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研究简报

三核镍配合物 $Ni_3(C_{14}H_8N_3O_5)_2(C_5H_5N)_4$ 的合成、晶体结构和抗癌活性

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Synthesis, Crystal Structure and Antitumor Activity of a New Trinuclear Ni(Ⅱ) Complex $Ni_3(C_{14}H_8N_3O_5)_2(C_5H_5N)_4$

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Abstract: The title complex $Ni_3(C_{14}H_8N_3O_5)_2(C_5H_5N)_4$ has been synthesized by the reaction of 2-hydroxy-*N*′-(4-nitrobenzoyl)benzohydraizide with nickel acetate in pyridine solution. Its molecular structure was characterized by elemental analysis, IR spectra and X-ray crystal structure determination. Crystal data for this compound: Monoclinic, space group $P2_1/c$, M_r=1 089.00, a=0.249 27(5) nm, b=0.161 40(3) nm, c=0.121 81(2) nm, β=94.59(3)°, V=4.885 2(17) nm^3, Z=4, D_c=1.481 Mg·m^{-3}, F(000)=2 232, R_1=0.049 7, wR_2=0.106 8 (observed reflections with $I>2\sigma(I)$) and R_1=0.105 1, wR_2=0.119 4 (all reflections), GOF=1.021. The complex was evaluated for their antitumor activities against two kinds of cell lines (K562 and BGC) by MTT method. A preliminary bioactivity study indicates that the complex shows distinct antitumor activity. CCDC: 627252.

Key words: Ni(Ⅱ) complex; synthesis; crystal structure; antitumor activity

Transition metal complexes containing hydrazide derivative and its analogs ligands have been of great interest for many years[1-10]. The complexes play an important role in the development of bioinorganic chemistry related to enzymatic reactions[2], antibacterial[3], antifungal[4], and antitumor[5]. Such compounds share a common hydrazide pharmacophore as one of the structural requirement for antitumor activity. To the best of our knowledge, there is no report on the transition metal chelating ability and the antitumor activity of such ligand (Fig.1). Recently, we have described the syntheses, crystal structures and antitumor activities of several transition metal complexes with salicyhydraizide derivative ligand[11-12]. As an extension of our work,

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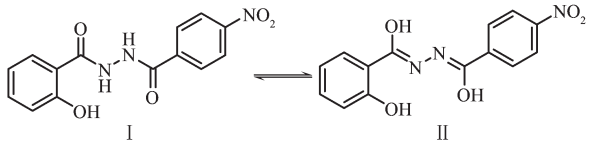

Fig.1 Tautomeric forms of the ligand

the syntheses, crystal structures and antitumor activities of a new trinuclear nickel complex with bent structures are reported herein. Trinuclear nickel complexes with bent structures are rare. As far as we know only $Ni_3(shi)_2(Hpko)_2(py)_2$, $Ni_3(p\text{-}nbzshz)_2(C_5H_5N)_4$, $[Ni_3(L_2)_2(OAc)_2(MeOH)(H_2O)][BF_4]_2$ and $[Ni_3(oxen)_2(en)_2][ClO_4]_2$ are reported in the literature[13-16]. As expected, our investigation shows that the title complex exhibits antitumor activity against K562 and BGC, which makes it promising for transition metal complexes become novel antitumor agents.

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 and were within ±0.4% of the theoretical values. IR spectra were recorded on a Nicolet AVATAR 360 series FTIR instrument using KBr pellets for spectra in the region 4 000~400 cm^{-1}. ^1H NMR spectra were recorded using DPX-500 Bruker Spectrometer with $CDCl_3$ as solvent.

1.2 Synthesis of the ligand

An anhydrous ethanolic solution (20 mL) of salicylhydrazide (0.15 g, 1.0 mmol) was added dropwise to the ethyl acetate solution (15 mL) of 4-nitrobenzoyl chloride (0.19 g, 1.0 mmol). The reaction mixture was stirred for 4 h at 120 ℃. Then the solution was concentrated to half of its initial volume and cooled to room temperature. The resulting products were filtered, washed with absolute ethanol, recrystallized from absolute ethanol and then dried in a vacuum desiccator over P_2O_5. Yield: 72%. Anal. Calc. for $C_{14}H_{11}N_3O_5$ (%): C, 55.82; H, 3.68; N, 13.95. Found (%): C, 55.46; H, 3.78; N, 13.64. ^1H NMR (500 MHz, $CDCl_3$): 6.96~8.39 (8H, m, Ar), 10.75 (1H, s, NH), 11.04 (1H, s, NH), 11.80 (1H, s, OH), Main IR absorption (KBr, cm^{-1}): 1 692(s), 1 590(s), 1 543(m) 1 520(m).

1.3 Synthesis of the title complex

2-hydroxy-*N*′-(4-nitrobenzoyl)benzohydraizide (0.15 g, 0.5 mmol) dissolved in absolute ethanol was added to an pyridine solution (1 mL) of nickel acetate (0.09 g, 0.5 mmol) at room temperature. The mixture was stirred at 50 ℃ for 0.5 h to give a deep black solution. Suitable block-shaped black single crystals of the complex for the structure determination were obtained by slow evaporation of the solution in air. Yield: 48% on the basis of the ligand. Anal. Calc. for $C_{48}H_{36}N_{10}Ni_3O_{10}$ (%): C, 52.94; H, 3.33; N, 12.86. Found (%): C, 52.85; H, 3.27; N, 12.68. Main IR absorption (KBr, cm^{-1}): 1 602 (s), 1 563(m), 1 518(m).

1.4 X-ray crystal structure analysis

Diffraction data for the complex were collected at 298(2) K using a Bruker SMART APEXII area-detector with Mo $K\alpha$ radiation (λ=0.071 073 nm). The collected data were reduced with the SAINT[17] program, and empirical absorption correction was performed using the SADABS[18] program. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 by using the SHELXTL[19] 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.

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Table 1 Crystal data and structure refinement for the title complex

Empirical formula	$C_{48}H_{36}N_{10}Ni_3O_{10}$	F(000)	2 232
Formula weight	1 089	Crystal size / mm	0.33×0.17×0.08
Temperature / K	298(2)	h_{min} / h_{max}	−29/29
Wavelength / nm	0.071 073	k_{min} / k_{max}	−19/19
Crystal shape, color	Block, black	l_{min} / l_{max}	−14/14

Continued Table 1

Crystal system	Monoclinic	Ref. collected / unique (R_{int})	29 349 / 8 563 (0.064 4)
Space group	$P2_1/c$	Completeness to θ=25.10° / %	98.3
a / nm	2.49 27(5)	Absorption correction	Multi-scan
b / nm	1.61 40(3)	Refinement method	Full-matrix least-squares on F^2
c / nm	1.21 81(2)	Data / restraints / parameters	8 563 / 0 / 641
β / (°)	94.59(3)	GOF	1.021
V / nm^3	4.885 2(17)	R_1, wR_2 [$I>2\sigma(I)$]	0.049 7, 0.106 8
Z	4	R_1, wR_2 (all data)	0.105 1, 0.119 4
D_c / (Mg·m^{-3})	1.481	Largest diff. peak and hole / (e·nm^{-3})	896 and 446
μ / mm^{-1}	1.212		

1.5 Antitumor activity determination

The antitumor activity of the title complex was assayed against two kinds of selected cancer cell lines (K562 and BGC). Cells were cultured at 37 ℃ under a humidified atmosphere of 5% CO_2 in RPMI 1640 medium supplemented with 10% fetal serum and dispersed in replicate 96-well plates with 1×10^4 cells/well. Complex was then added. After 24, 48, 72 h exposure to the toxins, the cell viability was determined by the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) antitumor assay by measuring the absorbance at 570 nm with an ESILA plate reader. Each test was performed in triplicate. The data represent the mean of three experiments and are expressed as means ±SD using Student t test. The IC_{50} value is defined as the concentration needed for a 50% reduction in absorbance calculated from the survival curves.

2 Results and discussion

2.1 IR spectra

The main IR absorption of the ligand and its complex is recorded in Table 2. The strong band at 1 692 cm^{-1} in the ligand may be assigned to $\nu_{C=O}$ and disappears in the title complex, indicating participation of enol form in coordination (Fig.1). The sharp band at 1 590 cm^{-1} in the ligand underwent a shift of 12 cm^{-1} in complexes confirming the formation of coordinate bond from hydrazide nitrogen to metal ion. From the infrared data, it is concluded that the ligand has linked with the transition metal ions through hydrazide nitrogen atoms, phenol oxygen atom and carbonyl oxygen atoms behaving as a penta-dentate ligand.

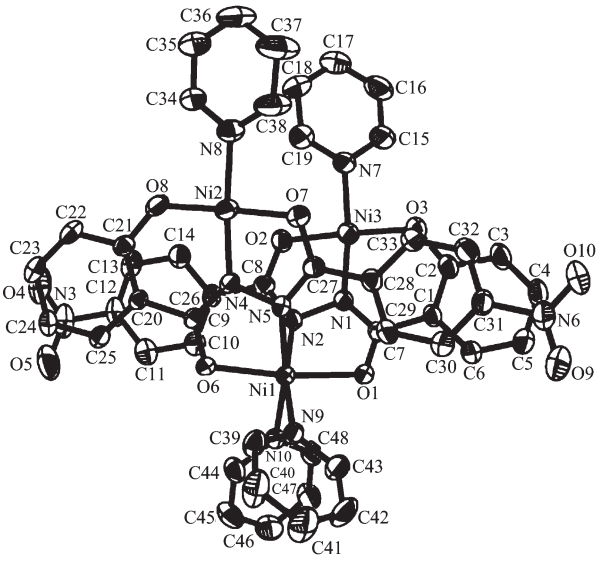
Table 2　IR spectra of the ligand and the complex

cm^{-1}

Compound	$\nu_{-C=O-}$	$\nu_{-C=N-}$	ν_{-CONH-}	ν_{-CONH-}
Ligand	1 692	1 590	1 543	1 520
Complex	—	1 602	1 563	1 518

2.2 Description of crystal structure

The perspective structure and the atomic numbering schemes for the title complex are shown in Fig.2. Selected bond lengths and angles are given in Table 3.



Thermal ellipsoids are plotted at 30% probability level, hydrogen atoms are omitted for clarity

Fig.2　Crystal structure of the title complex with the atom numbering

As shown in Fig.2, the title complex is a neutral tri-nuclear nickel complex with bent structures. The structure of the complex shows that the central Ni(1)(Ⅱ) ion is coordinated by four nitrogen atoms [N(2), N(5),

Table 3 Selected bond lengths (nm) and angles (°) of the title complex

Ni(1)-O(1)	0.203 7(3)	Ni(1)-N(2)	0.215 5(3)	Ni(3)-O(3)	0.180 4(3)
Ni(1)-O(6)	0.203 8(3)	Ni(2)-O(8)	0.181 4(3)	Ni(3)-N(1)	0.182 7(3)
Ni(1)-N(9)	0.209 9(3)	Ni(2)-N(4)	0.182 3(3)	Ni(3)-O(2)	0.183 5(3)
Ni(1)-N(10)	0.210 1(3)	Ni(2)-O(7)	0.184 0(3)	Ni(3)-N(7)	0.191 8(4)
Ni(1)-N(5)	0.213 4(3)	Ni(2)-N(8)	0.193 9(4)		
O(1)-Ni(1)-O(6)	172.68(11)	N(10)-Ni(1)-N(5)	169.95(13)	O(8)-Ni(2)-N(8)	90.49(17)
O(1)-Ni(1)-N(9)	92.50(13)	O(1)-Ni(1)-N(2)	76.98(12)	N(4)-Ni(2)-N(8)	174.93(17)
O(6)-Ni(1)-N(9)	92.41(12)	O(6)-Ni(1)-N(2)	97.91(12)	O(7)-Ni(2)-N(8)	91.30(17)
O(1)-Ni(1)-N(10)	92.00(13)	N(9)-Ni(1)-N(2)	169.35(13)	O(3)-Ni(3)-N(1)	95.41(15)
O(6)-Ni(1)-N(10)	93.76(13)	N(10)-Ni(1)-N(2)	95.94(13)	O(3)-Ni(3)-O(2)	173.44(15)
N(9)-Ni(1)-N(10)	85.96(13)	N(5)-Ni(1)-N(2)	83.91(13)	N(1)-Ni(3)-O(2)	83.63(15)
O(1)-Ni(1)-N(5)	97.74(12)	O(8)-Ni(2)-N(4)	94.45(15)	O(3)-Ni(3)-N(7)	90.68(17)
O(6)-Ni(1)-N(5)	76.34(12)	O(8)-Ni(2)-O(7)	177.78(14)	N(1)-Ni(3)-N(7)	171.24(17)
N(9)-Ni(1)-N(5)	96.05(13)	N(4)-Ni(2)-O(7)	83.79(14)	O(2)-Ni(3)-N(7)	91.02(16)

N(9), and (N10)] with Ni-N distances of 0.215 1(3), 0.213 4(3), 0.209 7(3), and 0.210 7(3) nm, and two oxygen atoms [O(1) and O(6)] with Ni-O distances of 0.204 0(3) and 0.204 0(3) nm. The central Ni(1) ion is well described as having an octahedron configuration with N(2), N(5), N(9), N(10), O(1), and O(6). But the structures of the terminal Ni ions are different from those of the central Ni ions. The terminal Ni(2) ion is four-coordinated by two nitrogen atoms [N(4) and N(8)] with Ni-N distances of 0.182 4(3) and 0.193 7(4) nm, and two oxygen atoms [O(7) and O(8)] with Ni-O distances of 0.184 4(3) and 0.181 0(3) nm. The structure of the other terminal Ni(3) ion is similar to that of the Ni(2) ion. The Ni⋯Ni separations are 0.454 7, 0.447 9, and 0.442 4 nm, respectively.

The array of three nickel atoms in title complex is bent with a dihedral angle Ni(2)-Ni(1)-Ni(3) of 58.68°, which is smaller than that of the corresponding values of 62.36°, 119.0° and 130.9° in the bent trinuclear Ni(Ⅱ) complexes with a same ligand[13] and different ligands[15-16], larger than the corresponding values of 46.50° in the bent trinuclear Ni(Ⅱ) complexes with the different ligand[14]. The neighboring Ni(1)⋯Ni(2) and Ni(1)⋯Ni(3) interatomic distances are 0.454 6 nm, 0.447 9 nm, respectively, which are shorter those in related complex[13]. The Ni(1)⋯Ni(3) separation is 0.442 4 nm, longer than that (0.356 nm) reported for the similar bent configuration[14] and shorter than that (0.469 3 nm) of the corresponding complex with a same ligand[13].

2.3 Antitumor activity

The title complex was evaluated for its cytotoxic activities *in vitro* against two kinds of cell lines (K562 and BGC) by MTT method. The 50% inhibitory concentrations (IC_{50}) of the complexes against K562 and BGC are presented in Table 4.

Table 4 Cytotoxic activity against selected Human tumor cells of the title complex

Time / h	IC_{50} / (μmol·L^{-1})	
	K562 / ADM	BGC-823
24	19.049	24.227
48	7.694	13.498
72	5.628	8.796

Antitumor activities are expressed as IC_{50} (50% inhibitory concentration) in two kinds of cell lines (K562 and BGC). Data are average data of triplicate assay.

From the data in Table 4, it suggests that the title complex shows obvious antitumor activity. On the basis of the bioassay result, the nickel complex, as an approach to enhancing inhibitory effect on proliferation of tumor cell lines[20], is worthy of further investigation. Further studies are underway to investigate the physical chemistry of the nickel complex.

3 Conclusion

In this paper, we present the syntheses, crystal

structure and antitumor activity of a novel trinuclear transition metal complex with salicyhydraizide derivative ligand. Three Ni atoms in title compound exhibit a square-planar/octahedral/square-planar coordination geometry mode. The title complex reveals a curved Ni_3 metal arrangement with a Ni(2)-Ni(1)-Ni(3) angle of 58.68°. It should be noted that the molecular structures are remarkably different with the same ligand and same bivalent transition metal but different solvents[13]. The complex was evaluated for antitumor activities against two kinds of cell lines by MTT method. The study indicates that the complex shows distinct antitumor activity.

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