Syntheses, Crystal Structures and Cytotoxities of Silver(I) Complexes of 2,2′-Bipyridines and 1,10-Phenanthroline

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The syntheses, characterizations and *in vitro* cytotoxities of seven soluble silver(I) compounds (1—7) with 2,2′-bipyridine (bpy), 5,5′-dimethyl-2,2′-bipyridine (dmbpy) and 1,10-phenanthroline (phen) are described. Two of the complexes, [Ag(dmbpy)(NO_3)] (1) and [Ag(dmbpy)]ClO_4(2), have been structurally established by single-crystal X-ray diffraction, which reveals the silver(I) atom in compound 1 is in a *Y*-shape coordination geometry with two N atoms (*av.* Ag—N = 227.8 pm) from a chelate dmbpy ligand and an O atom (Ag—O = 221.8(4) pm) from a monodentate nitrate. The Ag(I) atom in compound 2 is three-coordinated by three N atoms, two of which are from a chelate dmbpy, and one from an acetonitrile ligand. The seven compounds showed strong cytotoxities *in vitro* to both normal and carcinoma cells.

Keywords 2,2′-Bipyridine, 1,10-phenanthroline, silver(I), crystal structure, cytotoxity

Introduction

Coordination compounds of the coinage monovalent ions have received considerable attention in the last thirty years. In particular, the study of their biological activity is of importance. A notable example is the medical application of the complexes for treating rheumatoid arthritis and as cytotoxic agents.[1,2] Another promising application is the use of β-emitting radionuclides ^{111}Ag[3] and ^{198}Au[4] in selective internal radiotherapy of tumors as radio-metal-based bioconjugates.

Silver is by far the less investigated coinage metal in coordination chemistry, that possibly be attributed to the poor solubility of silver(I) compounds in common solvents and the sensitivity toward photodecomposition.[5] On the other hand, it has been found that many factors such as the nature of the ligands, solvents, counter-anions, *etc.*, appear to modulate the stereochemistry of silver complexes.[6] Our previous studies on the coordination of various silver(I) salts to a macrocyclic Schiff base have clearly shown the versatility.[7] As a continuation of these studies, we have synthesized and characterized seven coordination compounds of $AgNO_3$, $AgClO_4$ and $AgPF_6$ with bpy, dmbpy or phen, where bpy is 2,2′-bipyridine, dmbpy is 5,5′-dimethyl-2,2′-bipyridine, and phen is 1,10-phenanthroline. Surprisingly, we have also found that they exhibit strong cytotoxity *in vitro*. This observation along with their good stability and solubility in aqueous solvents suggests that silver(I)-bipyridyl compounds may be considered as potential antitumor agents.

Experimental

Materials and physical measurements

Reagents were used as obtained without further purification. Solvents were purified by standard methods before use. The C, H, N elemental analyses were performed on an Elementar Vario EL elemental analyzer. The IR spectra were recorded with KBr pellets in the

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4000—400 cm^{-1} region using a Nicolet 170SX FTIR spectrophotometer.

Synthesis of complexes

$[Ag(dmbpy)(NO_3)]$ (**1**)

To an acetonitrile solution (5 mL) of $AgNO_3$ (170 mg, 1 mmol) was added an acetonitrile solution (5 mL) of dmbpy (112 mg, 1 mmol) with stirring. Upon slow diffusion of diethyl ether into the resulting solution for 24 h, large colorless prismatic crystals of compound **1** were deposited and collected by filtration, washed with acetonitrile and diethyl ether and dried in a vacuum desiccator over silica gel (yield 92%). IR (KBr) ν: 3107w, 3015w, 2917w, 2860w (CH), 1595m, 1567m, 1475m (C=N, C=C), 1384s, 1278m (NO_2), 1032w (C—C) cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_3AgO_3$: C 40.7, H 3.4, N 11.9. Found: C 41.0, H 3.4, N 11.6.

$[Ag(dmbpy)(MeCN)]ClO_4$ (**2**)

Compound **2** was prepared as for compound **1** using $AgClO_4$ in place of $AgNO_3$. The large colorless prismatic crystals of compound **2** were obtained (yield 52%). IR (KBr) ν: 3008w, 2952w, 2917w, 2860w (CH), 2249w (C≡N), 1602w, 1560w, 1475m, (C=N, C=C), 1145s, 1095s (ClO_4^-), 1032w (C—C) cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_3ClO_4Ag$: C 38.9, H 3.5, N 9.7; Found: C 38.4, H 3.5, N 9.7.

$Ag(dmbpy)(MeCN)(PF_6)(H_2O)$ (**3**)

Compound **3** was prepared as for compound **1** using $AgPF_6$ in place of $AgNO_3$. The pale yellow needle-like crystals of compound **3** were obtained (yield 45%). IR (KBr) ν: 3416m (HO), 3008w, 2952w, 2917w, 2860w (CH), 2249w (C(N), 1602w, 1560w, 1475m, (C=N, C=C), 842s (PF_6^-), 1032w (C—C) cm^{-1}. Anal. Calcd for $C_{14}H_{17}N_3F_6OPAg$: C 33.9, H 3.5, N 8.5; Found: C 34.0, H 3.4, N 8.3.

$Ag_2(phen)_3(NO_3)_2(H_2O)$ (**4**)

To an acetonitrile solution (5 mL) of $AgNO_3$ (170 mg, 1 mmol) was added an acetonitrile solution (5 mL) of phen (270 mg, 1.5 mmol) with stirring. The yellow micro-crystals of compound **4** were deposited and collected by filtration, washed with acetonitrile and diethyl ether and dried in a vacuum desiccator over silica gel (yield 95%). IR (KBr) ν: 3451w (H—O), 3050w, 3000w (CH), 2250w 1588w, 1567w, 1510m, 1419m (C=N, C=C), 1377s, 1328m (NO_2), 1039w (C—C) cm^{-1}. Anal. Calcd for $C_{36}H_{26}N_8O_7Ag_2$. C 48.1, H 2.9, N 12.5; Found: C 48.0, H 3.0, N 12.6.

$Ag(phen)_2(MeCN)(PF_6)(H_2O)_2$ (**5**)

Compound **5** was prepared as for compound **4** using $AgPF_6$ in place of $AgNO_3$. The yellow crystals of compound **5** were obtained (yield 90%). IR (KBr) ν: 3416m (H—O), 3050w, 3001w (C—H), 2250w (C≡N), 1588w, 1567w, 1510m, 1419m (C=N, C=C), 842s (PF_6^-), 1039w (C—C) cm^{-1}. Anal. Calcd for $C_{26}H_{23}N_5F_6O_2PAg$: C 45.2; H 3.4, N 10.1; Found: C 45.4, H 3.4, N 10.3.

$Ag(phen)_2(ClO_4)\cdot 0.5H_2O$ (**6**)

Compound **6** was prepared as for compound **4** using $AgClO_4$ in place of $AgNO_3$. The yellow crystals of compound **6** were obtained (yield 95%). IR (KBr) ν: 3416w (H—O), 3050w, 3001w (C—H), 1588w, 1567w, 1510m, 1419m (C=N, C=C), 1117s, 1082s (ClO_4^-) cm^{-1}. Anal. Calcd for $C_{24}H_{17}N_4ClO_{4.5}$-Ag: C 50.0, H 3.0, N 9.7; Found: C 50.1, H 3.0, N 9.8.

$Ag(bpy)_2(NO_3)(HNO_3)$ (**7**)

Compound **7** was prepared as for compound **1** using bpy in place of dmbpy. The large colorless crystals of compound **7** were obtained (yield 85%). IR (KBr) ν: 3057w (CH), 1588w, 1560m, 1454m (C=N, C=C), 1384s, 1307m (NO_2), 1031w (C—C) cm^{-1}. Anal. Calcd for $C_{10}H_8N_4O_6Ag$: C 31.0, H 2.1, N 14.4; Found: C 31.1, H 2.1, N 14.5.

CAUTION! Although no problems were encountered in the preparation of the perchlorate salts care should be taken when handing such potentially explosive compounds.

X-ray Crystallography

Diffraction intensities for compounds **1** and **2** were

collected at 293(2) K on a Siemens R3m diffractometer using MoK_α radiation (λ = 71.073 pm). Absorption corrections were applied.[8] The structure solutions and full-matrix least-squares refinements based on F^2 were performed with the SHELX-97 program package.[9] All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated geometrically and allowed to ride on their parent carbon atoms. Analytical expressions of neutral-atom scattering factors were employed, and anomalous dispersion corrections were incorporated.[10] The crystallographic data for both compounds are summarized in Table 1. Selected bond distances and bond angles are given in Table 2. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 147908 and 147909).

Table 1 Crystal data for compounds **1** and **2**

Compound	**1**	**2**
Chemical formula	$C_{12}H_{12}N_2O_3Ag$	$C_{14}H_{15}N_3ClO_4Ag$
Fw	354.1	432.6
Space group	*C*2/*c*	*P*-1
a (nm)	0.7955(2)	1.3331(6)
b (nm)	1.8310(5)	1.3608(8)
c (nm)	1.7784(6)	1.3873(6)
α (deg)	90	95.76(1)
β (deg)	102.41(2)	98.72(1)
γ (deg)	90	100.21(1)
V (nm^3)	2.530(1)	2.427(2)
Z	8	6
λ (Mo K_α) (pm)	71.073	71.073
T (K)	293	293
ρ (g/cm^3)	1.859	1.776
μ (Mo K_α) (cm^{-1})	1.601	1.433
$R_1(I > 2\sigma(I))^a$	0.0376	0.0766
wR_2(all data)^a	0.0987	0.1911

$^a R_1 = \sum \| F_o| - |F_c \| / \sum |F_o|$, $wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o)^2 + (0.1(\max(0, F_o^2) + 2F_c^2)/3)^2]^{-1}$.

In vitro cytotoxity

Five human solid carcinoma cell lines, Hela (cervix adenocarcinoma), HepG2 (hepatocellular carcinoma), BGC (gastric carcinoma), 95-D (lung carcinoma), CNE (rhinocarcinoma) and two normal cell lines, NIH 3T3 (mouse normal fibroblast), and L-02 (human normal liver cell) were obtained from Shanghai Cell Institute of Chinese Science Academy. These cells were subcultured in media RMPI 1640 (GIBCO BRL product) with 10% fetal bovine serum (Hyclone product), at 37℃ with 5% CO_2. Cells were adjusted to a concentration of 10^5 cells·mL^{-1} and were planted in 96-well tissue culture plate, and were then exposed to the test compounds ranging in concentrations from 2.5 to 100 μg·mL^{-1} for 48 h. The cells were pigmented by MTT [3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide], and the O.D. values were measured by ELX800 (universal microplate reader, BIO-TEK Instruments, Inc) under 490 nm wavelength. The IC50 value (concentration of drug required to inhibit 50% growth) was calculated from linear regression of the percent viable cells versus the log of the drug concentration. The results are shown in Table 3.

Results and discussion

Structural descriptions

[Ag(dmbpy)(NO_3)] (**1**)

The molecular structure of compound **1** is shown in Fig. 1. Compound **1** crystallizes primarily in a mononuclear form, in which the silver atom is coordinated in a Y-shape fashion [N(1)-Ag(1)-N(2) = 72.51(13), N(2)-Ag(1)-O(1) = 136.57(14) and O(1)-Ag(1)-N(1) = 143.36(14)°] with the coordination of two nitrogen atoms from a dmbpy and an oxygen atom from a monodentate nitrate. The coordination geometry of compound **1** is different from a related compound [Ag(dmbp)(NO_3)] (dmbp = 6, 6′-dimethyl-2, 2′-bipyridine), in which the nitrate group acts in a chelate mode. The two Ag—N distances in compound **1** are approximately equivalent [*av*. 227.7(4) pm], and are slightly shorter than those found in [Ag(tmbp)$_2$]BF_4 (232.0 pm)[11] and [Ag(dmbp)(NO_3)] (235 pm).[12] The Ag—O(nitrate) bond length [221.8(4) pm] is much shorter than the Ag—O(nitrate) bond [243.4(3) pm] in [Ag($C_5H_5NCH_2CO_2$)(NO_3)][13] in which the nitrate groups also act in the monodentate mode, indicating a stronger Ag—O interaction in compound **1**. The two aromatic rings in each dmbpy ligand are approximately coplanar with a dihedral angle of 6.2°. It is noteworthy that the molecules of compound **1** are dimerized in the solid, where two centrosymmetrically related molecules

are interconnected by the weak intermolecular Ag···O [Ag(1)···O(2a) = 276.3(5) and Ag(1a)···O(2) = 276.3(5) pm] and Ag···Ag[Ag(1)···Ag(1a) = 324.4 (2) pm] interactions, which are further reinforced by the intermolecular offset π-π stacking interaction between the dmbpy ligands with the shortest atom-to-atom contact between N(1) and N(1a) atoms at 329 pm and the ring-to-ring distance between the pyridyl groups of the neighboring molecules at *ca*. 340 pm. The short stacking distances indicate a strong intermolecular π-π stacking interaction within the dimer.

Table 2 Selected bond lengths (pm) and bond angles (°) for compounds **1** and **2**

1			
Ag(1)—O(1)	221.7(4)	Ag(1)—N(1)	226.8(3)
Ag(1)—N(2)	228.6(4)		
O(1)-Ag(1)-N(1)	143.4(1)	Ag(1)···Ag(1a)	324.4(2)
N(1)-Ag(1)-N(2)	72.5(1)	O(1)-Ag(1)-N(2)	136.6(1)
2			
Ag(1)—N(7)	210.2(8)	Ag(1)—N(2)	222.1(7)
Ag(1)—N(1)	229.2(7)		
N(7)-Ag(1)-N(2)	165.9(3)	N(7)-Ag(1)-N(1)	119.7(3)
N(2)-Ag(1)-N(1)	73.8(3)		

Table 3 Cytotoxities of compounds **1** to **7**

Complex	IC_{50} (μM)						
	Hela	HepG2	BGC	95-D	CNE	L-02	NIH3T3
1	7.6	7.0	10.7	9.6	18.4	12.7	9.7
2	5.4	5.8	6.2	5.8	10.8	11.6	27.7
3	13.7	5.0	13.1	11.3	30.2	13.1	5.0
4	2.8	2.8	4.2	2.8	7.2	2.8	2.8
5	5.1	3.6	25.1	20.1	65.2	34.8	10.0
6	10.8	4.3	6.6	6.4	24.3	10.8	4.3
7	30.9	20.1	38.1	40.2	90.2	38.7	17.5

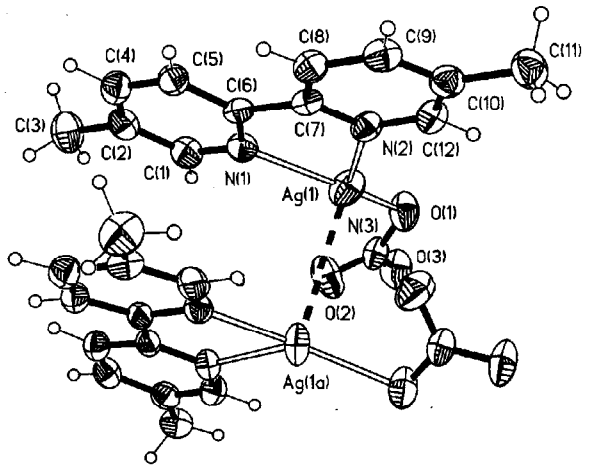

Fig. 1 Structure of a dimer of compound **1**.

[Ag(dmbpy)(MeCN)](ClO$_4$) (**2**)

The crystal structure of compound **2** consists of discrete [Ag(dmbpy)(MeCN)]$^+$ cations and perchlorate anions, which may be attributed to the week coordination ability of perchlorate anions. There are three crystallographically independent, but chemically identical molecules in an asymmetric unit. One of the cation is illustrated in Fig. 2, where the silver atom is ligated in a severely distorted *T*-shape fashion [N(1)-Ag(1)-N(2) = 73.8(3), N(2)-Ag(1)-N(7) = 165.9(3) and N(1)-Ag(1)-N(7) = 119.7(3)°] with the two nitrogen atoms of a chelate dmbpy ligand [Ag(1)—N(1) = 229.2(7) and Ag(1)—N(2) = 222.1(7) pm] and one nitrogen atom from an acetonitrile ligand [Ag—N(7) = 210.2(8) pm]. Although the two Ag—N(pyridyl) distances in the cation are slightly different, they are comparable with those found in **1**. It should be mentioned that, although not shown, the cations of compound **2** also form significant intermolecular π-π stacking interac-

tion in the solid.

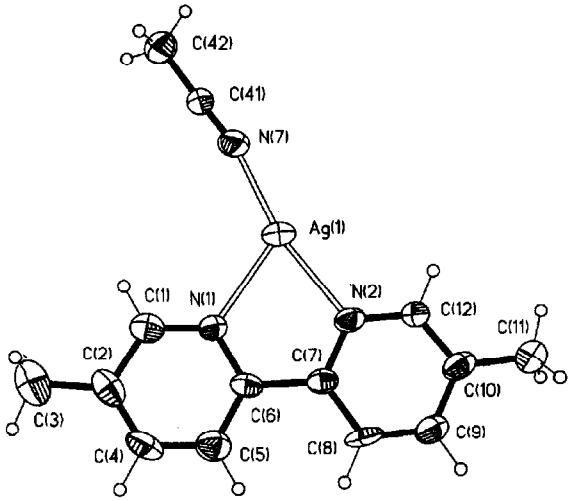

Fig. 2 Molecular structure of the cation in compound **2**.

Cytotoxity

The compound concentrations required to yield 50% inhibition of the viable cells (IC_{50}), determined by the literature method,[14] are listed in Table 3. The low IC_{50} concentrations of these seven complexes show that they are strong cytotoxic *in vitro*[15,16] both to normal cells and carcinoma cells. The high cytotoxities and good solubilities of these compounds in both acetonitrile and aqueous solutions imply that these compounds are potential candidates for antitumor agents. On the other hand, different kinds of the cells have different sensitivities to these compounds, therefore, further exploration in generating analogous silver(I) complexes through appropriate chemical modification is required for higher selectivity as well as for understanding the structure-function relation.

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