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Synthesis, Spectroscopy, and Anticancer Activity of Two New Nanoscale Au(III) N_4 Schiff Base Complexes

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Abstract—Mononuclear Au(III) Schiff base complexes are synthesized by the reaction of 4-aminoantipyrine with hydrazine. The chemical structures of new Schiff bases and their Au(III) complexes are elucidated from their conductance, XRD, and spectroscopic (IR, UV-Vis, ^{1}H, and ^{13}C NMR) data. Au(III) Ion is coordinated with the synthesized Schiff bases via four nitrogen atoms of the antipyrine and azomethine groups. Au(III) Complexes are electrolytes with three uncoordinated Cl^- ions, and have a square planar geometry. Their morphology is characterized by SEM and TEM methods. Cytotoxic effect of the complexes is tested against human breast cancer (MCF-7) and hepatocellular carcinoma (HepG-2) cell lines.

Keywords: Schiff base, aminoantipyrine, gold, complexes, TEM, nanoparticles, spectroscopy

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INTRODUCTION

4-Aminoantipyrine derivatives are used for treatment of oxidative damages as well as prophylactic of cancer [1]. Metal complexes of 4-aminoantipyrine are used in catalysis [2] and demonstrate biological activities as antimicrobial, anti-inflammatory, antiviral, and antitumor agents [3, 4].

Herein synthesis of two new tetradentate Schiff bases and their Au(III) complexes is presented. Their molar conductance, magnetic, SEM, TEM, UV-Vis, FTIR, ^{1}H, and ^{13}C NMR, and XRD characteristics are determined. Anticancer activity of the products is assessed.

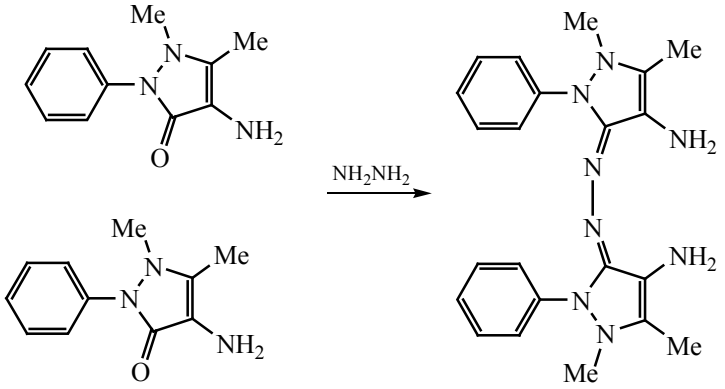
EXPERIMENTAL

Chemicals used were purchased from Sigma-Aldrich, and were of high analytical grade. Elemental analysis was carried out on a Perkin Elmer CHN 2400 analyzer. Electrolytic character was determined on a Jenway 4010 conductivity meter. IR spectra were recorded on a Bruker FTIR Spectrophotometer. UV-Vis spectra were recorded on a UV2 Unicam UV/Vis Spectrophotometer. NMR spectra were measured on a Varian Mercury VX-300 NMR Spectrometer using DMSO-d_6 as a solvent. Magnetic moments were measured on a Magnetic balance, Sherwood Scientific, Cambridge, England, at 25°C. X-ray diffraction was measured on an X'Pert PRO PAN analytical X-ray powder diffractometer, target copper with secondary monochromate. SEM images were produced on a Quanta FEG 250 equipment. TEM images were produced on a JEOL 100s microscope.

Synthesis of 4-aminoantipyrine hydrazine Schiff base (L1). A mixture of 4-aminoantipyrine (2.03 g, 0.02 mol) with hydrazine (0.32 g, 0.01 mol) was refluxed in methanol (20 mL) for 2 h. The precipitate was filtered off, recrystallized from methanol, and dried over anhydrous $CaCl_2$ under vacuum to accumulate the product as a yellow-orange solid, yield 72%, mp 180°C (Scheme 1).

Synthesis of 4-aminoantipyrine–benzaldehyde–hydrazine Schiff base (L2). 4-Aminoantipyrine (2 mmol) dissolved in methanol and benzaldehyde (2 mmol) were

Scheme 1. Synthesis of Schiff base chelate chelate (L1).

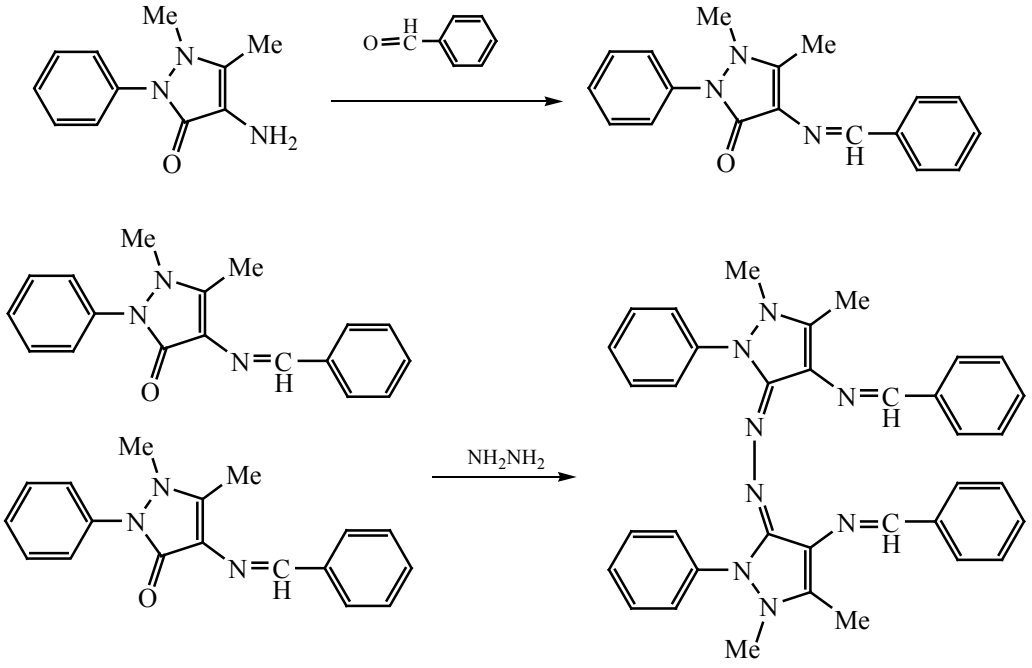


mixed and refluxed gently for 2 h. The precipitate was filtered off and re-crystallized from methanol as a pale yellow powder, which was washed with a mixture alcohol–ether and dried over $CaCl_2$ under vacuum. Thus formed intermediate (2 mmol) and hydrazine (1 mmol) were refluxed in methanol for 2 h upon constant stirring. Upon completion of the process, the reaction mixture was treated with crushed ice. A brownish yellow precipitate was filtered off and re-crystallized from methanol to give the product (L2). Yield 66%, mp 195°C. IR spectrum, ν, cm^{-1}: 3430 and 3330 (NH_2), 1645 and 1560 (C=N), 1275 (C–N) (Scheme 2).

Synthesis of Au(III) Schiff bases (L1, L2) complexes 1, 2. The mixture of an appropriate ligand (0.02 mol) with $AuCl_3$ (0.02 mol) in 50 mL of CH_3OH was refluxed for 2 h. The orange (L1) or brown (L2) solution formed was evaporated to half of its original volume. A precipitate was filtered off, washed with methanol and dried in a vacuum desiccator over anhydrous $CaCl_2$ to give the corresponding product.

$[Au(L1)]Cl_3$ (1). Yield 58%, T_{decomp} > 250°C. IR spectrum, ν, cm^{-1}: 1635 br (C=N), 3420 and 3130 (NH_2), ca 500 (Au-N). ^1H NMR spectrum, δ, ppm: 2.13 s (6H, $2CH_3$), 2.77 s (6H, $2NCH_3$), 3.42 s (4H, $2NH_2$), 7.28 m (4H, phenyl), 7.51 m (6H, phenyl). ^{13}C NMR spectrum, δ, ppm: 9.8, 40.1, 120.0, 121.8, 125.1, 128.8, 135.5, 161.4. Found, %: C 37.21; H 3.60; N 15.53; Au 27.49. Calculated, %: C 37.44; H 3.71; N 15.88; Au 27.91.

Scheme 2. . Synthesis of Schiff base chelate (L2).



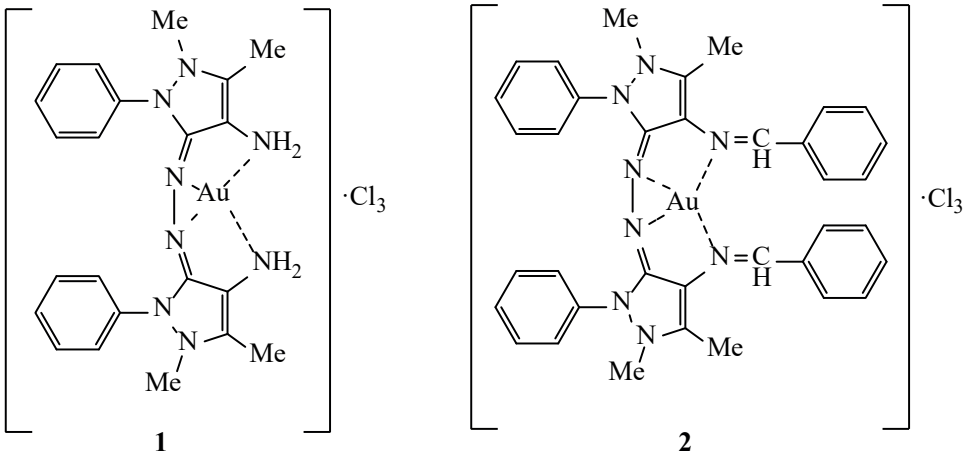


Fig. 1. Speculated structures of complexes **1** and **2**.

[Au(L2)]Cl_3 (2). Yield 61%, T_{decomp} > 250°C. IR spectrum, ν, cm^{-1}: 1623 and 1511 (C=N), ca 495 (Au-N). ^1H NMR spectrum, δ, ppm: 2.11 s [6H, $2CH_{3(C3)}$], 3.18–3.42 s (6H, $2NCH_3$), 7.39–8.73 m (20H, phenyl), 9.62 s (2H, N=CH). ^{13}C NMR spectrum, δ, ppm: 9.7, 38.5, 116.3, 124.6, 128.6, 130.1, 134.5, 137.5, 152.1, 154.4, 159.6, 161.4. Found, %: C 48.94; H 3.81; N 12.64; Au 22.12. Calculated, %: C 49.02; H 3.89; N 12.70; Au 22.33.

Anti-cancer activity. Human breast cancer (MCF-7) and hepatocellular cancer (HepG-2) cells were gained from the American culture collection. The cells were grown in RPMI-1640 medium and supplemented with 10% and 50 μg/mL fetal calf serum and gentamycin. The 50% inhibitory concentration (IC_{50}) was estimated from graphic plots [5,6]. The standard drugs cisplatin and doxorubicin were used in the tests.

RESULTS AND DISCUSSION

The synthesized compounds had low solubility in cationic and anionic solvents, and high solubility in DMF and DMSO. Molar conductance of the complexes **1** and **2** was measured to be 67 and 70 μs/cm, respectively. Electrolytic measurements of the complexes indicated that Cl^- anions were uncoordinated and existed outside the coordination sphere [7]. The test of the complexes on Cl^- carried out with $AgNO_3$ was positive, which also confirmed the anions existence in the outer coordination sphere. According to the elemental analysis, the molar ratio Au(III) : ligand was 1 : 1. The coordination mode is presented in Fig. 1.

Electronic and magnetic measurements. Au(III) Schiff bases complexes (**1** and **2**) had diamagnetic nature, and low spin d^8, characteristic for square planar

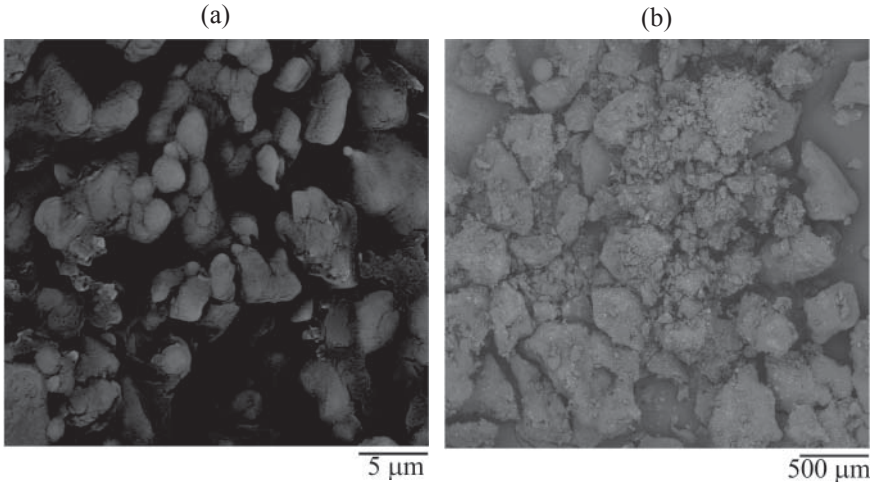


Fig. 2. SEM images of (a) [Au(L1)]·Cl_3 and (b) [Au(L2)]·Cl_3 complexes.

The concentration dependent inhibitory activity of the synthesized complexes against MCF-7 and HepG-2 cell lines

Sample concentration, μg/mL	Inhibitory, %							
	HepG-2 cell				MCF-7 cell			
	Cisplatin	Doxorubicin	Au-L1	Au-L2	Cisplatin	Doxorubicin	Au-L1	Au-L2
500	96.92	98.28	68.22	74.11	96.28	98.49	88.11	65.48
250	95.69	97.30	50.75	57.22	95.02	97.64	75.35	42.16
125	93.25	95.78	27.69	39.06	92.17	96.79	61.59	20.59
62.5	87.61	93.87	13.08	24.87	85.32	94.93	30.48	6.14
31.25	77.02	86.95	5.72	13.16	76.21	93.07	11.83	0.52
15.60	68.13	81.87	0.53	5.94	65.38	84.54	2.77	0
7.80	59.38	79.19	0	1.29	53.29	80.11	0	0
3.90	52.11	74.41	0	0	47.15	75.02	0	0
2.0	39.25	70.50	0	0	38.26	68.31	0	0
1.0	31.83	61.61	0	0	29.12	59.83	0	0
IC_{50}	3.67	0.36	23.5	24.7	5.71	0.35	6.0	18.4

geometry [8]. The electronic spectra of free Schiff base ligands exhibited bands at 290 and 350 nm attributed to π–π* and *n*–π* transitions in benzene rings, NH_2 and the azomethine groups. Electronic spectra of the complexes demonstrated three absorption bands at 380, 350 and 285 nm due to $^1A_{1g}\rightarrow{}^1A_{2g}$, $^1A_{1g}\rightarrow{}^1B_{1g}$, $^1A_{1g}\rightarrow{}^1E_g$ and charge transfer transitions, respectively. The bands were in agreement with low-spin square planar configuration [9].

Crystalline structure and morphological studies. Crystallinity of the synthesized complexes was calculated from the major diffraction patterns using the Deby-Scherrer equation [10]. The calculated grain sizes were determined to be 10 nm for $[Au(L1)]\cdot Cl_3$ complex (**1**). The X-ray diffraction of $[Au(L2)]\cdot Cl_3$ complex referred to its amorphous feature. The crystallite sizes (*D*) were calculated using the Scherrer formula [11] from the full-width half-maximum (FWHM) (β). The strain ($\varepsilon = 1.60\times10^{-4}$) was calculated using the equation

$$\beta = \lambda/D\cos\theta - \varepsilon\tan\theta.$$

Since the dislocation density and strain are the manifestation of dislocation network in the complexes, the decrease in the strain and dislocation density indicate the formation of high quality complexes. The dislocation density ($\delta = 0.007\times10^{12}$ lin/m^2) was calculated by equation $\delta = 1/D^2$ [12]. The diffraction patterns present at $2\theta = 38$, 44, 65, and 78 were assigned to the planes (111), (200), (220), and (311) of face centered cubic crystal lattice structure of AuNPs [13].

SEM images (Fig. 2) of the complexes $[Au(L1)]\cdot Cl_3$ (**1**) and $[Au(L2)]\cdot Cl_3$ (**2**) demonstrated that complex (**1**) had a semispherical with aggregation character, and complex (**2**) exhibited irregularly shaped particles.

TEM photograph of $[Au(L1)]\cdot Cl_3$ (**1**) indicated spherical NPs of Au(III) and the diameter was in the range of 10 nm, which was identical with the XRD values.

Anticancer assessments. The cytotoxic assessment of Au(III) complexes was carried out on human breast (MCF-7) and hepatocellular cancer (HepG-2) cell lines in presence of the standard drugs cisplatin and doxorubicin (see the table). According to the accumulated data Au(III)-L1 complex (**1**) was more efficient against HepG-2 and MCF-7 cell lines than Au(III)-L2 complex (**2**).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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