

SYNTHESIS, CHARACTERIZATION AND CRYSTAL STRUCTURE OF A POLYMERIC SILVER(I) COMPLEX WITH CYTOTOXIC PROPERTY

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ABSTRACT

A new polymeric silver(I) complex, $[\text{Ag}_2(\text{L}^1)_2(\text{L}^2)(\text{OH}_2)]_n$, was obtained by the reaction of 3-aminopyrazine-2-carboxylic acid (HL^1), 2-amino-5-methylpyridine (L^2) and silver oxide in aqueous ammonia. The complex was characterized by elemental analysis, IR spectra and single crystal X-ray determination. The smallest repeat unit contains a $[\text{Ag}_2(\text{L}^1)_2(\text{L}^2)(\text{OH}_2)]$ moiety. The $\text{Ag} \cdots \text{Ag}$ distance is 7.490(2) Å. One Ag atom is coordinated by three pyrazine N and two carboxylate O atoms from four L^1 ligands, forming a square pyramidal coordination, and the other one is coordinated by one pyrazine N and one carboxylate O atoms from a L^1 ligand, one pyridine N atom from a L^2 ligand, and one water O atom, forming a square planar geometry. In the crystal structure of the complex, the dinuclear silver moieties are linked through L^1 ligands, to form 1D chains along the x -axis direction. The chains are further linked through intermolecular hydrogen bonds in the y - and z -axis directions, forming a 3D network. In addition, there are $\pi \cdots \pi$ interactions among the chains. The complex showed effective cytotoxic property on human lung cancer cell line A549.

Keywords: Silver complex; Polymeric complex; 3-Aminopyrazine-2-carboxylate; 2-Amino-5-methylpyridine; Crystal structure; Cytotoxicity

INTRODUCTION

The compounds bearing both pyridine/pyrazine and carboxylate groups are a kind of interesting ligands for the coordination of silver, and such complexes have received particular attention in coordination chemistry¹⁻⁵. Silver has versatile coordination numbers and geometries⁶⁻¹⁰. By varying the synthetic method, solvents, anions, and proportion of starting materials, one can construct different structures of silver complexes. But until now, one can not precisely predicates what structures will be finally formed for the silver complexes. So, more work needs to be carried out to understand the influence effects of such complexes. In addition, most silver complexes have shown interesting luminescence property¹¹⁻¹³ and biological activities¹⁴⁻¹⁷. Lung cancer is one of the most common and life-threatening malignancies worldwide. The poor prognosis of lung cancer is largely attributed to the frequent occurrence of metastasis, since most metastatic tumours are unresectable at the time of presentation. The severe morbidity and poor prognosis of lung cancer highlight the importance of searching for new and effective agents against lung cancer^{18,19}. It is notable that the cytotoxicity property of the silver complexes has received particular attention²⁰⁻²². 3-Aminopyrazine-2-carboxylic acid (HL^1) is a hopeful ligand containing carboxylic group, amine and pyrazine nitrogen atoms. Some nickel, cobalt, mercury, zinc, manganese and lanthanide²³⁻²⁸ complexes derived from HL^1 have been reported. However, no silver complex has been reported so far. In the present work, a new polymeric silver(I) complex, $[\text{Ag}_2(\text{L}^1)_2(\text{L}^2)(\text{OH}_2)]_n$, is presented. The aim was to investigate the anticancer effects of the complex on human lung cancer cell A549.

EXPERIMENTAL

Materials and Measurements: 3-Aminopyrazine-2-carboxylic acid, 2-amino-5-methylpyridine and silver oxide were purchased from Fluka and used as received. The solvents used were of reagent grade. Elemental analyses were carried out using a Perkin–Elmer 2400 II elemental analyser. The infrared spectrum was recorded on a Perkin–Elmer FT-IR spectrophotometer with a KBr disc. The X-ray diffraction was carried out on a Bruker SMART 1000 CCD area diffractometer at 298(2) K.

Synthesis of the complex. 3-Aminopyrazine-2-carboxylic acid (0.28 g, 2 mmol) and Ag_2O (0.23 g, 1 mmol) were mixed and stirred in a 30% aqueous ammonia (30 mL). The mixture was stirred at room temperature until all solid dissolved. Then, to the mixture was added 2-amino-5-methylpyridine (0.11 g, 1 mmol). The final mixture was further stirred at dark for 30 min. The clear colorless solution was kept still at room temperature in dark for several days, to give small block-like single crystals. Yield: 27%. IR (KBr, cm^{-1}): 3287w, 1613s, 1555s, 1470s, 1401m, 1376m, 1277w, 1236w, 1159w, 1120w, 1043m, 963m, 822s, 715m, 677w, 621w, 575m, 447w. Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{Ag}_2\text{N}_8\text{O}_5$: C, 31.09; H, 2.94; N, 18.13%. Found: C, 31.23; H, 2.82; N, 17.97%.

X-ray Crystallography: A suitable single crystal of the complex was mounted on the top of a glass fiber. Graphite-monochromatized Mo-K α radiation ($\lambda = 0.71073$ Å) and the ω scan technique were used to collect the diffraction data. Absorption correction was applied with SADABS²⁹. The structure of the complex was solved with direct method and refined with a full-matrix least-squares technique with SHELXTL³⁰. Anisotropic thermal parameters were applied to all non-hydrogen atoms. The hydrogen atoms of the amino groups were located from electronic density maps, with N–H and H \cdots H distances restrained to 0.90(1) and 1.43(2) Å, respectively. The other hydrogen atoms were generated geometrically. The crystallographic data and the details of the data collection and refinement for the complex are listed in Table 1. Selected bond lengths and angles are given in Table 2. Hydrogen bonding information is given in Table 3.

Table 1. Crystallographic data for the complex

Parameter	Value
Empirical Formula	$\text{C}_{16}\text{H}_{18}\text{Ag}_2\text{N}_8\text{O}_5$
FW	618.1
Crystal shape/colour	Block/colorless
Crystal size /mm	0.15 x 0.13 x 12
Crystal system	Monoclinic
Space group	$P2_1/n$
λ (MoK α) /Å	0.71073
T /K	298(2)
μ/mm^{-1} (Mo-K α)	2.058
Unit cell dimensions	
a /Å	7.236(2)
b /Å	19.573(3)
c /Å	14.168(3)
β /°	103.571(3)
V /Å ³	1950.6(7)
Z	4
T_{min}	0.7477
T_{max}	0.7903

No. of measured reflections	9052
No. of unique reflections	3141
No. of observed reflections [$I \geq 2\sigma(I)$]	2500
data/restraints/parameters	3141/12/305
R_{int}	0.0349
$F(000)$	1216
Goodness of fit on F^2	1.063
R_1, wR_2 [$I \geq 2\sigma(I)$]	0.0427, 0.1161
R_1, wR_2 (all data)	0.0777, 0.1349

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

Bond	<i>d</i> , Å	Bond	<i>d</i> , Å
Ag(1)-N(1)	2.301(5)	Ag(1)-N(2A)	2.330(5)
Ag(1)-N(5)	2.494(5)	Ag(1)-O(4B)	2.621(5)
Ag(1)-O(1)	2.611(5)	Ag(2)-N(7)	2.195(5)
Ag(2)-N(4)	2.235(5)	Ag(2)-O(3)	2.580(5)
Ag(2)-O(5)	2.582(6)		
Angle	ω , deg	Angle	ω , deg
N(1)Ag(1)N(2A)	150.3(2)	N(1)-Ag(1)-N(5)	118.5(2)
N(2A)Ag(1)N(5)	89.7(2)	N(1)Ag(1)O(1)	66.9(2)
N(2A)Ag(1)O(1)	102.3(2)	N(5)Ag(1)O(1)	97.4(2)
N(1)Ag(1)O(4B)	91.4(2)	N(2)Ag(1)O(4B)	101.4(2)
N(5)Ag(1)O(4B)	84.1(2)	O(1)Ag(1)O(4B)	156.3(2)
N(7)Ag(2)N(4)	175.3(2)	N(7)Ag(2)O(3)	106.8(2)
N(4)Ag(2)O(3)	68.8(2)	N(7)Ag(2)O(5)	92.8(2)
N(4)Ag(2)O(5)	91.8(2)	O(3)Ag(2)O(5)	158.6(2)

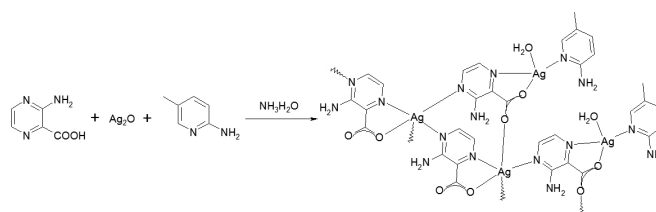
Symmetry codes: A: $-1 + x, y, z$; B: $1/2 + x, 1/2 - y, 1/2 + z$.**Table 3.** Hydrogen-bonding geometry (Å, °).

<i>D</i> -H... <i>A</i>	<i>D</i> -H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> -H... <i>A</i>
N(3)-H(3A)...O(2)	0.90(1)	2.09(6)	2.660(7)	120(5)
N(3)-H(3B)...O(1) ⁱ	0.90(1)	2.22(2)	3.110(7)	168(7)
N(6)-H(6A)...O(4)	0.90(1)	1.99(5)	2.663(7)	130(6)
N(6)-H(6B)...O(1)	0.90(1)	2.32(4)	3.141(7)	152(7)
N(8)-H(8A)...O(1) ⁱⁱ	0.90(1)	2.17(2)	3.030(7)	161(6)
N(8)-H(8B)...O(3)	0.90(1)	2.11(2)	2.999(8)	170(8)
O(5)-H(5A)...O(3) ⁱⁱⁱ	0.85(1)	2.07(4)	2.890(8)	160(10)
O(5)-H(5B)...O(2) ^{iv}	0.85(1)	1.88(2)	2.733(8)	175(10)

Symmetry codes: i): $1 + x, y, z$; ii): $-1 - x, -1 - y, 1 - z$; iii) $-1/2 + x, 1/2 - y, 1/2 + z$.

RESULTS AND DISCUSSION

Synthesis: The synthetic procedure of the complex is described as follows:



In the present complex, the Ag atom combines with the pyrazine N and carboxylate O atoms, instead of the amino N atom. This is due to the strain of the five-membered chelate ring is weaker than the four-membered chelate ring. Elemental analyses of the complex are in good agreement with expected values. Even though most silver complexes are sensitive to light, the present sample is very stable.

Infrared Spectrum: The weak and sharp absorption at 3287 cm^{-1} is resulted from the N-H vibrations of the amino groups. The $\nu_{\text{as}}(\text{COO})$ is related to the strong band observed at 1613 cm^{-1} , whereas the $\nu_{\text{s}}(\text{COO})$ is attributed to the medium band observed at 1376 cm^{-1} . This gives rise to a $\Delta\nu$ of 237 cm^{-1} characteristic of bidentate coordination of the carboxylate group³².

Structure Description of the Complex: The molecular structure of the complex is shown in Figure 1. The smallest repeat unit contains a $[\text{Ag}_2(\text{L}^1)_2(\text{L}^2)(\text{OH})]$ moiety. The $\text{Ag}(1)\cdots\text{Ag}(2)$ distance is $7.490(2)\text{ \AA}$. The $\text{Ag}(1)$ atom is coordinated by three pyrazine N and two carboxylate O atoms from four L^1 ligands, forming a square pyramidal coordination. The Ag atom deviates from the least squares basal plane defined by $\text{O}(1)$, $\text{N}(1)$, $\text{N}(2\text{A})$ and $\text{O}(4\text{B})$ by $0.232(1)\text{ \AA}$. The *cis* and *trans* coordinate bond angles in the basal plane are $66.9(2)^\circ$ - $102.3(2)^\circ$ and $150.3(2)^\circ$ - $156.3(2)^\circ$, respectively. The bond angles between the apical donor atom $\text{N}(5)$ and the basal donor atoms are in the range $84.1(2)^\circ$ - $118.5(2)^\circ$. The deviation from the ideal values of square pyramidal geometry indicates the distortion of the coordination geometry. The $\text{Ag}(2)$ atom is coordinated by one pyrazine N and one carboxylate O atoms from a L^1 ligand, one pyridine N atom from a L^2 ligand, and one water O atom, forming a square planar geometry. The $\text{Ag}(2)$ atom deviates from the least squares basal plane defined by the four donor atoms by $0.080(1)\text{ \AA}$. The *cis* and *trans* coordinate bond angles defined by the donor atoms are $68.8(2)^\circ$ - $106.8(2)^\circ$ and $158.6(2)^\circ$ - $175.3(2)^\circ$, respectively. This also indicates that the square planar coordination is distorted. In addition, the distortion of the coordination can be observed from the bond lengths and angles related to the Ag atom. The Ag-O bonds are much longer than the Ag-N bonds. Due to the strain created from the five-membered chelated rings $\text{Ag}(1)\text{-N}(1)\text{-C}(1)\text{-C}(5)\text{-O}(1)$ and $\text{Ag}(2)\text{-N}(4)\text{-C}(8)\text{-C}(10)\text{-O}(3)$, the angles $\text{N}(1)\text{-Ag}(1)\text{-O}(1)$ and $\text{N}(4)\text{-Ag}(2)\text{-O}(3)$ are much small. Yet, the Ag-O and Ag-N bonds are comparable to those observed in similar silver complexes^{33,34}. In the crystal structure of the complex, Figures 2 and 3, the dinuclear silver moieties are linked through L^1 ligands, to form 1D chains along the *x*-axis direction. The chains are further linked through intermolecular hydrogen bonds (Table 3) in the *y*- and *z*-axis directions, forming a 3D network. In addition, there are $\pi\cdots\pi$ interactions among the chains (Table 4).

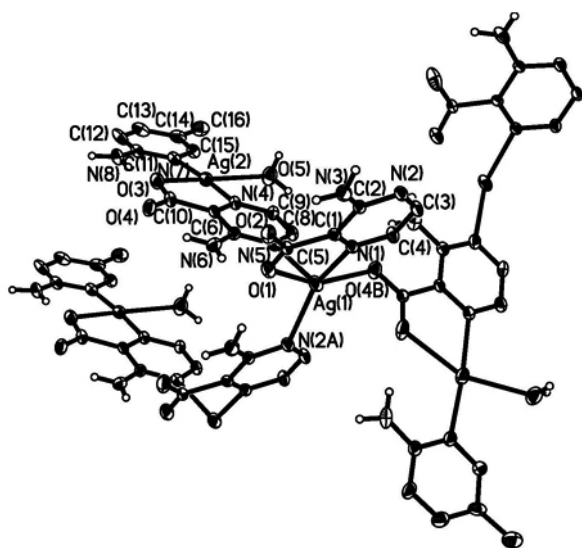


Figure 1. Molecular structure of the silver complex with 30% probability level.

Cytotoxic Property: A549 lung cancer cells and L-02 human normal liver cell were used by MTT method to study the growth inhibitory effects of the complex. The IC_{50} values for the complex are $14.2 \pm 1.3\text{ }\mu\text{M}$ for A549 and $57.3 \pm 3.7\text{ }\mu\text{M}$ for L-02. As a comparison, the silver nitrate and cisplatin showed IC_{50} values of $8.7 \pm 0.9\text{ }\mu\text{M}$ and $6.9 \pm 1.1\text{ }\mu\text{M}$ for A549, and the ligands themselves showed no activity. Thus, the cytotoxic property of the complex is to some extent weak than the silver nitrate and cisplatin. However, considering

the obvious side effects of the silver nitrate and cisplatin, the present silver complex is also a promising drug, which deserves further study.

Appendix A. Supplementary data

CCDC -1008308 for the complex contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/const/retrieving.html> or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

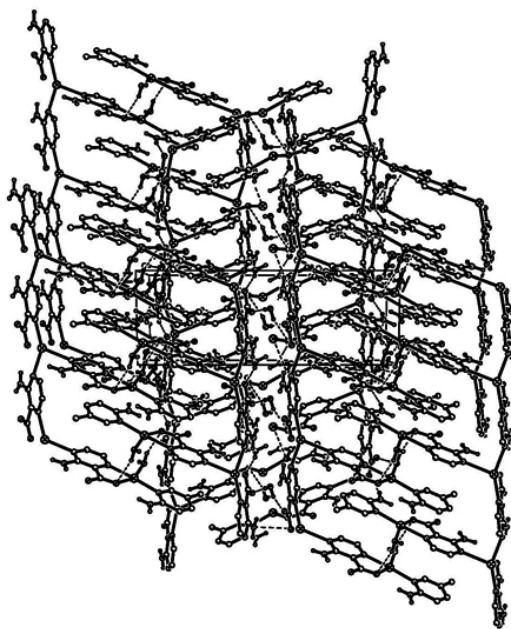


Figure 2. Molecular packing of the complex, viewed along the *z* axis. Hydrogen bonds are shown as dashed lines.

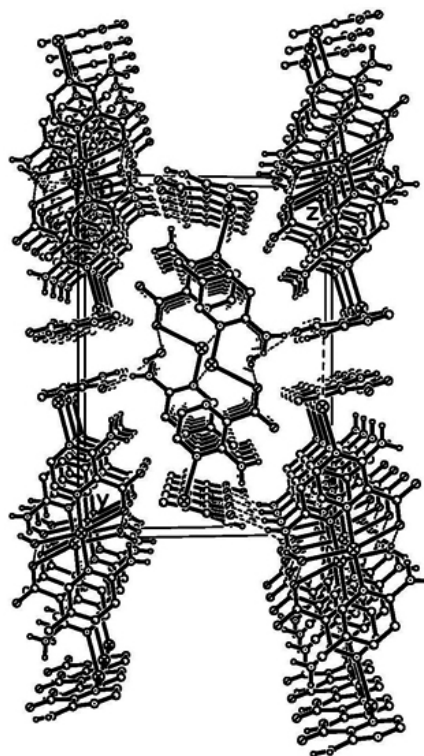


Figure 3. Molecular packing of the complex, viewed along the *x* axis. Hydrogen bonds are shown as dashed lines.

Table 4. Parameters between the planes for the complex.

Cg	Distance between ring centroids (Å)	Dihedral angle (°)	Perpendicular distance of Cg(I) on Cg(J) (Å)	Perpendicular distance of Cg(J) on Cg(I) (Å)	Slippage
Cg(1)-Cg(1) ^{iv}	4.318	0	3.342	3.342	2.734
Cg(1)-Cg(4) ^{iv}	3.950	3	3.413	3.401	
Cg(2)-Cg(3) ^v	3.762	5	-3.396	-3.245	
Cg(2)-Cg(3) ^{vi}	4.728	5	3.187	3.430	
Cg(4)-Cg(4) ^{iv}	4.847	0	3.341	3.341	3.511
Cg(4)-Cg(5) ^{vii}	4.894	65	-3.611	-4.512	
Cg(5)-Cg(3) ^v	3.992	6	-3.228	-3.411	
Cg(5)-Cg(3) ^{vi}	3.600	6	3.355	3.430	

Symmetry codes: iv): $1-x, 1-y, -z$; v): $-1-x, -y, -z$; vi): $-x, -y, -z$. Cg(1), Cg(2), Cg(3), Cg(4) and Cg(5) are the centroids of Ag(1)-O(1)-C(5)-C(1)-N(1), Ag(2)-N(4)-C(6)-C(10)-O(3), N(7)-C(11)-C(12)-C(13)-C(14)-C(15), N(1)-C(1)-C(2)-N(2)-C(3)-C(4) and N(4)-C(6)-C(7)-N(5)-C(8)-C(9), respectively.

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