Synthesis, Crystal Structure and Antitumor Study of a Zinc Complex of the 2-Benzoylpyridine Thiosemicarbazone Ligand

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Z. Naturforsch. **2008**, *63b,* 280 – 284; received October 19, 2007

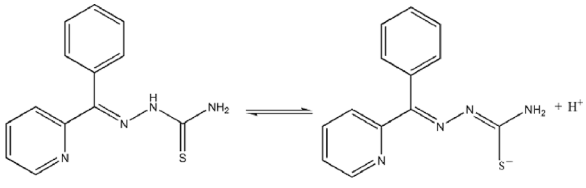
A zinc complex of the 2-benzoylpyridine thiosemicarbazone (Hbpt) ligand, $Zn(bpt)_2 \cdot DMF$, has been synthesized and characterized by elemental analysis, IR spectra and single crystal X-ray diffraction. The molecular structure has a Zn^{2+} cation bonded to two perpendicular bpt ligands in a distorted octahedral geometry through two sulfur and four nitrogen atoms. The crystal contains a disordered DMF solvate molecule. Adjacent molecules are interconnected by means of hydrogen bonding generating a 1-D chain structure. The cytotoxic activity measurement indicates that the complex exhibits higher antitumor activity against lung cancer A549 cell lines than the free ligand.

Key words: Thiosemicarbazone Complex, Crystal Structure, Cytotoxic Activity

Introduction

The systematic and predictive use of hydrogen bonding motifs for the design and exploitation of crystal structures is one of the focal points in crystal engineering [1]. In this regard, strong hydrogen-bond interactions such as O–H···O and N–H···O as well as weaker hydrogen bonds such as C–H···O have been successfully used for linking neighboring metal complexes into 1-D, 2-D or even 3-D assemblies [2].

Recently, thiosemicarbazones and their metal complexes have attracted considerable interest in coordination and medicinal chemistry, because of their versatile bonding performance resulting from the presence of several donor sites, an impressive structural diversity, a wide range of applications as antiviral, antibacterial, antimalarial and antitumor agents, and nonlinear optical properties [3 – 5]. Thiosemicarbazones are versatile multifunctional chelating ligands that can coordinate as neutral groups or in the deprotonated form, and also are flexible spacers with potential multiple binding sites that can be used to construct coordination polymers with multi-dimensional or supramolecular architectures [6]. The hydrogen atoms attached to the amino nitrogen atoms of the thiosemicarbazone moiety also have the ability to form donor hydrogen bonds through which small, simple fragments can be assembled into products with cavities, which is important in host-guest chemistry and has applications in chemistry, biology, and materials science [7]. To date, many thiosemicarbazones such as marboran or triapine have been already extensively used in medical practice. The antitumor activities can be increased by coordinating the thiosemicarbazone to metal cations [8].



Scheme 1. Schematic drawing of the ligand Hbpt.

Heterocyclic thiosemicarbazones, especially those containing a pyridine ring, are of importance owing to their possible antitumor activities [9]. Hitherto, a large number of thiosemicarbazones derived from 2-formyl- and 2-acetyl-pyridine have been extensively investigated [10], however, much less attention has been paid to those derived from 2-benzoyl pyridine (Scheme 1) [10a, 11]. In this paper, we presents the synthesis, IR spectra and crystal structure of the zinc complex $Zn(bpt)_2 \cdot DMF$ with a 1-D infinite chain structure formed by hydrogen bonding interactions. The antitumor activity against lung cancer A549 cell lines has been evaluated for the free ligand and the title complex.

0932–0776 / 08 / 0300–0280 $ 06.00

Experimental Section

General

Materials: According to the literature method, replacing of di(2-pyridyl)ketone by 2-benzoyl pyridine, 2-benzoyl pyridine was reacted with thiosemicarbazide in methanol at reflux in the presence of acetic acid as a catalyst. A white solid (2-benzoylpyridine thiosemicarbazone, Hbpt) was formed [12]. All other chemicals were commercially available and used without further purification.

Instrumentation: C, H and N elemental analyses were performed on a Perkin-Elmer 240C analyzer. The infrared spectra were recorded as KBr pellets on a Nicolet 170 FT-IR spectrophotometer in the range of 4000 – 400 cm^{-1}.

Synthesis

$Zn(OOCCH_3)_2 \cdot 2H_2O$ (0.110 g, 0.500 mmol) and 2-benzoyl pyridine thiosemicarbazone (0.256 g, 1.00 mmol) were suspended in 30 mL of ethanol and refluxed for 4 h with stirring. The resulting colorless precipitate was filtered off, washed with cold ethanol and dried in a vacuum. Colorless crystals suitable for X-ray diffraction were obtained by slow evaporation of a DMF solution.

Elemental analysis: $C_{29}H_{29}N_9OS_2Zn$: calcd. C 53.66, H 4.50, N 19.42; found C 53.61, H 4.47, N 19.41.

X-Ray crystallographic study

The crystal structure of the title complex was determined from single-crystal X-ray diffraction data. Intensity data were collected on a Siemens SMART-CCD diffractometer with graphite monochromated MoK_α radiation (λ = 0.71073 Å) using the programs SMART and SAINT [13]. The intensity data were corrected for Lorentz and polarization effects as well as empirically for absorption. Of 7820 reflections collected, 5179 were independent (R_{int} = 0.0412) and used in all further calculations. The structure was solved by Direct Methods and refined by full-matrix least-squares on F^2. The weighting scheme used was: $w = 1/[\sigma^2(F_o^2) + (0.1014P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. All hydrogen atoms were located according to geometrical calculations. A summary of crystal and refinement data for the complex is given in Table 1.

CCDC 660422 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

In vitro cytotoxicity study

A549, a human lung cancer cell line (purchased from the Institute of Biochemistry and Cell Biology, SIBS, CAS) was cultured in a RPMI-1640 medium supplemented with 10 % FBS, 100 U mL^{-1} of penicillin, and 100 μg mL^{-1} of streptomycin at 37 °C in humid air atmosphere of 5 % CO_2. Cell cytotoxicity was assessed by the MTT assay. Briefly, cells were placed into a 96-well-plate (5×10^3 cells per well). The next day the compound diluted in culture medium at various concentrations was added (200 μL per well) to the wells. 48 h later 20 μL of MTT (0.5 mg mL^{-1} MTT in PBS) was added, and cells were incubated for a further 4 h. 200 μL of DMSO were added to each culture to dissolve the 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 title complex.

Formula	$C_{29}H_{29}N_9OS_2Zn$
Mr	649.10
Crystal size, mm^3	$0.2 \times 0.15 \times 0.12$
Crystal system	triclinic
Space group	$P\bar{1}$
a, Å	11.065(2)
b, Å	12.651(2)
c, Å	15.021(3)
α, deg	114.137(4)
β, deg	96.486(3)
γ, deg	103.232(3)
V, $Å^3$	1816.8(6)
Z	2
D_{calcd}, g cm^{-3}	1.187
μ(MoK_α), cm^{-1}	0.824
θ range for data collection, deg	1.85 – 23.31
F(000), e	672
hkl range	$-12 \le h \le 12$, $-14 \le k \le 13$, $-16 \le l \le 13$
Refl. measured	5179
Refl. unique	3717
R_{int}	0.0418
Param. refined	469
$R1(F)/wR2(F^2)$ [$I \ge 2\sigma(I)$]	0.064/0.171
$R1(F)/wR2(F^2)$ (all reflexions)	0.081/0.230
GoF (F^2)	1.016
$\Delta\rho_{fin}$ (max/min), e $Å^{-3}$	0.790/−0.323

Results and Discussion

IR spectra

In the infrared spectrum of the complex, the strong absorption band of the bpt ligand centered at 1594 cm^{-1} is ascribed to the ν(C=N) stretching vibration, which is shifted by 6 cm^{-1} to lower energy in comparison with Hbpt, indicating the coordination of the azomethine nitrogen atoms (N7 and N3; see Fig. 1a) [14]. The band at 446 cm^{-1} is assigned to the

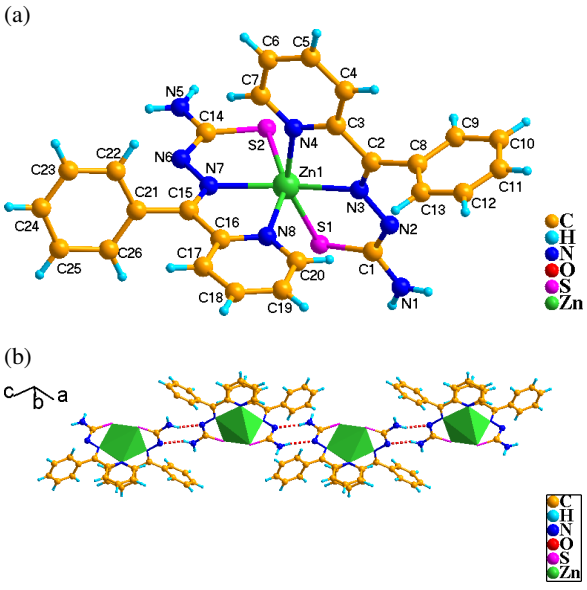


Fig. 1. (a) The molecular structure of the title compound along with the atom numbering scheme. (b) The one-dimensional infinite chain structure formed through hydrogen bonding interactions.

ν(Zn–N) vibration for the azomethine nitrogen [11a]. The ν(C=S) stretching vibration band in the spectra of the free thiosemicarbazone is assigned in the range of 830 – 860 cm^{-1} [11a]. In the complex this band has a red-shift of 50 cm^{-1} to lower energy, indicating the coordination of the thione sulfur atom. These observations have been confirmed by X-ray single crystal structural analysis.

X-Ray crystal structure

The molecular structure of the complex along with the atomic numbering scheme and the one-dimensional infinite chain structure arising from hydrogen bonding interactions are shown in Fig. 1. The space-filling arrangements are illustrated in Fig. 2. Selected bond lengths and angles are listed in Table 2, hydrogen bond lengths and angles in Table 3.

As shown in Fig. 1, the Zn^{2+} cation is coordinated by two deprotonated bpt ligands in a distorted octahedral geometry. The equatorial plane with a mean deviation of 0.040 Å is formed by two imino nitrogen atoms (N3, N7), one pyridine nitrogen atom (N8) and one thiosemicarbazonato sulfur atom (S2) from two bpt ligands with Zn–N and Zn–S distances of 2.175(4)–2.244(4) Å and 2.420(2) Å, respectively. One pyridine nitrogen atom (N4) and one

Table 2. Selected bond lengths (Å) and angles (deg) of the title complex.

Zn(1)–N(4)	2.216(5)	Zn(1)–N(8)	2.244(4)
Zn(1)–N(3)	2.184(4)	Zn(1)–N(7)	2.175(4)
Zn(1)–S(1)	2.403(2)	Zn(1)–S(2)	2.420(2)
S(1)–C(1)	1.720(6)	S(2)–C(14)	1.717(6)
N(3)–C(2)	1.284(7)	N(7)–C(15)	1.279(6)
N(2)–N(3)	1.351(6)	N(6)–N(7)	1.366(6)
N(2)–C(1)	1.341(7)	N(6)–C(14)	1.331(7)
N(1)–C(1)	1.335(7)	N(5)–C(14)	1.340(7)
N(3)–Zn(1)–N(7)	156.2(2)	N(4)–Zn(1)–S(1)	151.4(2)
N(8)–Zn(1)–S(2)	152.9(2)	N(7)–Zn(1)–S(2)	79.6(2)
N(3)–Zn(1)–N(4)	73.5(2)	N(7)–Zn(1)–N(8)	73.4(2)
N(3)–Zn(1)–S(1)	78.8(2)	S(1)–Zn(1)–S(2)	96.1(1)
S(1)–Zn(1)–N(8)	96.4(2)	N(4)–Zn(1)–N(7)	93.2(2)
N(3)–Zn(1)–S(2)	119.6(2)	N(4)–Zn(1)–S(2)	91.7(2)
N(8)–Zn(1)–N(3)	86.4(2)	N(7)–Zn(1)–S(1)	115.3(2)
N(4)–Zn(1)–N(8)	88.8(2)		

Table 3. Hydrogen bond lengths (Å) and bond angles (deg).

D–H···A	*d*(H···A)	*d*(D···A)	∠(DHA)
N(1)–H(1A) ···N(2)	2.18	3.026(7)	167.2
N(5)–H(5A) ···N(6)	2.22	3.046(7)	161.8

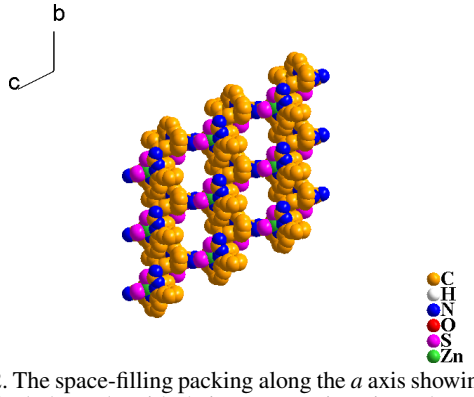


Fig. 2. The space-filling packing along the *a* axis showing the elliptical channels with their cross-section size. The solvate molecules in the channels are omitted for clarity.

thiosemicarbazonato sulfur atom (S1) from one bpt ligand occupy the apical positions with Zn–N and Zn–S distances of 2.216(5) Å and 2.403(2) Å, respectively. The two bpt ligands are approximately perpendicular and function as tridentate groups forming two five-membered chelating rings. Although a five-coordinate $[Cu(Hbpt)Cl_2]$ complexes [10a], a macrocyclic tetranuclear copper(II)-copper(I) mixed-valence complex $[Cu^{II}(bpt)(SCN)Cu^{I}(SCN)(CH_3CN)]_2$ [15] and a four-coordinate [Pd(bpt)Cl] [16] have been reported, to the best of our knowledge, the title complex represents the first Zn-containing bpt derivative.

In the supramolecular structural architecture, the imino nitrogen atoms of the thiosemicarbazone moi-

eties act as hydrogen-bond acceptors while the uncoordinated terminal amino nitrogen atoms act as donors. The separations N(1)···N(2) and N(5)···N(6) are 3.026(7) and 3.046(7) Å with N–H···N angles of 167.2 and 161.8°, respectively. Additionally, intermolecular π-π stacking interactions may be present between the pyridine rings of neighboring chains. The spatial arrangements of the complex along the *a* axis are of interest. The packing representation along the *a* axis exhibits larger elliptical channels with a cross-section of 11.6×10.8 Å, into which the DMF solvate molecules are filled (Fig. 2).

In vitro cytotoxic activity

IC_{50} values (compound concentration that produces 50 % of cell death) were calculated for the free ligand and the title complex against lung cancer A549 cell lines. The Hbpt ligand and its complex all exhibited significant antitumor activity. It is worth noting that the title complex showed a lower IC_{50} value (4.8 μM) than the free ligand (14.1 μM), indicating that the antitumor activity of the complex is greater than that of the free ligand. In addition, the antitumor activity of the complex also was higher than that of the cobalt (II) complex against the same cell line [17]. The Zn complex has the potential to be used for medical practice as a metal-based drug.

Acknowledgement

This work was financially supported by the Natural Science Foundation of Henan Province (No. 0611011900) and the Foundation of Educational Department of Henan Province (No. 2007150012).

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