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# Synthesis, Spectral Properties and Antitumor Activity of Some Transition Metal Complexes with a Schiff Base Ligand

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Four complexes of transition metals, namely: $[Mn(L)_2]$ (complex 1), $[Ni(L)_2\cdot 0.5H_2O]$ (complex 2), $[Cu(L)_2\cdot 4H_2O]$ (complex 3) and $[Zn(L)_2\cdot 0.5H_2O]$ (complex 4), (L = Schiff base derived from trimethylol amino methane and salicylic aldehyde), have been synthesized. The complexes were characterized by elemental analysis, IR, $^1$H NMR, UV and TG-DTA spectra. Tentative structures for the complexes have been proposed. The antitumor activity against HL-60 human leukemia cells of free ligand and its Mn, Ni, Cu complexes were studied by MTT method.

**Key words:** synthesis, transition metals, complexes, antitumor activity

Metal complexes of Schiff base derived from salicylic aldehyde have received considerable attention over the past two decades [1–4]. This may be attributed to unusual structural features in the resultant metal complexes and their biological activities. Some of the metal complexes have antitumor properties [2–5], antioxidative activities [6], electronic and photophysical properties [7]. As a part of our studies on synthesis and biological activities of Schiff base ligands and their metal complexes, we report the synthesis, spectroscopic studies and antitumor activity of some transition metal complexes with a new Schiff base ligand (HL) derived from salicylic aldehyde and trimethylol amino methane.

## EXPERIMENTAL

***Materials:*** All the starting materials used in the syntheses were analytical grade.
***Physical measurements:*** Carbon, hydrogen and nitrogen were analyzed on a Elementar Vario elemental analyzer. Infrared spectra (4000–400 cm$^{-1}$) were determined with KBr optics on a Nicolet NEXUS 670 FTIR spectrophotometer. Ultraviolet spectra in the 190–700 nm region in DMF were recorded on a thermo UV-340 spectrophotometer. The thermal behavior was monitored on a WCT-2A thermal analyzer. The molar conductance values were determined on a DDS-11A conductivity meter with DMF as solvent ($10^{-3}$ mol L$^{-1}$ solution) at 25°C $^1$H NMR was measured with an FT-80A nuclear magnetic resonance instrument using acetone-$d_6$ as solvent and TMS as internal reference.

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***MTT assay:*** HL-60 human leukemia cells were propagated continuously in culture and grown in RPMI 1640 medium with 10% inactivated fetal calf serum (FCS) and antibiotics. Cell harvested from exponential phase were seeded equivalently into 96 well plates and incubated for 24 h, then compounds studied were added in a concentration gradient. The final concentrations were maintained at $c/(\mu\text{g mL}^{-1})$ 10, 5, 0.5, 0.05, respectively. The plates were maintained at 37°C in a humidified 5% $CO_2$-90% $N_2$-5% $O_2$ atmosphere and incubated for 48 h, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution was added, the following procedure referred to [8]. The measurements of absorption of the solution concerned with the number of live cells were performed on ELISA spectrophotometer at 570 nm.

***Preparation of the HL ligand:*** Trimethylol amino methane (10 mmol) was added to a solution of salicylic aldehyde (10 mmol) in 20 mL ethanol and the contents were stirred continuously for 6 h at room temperature. The yellow precipitate was obtained by filtration and purified by crystallization with anhydrous ethanol. Yield 86%, m.p. 144~145°C. The composition of the ligand has been confirmed by elemental analysis, $^1$H NMR and IR spectra.

***Preparation of metal complexes:*** A solution of $Cu(OAc)_2 \cdot 4H_2O$ (2.5 mmol) in 10 mL ethanol was added dropwise to a solution of HL (5 mmol) in 10 mL ethanol. After stirring for 3 h at room temperature, the precipitate was separated by filtration, washed several times with ethanol and dried in a vacuum. Yield 78%. The other complexes were also synthesized by this method.

The analysis confirmed the compositions of the complexes prepared.

## RESULTS AND DISCUSSION

All complexes are soluble in DMSO, DMF and methanol, a little soluble in ethanol and acetone, insoluble in benzene, diethyl ether and tetrahydrofuran. The molar conductivity values of the Mn, Ni, Cu and Zn complexes in DMF at 25°C are 9.2, 7.3, 5.5 and 4.4 $S \cdot cm^2 \cdot mol^{-1}$, respectively. This shows that all the complexes are non-electrolytes in DMF [9]. The elemental analyses show that the formula of the complexes is $M(L)_2 \cdot nH_2O$ (M = Cu, n = 4, Mn, n = 0, Ni, Zn, n = 0.5), indicating that all these complexes conform to 1:2 metal-to-ligand stoichiometry.

***Infrared spectra:*** The IR spectra of the four complexes are strikingly similar in relative positions and intensities of the peaks, which suggest a close structural relationship among the compounds. The main stretching frequencies of the IR spectra of the ligand (HL) and its complexes are tabulated in Table 1. $\nu$(C=N) vibration of the free ligand is at 1638 $cm^{-1}$ and for the complexes shifts to 1605~1630 $cm^{-1}$, which strongly suggests the nitrigon atom of C=N coordinates to metal ions [10]. The strong band at 1223 $cm^{-1}$ in the free ligand assigned to $\nu$(C–O) vibration of phenolic group, however, it shifts to 1194~1205 $cm^{-1}$ in the complexes. This shows that the oxygen atom of phenolic hydroxyl coordinates to the metal ions. The weak bands at 449~459 $cm^{-1}$ may be assigned to M–O (phenolic oxygen) vibrations [11]. In addition, there do not appear new bands at 1610~1550 $cm^{-1}$ and 1420~1300 $cm^{-1}$, indicating that the complexes do not contain $CH_3COO^-$ anions, which is in accordance with the results of molar conductances and elemental analyses of the complexes. No bands were observed at *ca.* 950 $cm^{-1}$ in the IR spectra of the complexes, proving the water molecules in the complexes (Ni(II), Cu(II), Zn(II)) are lattice water molecules, which is consistent with the thermal analysis.

**Table 1.** Most important IR bands ($cm^{-1}$).

| Compounds | $\nu$(C=N) | $\nu$(C–O) | $\nu$(M–O) | $\nu$(OH) |
|---|---|---|---|---|
| HL | 1638 | 1223 | | 3319 |
| $Mn(L)_2$ | 1605 | 1205 | 449 | 3277 |
| $Ni(L)_2 \cdot 0.5H_2O$ | 1630 | 1194 | 459 | 3225 |
| $Cu(L)_2 \cdot 4H_2O$ | 1624 | 1200 | 458 | 3318 |
| $Zn(L)_2 \cdot 0.5H_2O$ | 1629 | 1193 | 456 | 3276 |

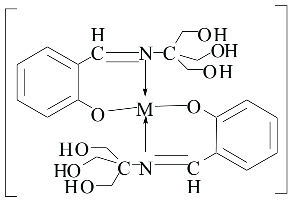
***Ultraviolet spectra:*** UV spectral data of ligand and complexes are listed in Table 2. The free ligand exhibits three strong absorption bands at 285 nm, 304 nm and 317 nm. The complexes yield new peaks at approximately 333 nm, 365 nm, 383 nm and 454 nm, which may be attributed to the $\pi \rightarrow \pi^*$ transitions of the ligand according to their positions and molar absorption coefficient. The absorption bands at 454 nm and 463 nm are in the region observed. This shows that there is a conjugate system formed in the complexes. The very weak absorption of Mn(II), Ni(II) and Cu(II) complexes at 620 nm, 653 nm and 639 nm, respectively, were assigned to *d*-*d* transition.

**Table 2.** Ultraviolet spectral data.

| Compounds | $\lambda_{max}$ (nm), $\varepsilon \times 10^{-3}$ (L $mol^{-1}$ $cm^{-1}$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $\lambda_1$ | $\varepsilon_1$ | $\lambda_2$ | $\varepsilon_2$ | $\lambda_3$ | $\varepsilon_3$ | $\lambda_4$ | $\varepsilon_4$ | $\lambda_5$ | $\varepsilon_5$ |
| HL | 285 | 1.25 | 304 | 3.53 | 317 | 3.75 | | | | |
| $Mn(L)_2$ | 288 | 1.98 | 297 | 3.03 | 379 | 3.45 | | | | |
| $Ni(L)_2 \cdot 0.5H_2O$ | 286 | 1.28 | 322 | 3.90 | 332 | 5.16 | 352 | 5.22 | 384 | 3.23 |
| $Cu(L)_2 \cdot 4H_2O$ | 285 | 1.29 | 292 | 3.18 | 337 | 4.23 | 375 | 3.39 | 383 | 3.47 |
| $Zn(L)_2 \cdot 0.5H_2O$ | 286 | 1.50 | 300 | 4.33 | 333 | 5.16 | 454 | 5.10 | 463 | 4.50 |

***Thermal analysis:*** All the complexes are stable in air. DTA and TG curves show that the Ni complex exhibits an endothermic peak at about 72°C and loses about 1.1% of its weight at 50~120°C, which corresponds to the loss of half water molecule (calcd. for 0.5 $H_2O$, 1.7%). This indicates that only lattice water molecules are in the complexes.

According to the aforementioned data, for the complexes prepared, we propose the structure shown in Fig. 1.



$\cdot\ nH_2O$ (n=0, 0.5 or 4)

M = Mn, Ni, Cu, Zn

**Figure 1.** Suggested structure of the complexes.

***Antitumor activity:*** The data of the antitumor activity of HL and some complexes are given in Table 3. The concentration of DMSO was controlled under 1% to assure not to affect the results [12]. As can be seen, the inhibitory rates of HL and some complexes against HL-60 human leukemia cells increased with the increasing of dose. The inhibitory effects are, in the case of Ni complex, significantly higher than HL and other complexes. The largest inhibitory rate of Ni complex is 58.7% and studies are continuing to explore its possible clinical use.

**Table 3.** Antitumor activity of against HL-60 cells.

| Compounds | Dose ($\mu$g mL$^{-1}$) | Inhibitory rate [a] (%) |
|---|---|---|
| HL | 0.05 | 3.5 |
| | 0.5 | 12.4 |
| | 5.0 | 16.7 |
| | 10 | 26.9 |
| $Mn(L)_2$ | 0.05 | 0.5 |
| | 0.5 | 3.7 |
| | 5.0 | 9.9 |
| | 10 | 13.8 |
| $Ni(L)_2{\cdot}0.5H_2O$ | 0.05 | 11.7 |
| | 0.5 | 23.9 |
| | 5.0 | 47.2 |
| | 10 | 58.7 |
| $Cu(L)_2{\cdot}4H_2O$ | 0.05 | –7.3 |
| | 0.5 | –1.2 |
| | 5.0 | 1.3 |
| | 10 | 3.7 |

[a] ‘Inhibitory rate’ is 100% (control group – test group)/control group.

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