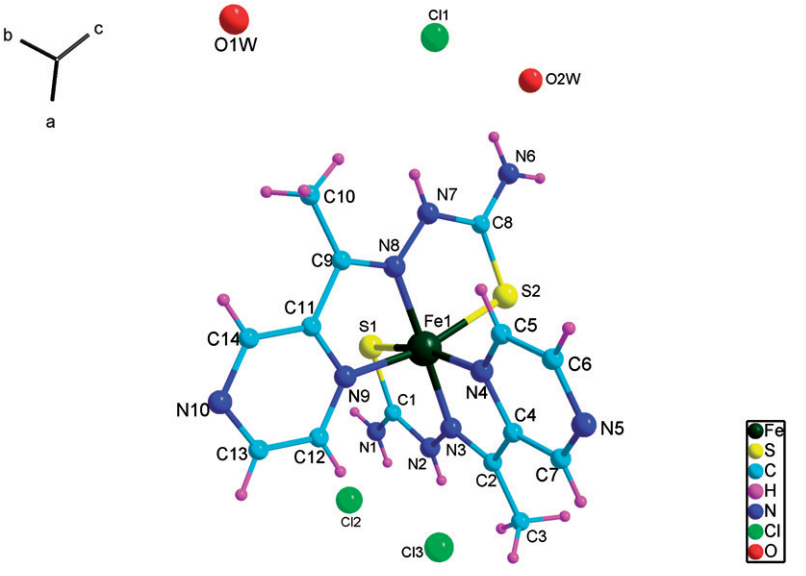


Figure 1. The molecular structure of the iron complex along with the atom numbering scheme.

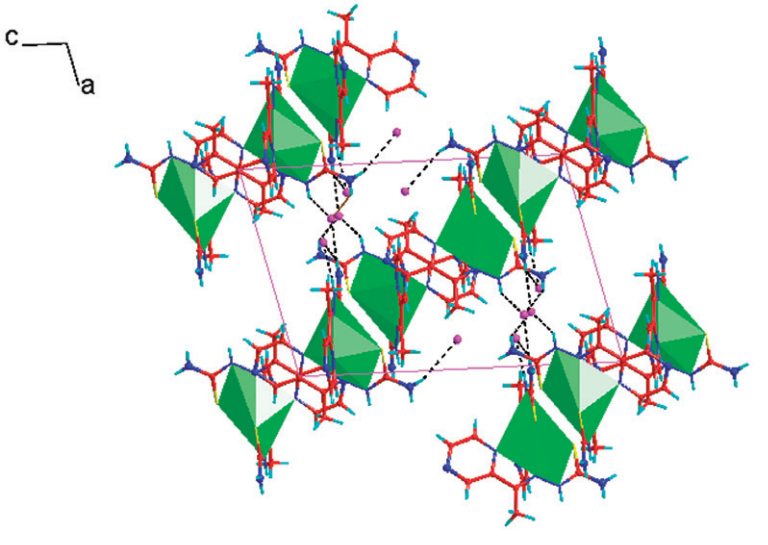


Figure 2. The packing diagram for the iron complex.

In the two coordinated ligands, the S1–C1 and S2–C8 bond distances [1.698(5) and 1.687(5) Å, respectively] are within the normal range of C=S bonds, demonstrating that they are double bonds and coordinate to iron in the thione form [20]. In addition, the C2–N3 and C9–N8 bond lengths are 1.311(6) and 1.279(6) Å, which are within the range of typical C=N bonds.

The planes of Fe1–N9–N8–S2–N3 and Fe1–N4–N3–S1–N8 have mean plane deviations of 0.0210 and 0.0127 Å, respectively, and are at an angle of 88.1° to each other, close to the idealized 90° for a regular octahedron. The two pyrazine rings (mean plane deviations of 0.0082 and 0.0010 Å) form a dihedral angle of 88.9°.

Since the thiosemicarbazone moieties have hydrogen bond donors while the counterion (Cl^-) can act as acceptors, they provide the possibility to form abundant hydrogen bonds in the crystal. The amino nitrogens (N1 and N6) form hydrogen bonds with Cl2. The separations for N1···Cl2 and N6···Cl2 are 3.146(6) and 3.138(5) Å with N–H···Cl angles of 121.1 and 141.3°. The hydrazine nitrogens (N2 and N7) of the thiosemicarbazone also participate in two hydrogen bonds (N2–H2A···Cl3 = 2.768(5) and N7–H7A···Cl2 = 3.089(4) Å). There are two hydrogen bonds among the waters of crystallization, which are O2W–H2WA···Cl1 and O2W–H2WB···Cl1. Additionally, the intermolecular π–π stacking interactions may be present between the pyrazine rings. The hydrogen bonding interactions and intermolecular π–π stacking interactions are responsible for stabilization of the complex (figure 2) [21].

3.2. *Infrared spectroscopy*

The difference of the IR bands between the acetylpyrazine thiosemicarbazone ligand and the title complex provides significant indications regarding the bonding sites of the ligand. The IR spectra of the free ligand and the title complex all have three bands from 3140 to 3420 cm^{-1}, a medium band in the range 3129–3158 cm^{-1} of the $\nu(^2N–H)$ vibration, provides strong evidence for ligand coordination in its neutral form. The ν(C=N) bands of thiosemicarbazone and of the complex are found at 1595 and 1552 cm^{-1}, respectively. The decrease in frequency of this band in the spectra of the complex is evidence for coordination via azomethine nitrogen [22]. The ν(N=N) bands of the free ligand are found at 1104 cm^{-1}. The increase in frequency of this band for the title complex is an evidence for enolization of the ligand and coordination via the azomethine nitrogen [23]. The band at 850 cm^{-1} observed for the ligand can be attributed to the ν(C=S) vibration. In the complex this band had a red-shift of 12 cm^{-1} to lower energy, indicating coordination of the thione sulfur.

3.3. *Cytotoxic activity*

The cytotoxic potency of the title complex was investigated in the human tumor cell lines Ec9706 (esophagus cancer) and exhibited inhibitory activity. In our experiment, IC_{50} value (compound concentration that produces 50% of cell death) is 10.50 μM, which is markedly smaller than that of free ligand and its cobalt(II) complex against the A549 cell lines (IC_{50} values are 18.9 and 265.3 μM, respectively) [9]. On the whole, the iron(III) complex of the 2-acetylpyrazine thiosemicarbazone has the potential to be used for medical practice as a metal-based drug. These results stimulate further investigations of metal complexes with 2-acetylpyrazine thiosemicarbazone, in particular on the spectrum of their antitumor activity and mechanistic properties.

Supplementary data

Crystallographic data for the structural analyses reported in this article have been deposited with the Cambridge Crystallographic Data Centre with CCDC

numbers 692920. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; Email: deposit@ccdc.cam.ac.uk).

Acknowledgment

This work was financially supported by the Foundation of Educational Department of Henan Province (No. 2007150012).

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