

单核铜配合物 $\text{Cu}(\text{C}_{16}\text{H}_{13}\text{N}_2\text{OS}_2)_2$ 的合成、晶体结构和生物活性

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Synthesis, Crystal Structure and Biological Activity of a New Mononuclear Copper Complex $\text{Cu}(\text{C}_{16}\text{H}_{13}\text{N}_2\text{OS}_2)_2$

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Abstract: A planar copper complex $\text{Cu}(\text{L})_2$, $\text{HL}=(E)\text{-benzyl-2-(4-formylbenzylidene)-Hydrazinecarbodithioate}$, has been prepared via the template effect of copper ion. Crystal structure of the complex was determined by X-ray single-crystal diffraction analysis. The crystal data for this complex: Orthorhombic, space group $Pbcn$, $a=2.250\,0(14)$ nm, $b=1.660\,0(11)$ nm, $c=0.830\,4(5)$ nm, $V=3.102(3)$ nm³, $Z=4$, $\mu=1.011$ mm⁻¹, $D_c=1.478$ g·cm⁻³, $F(000)=1\,420$, $R_1=0.050\,1$, $wR_2=0.087\,2$ (observed reflections with $I>2\sigma(I)$) and $R_1=0.129\,1$, $wR_2=0.100\,9$ (all reflections) GOF=1.011. In the compound, Cu(II) atom is four-coordinated with two N atoms and two S atoms from two bidentate ligands and located in the inversion center. The preliminary bioassay indicates that the complex exhibits distinct antitumor activity. CCDC: 763155.

Key words: copper(II) complex; Schiff base; crystal structure; biological activity

Dithiocarbazate $\text{NH}_2\text{NHCS}_2^-$ and its substituted derivatives remain of interest to researchers because of their dramatic variation in structure and peculiar properties^[1-11]. Some of these compounds have tunable electronic behavior which can be employed in nonlinear optical materials^[2-5] and some show good biological activities^[6-12]. Furthermore, some of metal complexes derived from dithiocarbazate are well known to accelerate drug action and the efficiency of a therapeutic agent can be

enhanced upon coordination with a metal ion^[13]. As part of our study on ligands derived from *S*-benzylidithiocarbazate (SBDTC), the structure of transition metal complexes with SBDTC derivative have already been reported^[14]. To evaluate their coordination chemistry and their potential as antitumor agents, we report here synthesis, crystal structure and bioactivity of a new planar copper complex with bidentate Schiff base derived from SBDTC.

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1 Experimental

1.1 Reagent and apparatus

All chemicals were of reagent grade and were used as received. The solvents were purified using conventional methods. Elemental analyses were performed on a CHN-O-Rapid instrument.

1.2 Synthesis of the Schiff base (HL)

S-benzylthiocarbamate (SBDTC) was prepared as previously reported^[15]. The Schiff base was prepared by adding a solution of SBDTC (1.99 g, 0.01 mol) in absolute EtOH (20 mL) to an equimolar solution of *p*-phthalaldehyde (1.34 g, 0.01 mol) of the same solution (10 mL). The mixture was heated on a steam bath for 1 h and then cooled to 0 °C in an ice bath until the Schiff base precipitated. After being filtered, washed with cold EtOH and dried in vacuo over P₂O₅, the yield of the product is 58%. Anal. Calc. for C₁₆H₁₄N₂OS₂ (%):C, 61.12; H, 4.49; N, 8.91. Found(%): C, 61.04; H, 4.45; N, 8.96.

1.3 Synthesis of the copper complex Cu(L)₂

Schiff base (0.16 g, 0.5 mmol) dissolved in absolute ethanol was added to and ethanol solution (15

mL) of copper acetate (0.09 g, 0.5 mmol). The mixture was stirred at room temperature for 0.5 h to give a black solution. Suitable rod-shaped black single crystals of the title complex for the structure determination were obtained by slow evaporation of the solution in air. Yield: 61% on the basis of HL. Anal. Calc. for C₃₂H₂₆CuN₄O₂S₄ (%):C, 55.67; H, 3.80; N, 8.12. Found (%):C, 55.59; H, 3.78; N, 8.14.

1.4 X-ray crystal structure analysis

Diffraction data for the complex were collected at 298(2) K using a Bruker SMART APEX II CCD area-detector with Mo K α radiation (λ =0.071 073 nm). The collected data were reduced with the SAINT^[16] program, and empirical absorption correction was performed using the SADABS^[17] program. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 by using the SHELXTL^[18] software package. All of the non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in geometrically idealized positions. The summary of the crystal data, experimental details and structure refinement parameters are recorded in Table 1.

CCDC: 763155.

Table 1 Crystal data and structure refinement for the title complex

Empirical formula	C ₃₂ H ₂₆ CuN ₄ O ₂ S ₄	Absorption coefficient / mm ⁻¹	1.011
Formula weight	690.35	Crystal size / mm	0.18×0.11×0.07
Temperature / K	298(2)	h_{\min} / h_{\max}	-26 / 25
Wavelength / nm	0.071 073	k_{\min} / k_{\max}	-19 / 19
Crystal shape, color	Block, black	l_{\min} / l_{\max}	-9 / 9
Crystal system	Orthorhombic	Ref. collected / unique (R_{int})	14 618 / 2 703 (0.118 0)
Space group	<i>Pbcn</i>	Completeness to $\theta=24.99^\circ$ / %	98.9
a / nm	2.250 0(14)	Absorption correction	Multi-scan
b / nm	1.660 0(11)	θ range for data collection / (°)	2.89~24.99
c / nm	0.830 4(5)	Data / restraints / parameters	2 703 / 6 / 196
V / nm ³	3.102 (3)	GOF	1.011
Z	4	R_1, wR_2 ($I>2\sigma(I)$)	0.050 1, 0.087 2
D_c / (g·cm ⁻³)	1.478	R_1, wR_2 (all reflections)	0.129 1, 0.100 9
$F(000)$	1 420	Largest diff. peak and hole / (e·nm ⁻³)	392 and -293

1.5 Biological activity assay

As a preliminary screening for antitumor activity, biological activity of the title complex was used MTT method described in our previous paper^[19]. The copper complex dissolved in DMF was tested against MKN45

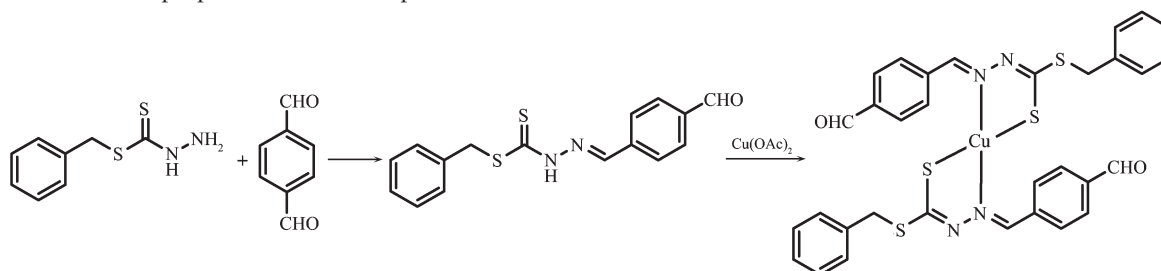
and HEPG2. For the comparison, 5-fluorouracil was also tested.

2 Results and discussion

The synthetic route of the target complex prepared

in absolute ethanol solution is shown in Scheme 1. The elemental analyses are in good agreement with the chemical formulae proposed for the complex. The title

complex is stable in air at room temperature, soluble in DMF, but slightly soluble in MeOH and EtOH, insoluble in water and Me_2O .



Scheme 1 Synthesis route for the title complex

2.1 Description of crystal structure

The molecular structure and the selected bond lengths and angles of the title complex are listed in Fig. 2 and Table 2, respectively. As shown in Fig. 2, $\text{Cu}(\text{II})$ complex exhibits central symmetry and the $\text{Cu}(\text{II})$ atom sits on crystallographic inversion center. In the complex the copper atom is four-coordinate with two N atoms and two S atoms from two bidentate Schiff base ligands derived from *S*-benzylthiocarbonylhydrazide and forms in a slightly distorted square-planar geometry, which is similar to that of the reported work^[4]. The two trans angles at the copper(II) center are exactly 180° , by virtue of the crystallographic symmetry (Table 2), and other angles are close to 90° , viz. $83.88(12)^\circ$ and $96.12(12)^\circ$, indicating a slight deviation from perfect square-planar geometry. The coordinated sulfur and nitrogen atoms in the two ligands are in opposite positions. The Cu-S and Cu-N bond length of $0.225\ 60(16)$

and $0.201\ 1(3)$ nm are slightly longer than those observed in the two similar copper complexes [$0.215\ 6(1)$, $0.225\ 1(1)$, $0.192\ 9(4)$ and $0.203\ 1(2)$ nm]^[4]. Two ligands coordinate with the center copper(II) ion and form two five-membered rings. The mean deviation of the five-membered ring is $0.006\ 95$ nm.

The C(9)-S(1) bond length of $0.170\ 2(4)$ nm is intermediate 0.182 nm for C-S single bond and 0.156 nm for C=S double bond^[18]. It is agreement with the reported value in the similar complexes^[4]. The N(2)-C(9) and N(1)-C(8) bond distances of $0.128\ 8(5)$ and $0.129\ 1(5)$ nm, respectively, indicate a strong electron delocalization in the conjugation of the C-N-N-C moiety compared with the bidentate complex of zinc, $[\text{Zn}(\text{C}_8\text{H}_9\text{N}_2\text{OS}_2)_2]$ ^[9]. The N(1)-N(2) bond distances of $0.139\ 7(4)$ nm are slightly shorter than the corresponding bond lengths in the copper complex ($0.140\ 9(5)$ nm)^[4]. Thus, Schiff base in the title complex behaves as

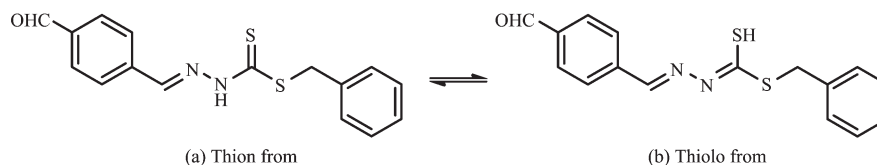
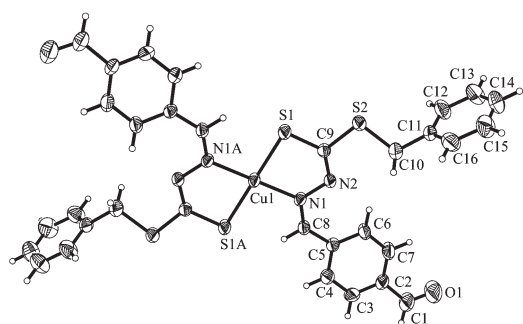


Fig. 1 Tautomeric forms of Schiff base

Table 2 Selected bond lengths (nm) and angles ($^\circ$) of the title complex

Cu(1)-N(1)#1	0.201 1(3)	Cu(1)-S(1)#1	0.225 60(16)	S(1)-C(9)	0.170 2(4)
S(2)-C(9)	0.173 7(4)	S(2)-C(10)	0.179 3(5)	N(1)-C(8)	0.129 1(5)
N(1)-N(2)	0.139 7(4)	N(2)-C(9)	0.128 8(5)		
N(1) #1-Cu(1)-N(1)	180.0(2)	N(1)#1-Cu(1)-S(1)	96.12(12)	N(1)-Cu(1)-S(1)#1	83.88(12)
C(9)-S(1)-Cu(1)	95.50(16)	C(9)-S(2)-C(10)	102.7(2)	C(8)-N(2)-N(1)	116.3(3)
C(9)-N(1)-N(2)	112.5(4)	O(1)-C(1)-C(2)	121.3(6)		

Symmetry codes: #1: $-x+2, -y, -z+2$.



Symmetry code: #1: $-x+2, -y, -z+2$

Fig.2 ORTEP view of the title complex with 30% probability displacement ellipsoids, showing the atom-labeling scheme

the deprotonated enethiolate form and coordinates with metal ion (Fig.1).

The crystal packing in the unit cell is shown in Fig.3. The molecular packing in the crystal is stabilized through aromatic interactions via phenyl-phenyl stacking.

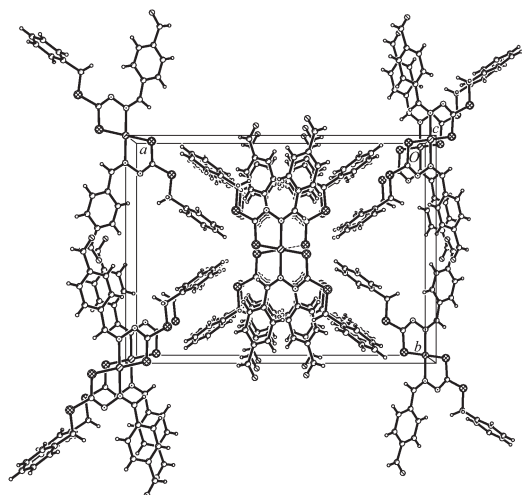


Fig.3 Packing diagram of the title complex, viewed along the c axis

2.2 Biological activity

The title complex was evaluated for its antitumor activities in vitro against HepG2 and MKN45 by MTT method. The data represent the mean of three experiments performed in triplicate. IC_{50} values of the title complex against MKN45 and HepG2, which is the concentration at which 50% survival of cells, are presented in Table 3.

The Cu(II) complex was cytotoxic to the human gastric cancer cells MKN45 with IC_{50} values of $8.4 \mu\text{g} \cdot \text{cm}^{-3}$

Table 3 Antitumor activity against tumor cells of the title complex and Schiff base

Compound	$IC_{50} / (\mu\text{g} \cdot \text{cm}^{-3})$	
	MKN45	HepG2
$\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}_2$	15.7	26.4
$\text{C}_{32}\text{H}_{26}\text{CuN}_4\text{O}_2\text{S}_4$	8.4	19.7

^a 5-FU IC_{50} (MKN45)=0.89 IC_{50} (HepG2)=1.36

^a Used as a positive control. IC_{50} =inhibition concentration at 50%, i.e., the concentration to reduce growth of cancer cells by 50%.

cm^{-3} and to human hepatoma cells HepG2 with IC_{50} values of $19.7 \mu\text{g} \cdot \text{cm}^{-3}$, respectively. Following the suggestion^[21], IC_{50} values more than $10 \sim 25 \mu\text{g} \cdot \text{cm}^{-3}$ indicate weak inhibitory activity while compounds with IC_{50} values less than $5 \mu\text{g} \cdot \text{cm}^{-3}$ are considered to be very active. Those having intermediate values ranging from $5 \sim 10 \mu\text{g} \cdot \text{cm}^{-3}$ are classified as moderately active. The results have been compared with an anticancer drug, 5-fluorouracil (5-FU). Among the present compounds, the Schiff base and Cu(II) complex are less effective than 5-FU. However, Cu(II) complex are more effective than the Schiff base towards cancer cells. Complexation of the metal ions enhances the anticancer behavior as is evident from the lower IC_{50} values of the complex compared with the Schiff base (Table 3). This result is consistent with the previous study^[22].

3 Conclusion

In this paper, the syntheses, crystal structure of Cu(II) complex containing two Schiff bases of *S*-benzylthiocarbamate and biological activity of this Schiff base and the metal complex synthesized were investigated. The complex is central symmetry in which the copper(II) ion lies in a four-coordinate, distorted square-planar environment. The complex was evaluated for antitumor activities against two kinds of cell line by MTT method. The study indicates that the complex shows moderate activity against MKN45 cells and weak activity against HepG2 cells.

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