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Antibacterial Activity and Molecular Modeling of Ni(II)-, Cu(II)- and Mn(II)-Salophen Complexes

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ABSTRACT

Nickel, copper and manganese complexes **1**-**3** were synthesized from the reaction of the salophen ligand, **Slp** with their respective acetate salts. All compounds were characterized with ^{1}H and ^{13}C NMR, FT-IR and ESI-MS spectroscopy. In addition, antibacterial activities of the ligand and its complexes were studied. The investigation of antibacterial activity against Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus and carbapenem &colistin resistant Klebsiella pneumoniae showed all the complexes have remarkable antibacterial activity. The antibacterial effect of all the complexes against K. pneumoniae is of great interest as the bacterium, is resistant to two most important therapeutic options for treatment of multi-drug resistant Gram-negative bacteria, including polymyxins and carbapenems. The 3D molecular modeling of a representative complex was carried out on ChemDraw Ultra 12.0 software.

Keywords: Antibacterial Activity; Molecular Modeling; Ligand; Metal Complex.

INTRODUCTION

Salophens are very common type of tetradendate ligands in coordination chemistry[1, 2]. These ligands are synthesized simply from condensation reaction of *o*-phenylenediamine or their derivatives with salicylaldehyde. Metal complexes of salophen ligand are produced by the reaction of both transition and main metal ions. The synthesis method of theses ligands and complexes is very easy and simple. Usually, the N_2O_2 donor ligand coordinates to a metal ion in a deprotonated form. Consequently, these class of ligands form neutral metal complexes when coordinate with divalent metal ions[3]. Metal salophen complexes show widespread

applications in many fields. Some of these complexes display considerable catalytic activity in a diversity of reactions such as hydrogenation, hydroxylation, oxidation, epoxidation, and cycloaddition reaction of CO_2 to propylene oxide[4-11]. Some of them exhibit superior optical properties[12]. Moreover, they found applications as electroluminescent materials[13, 14] and biological activities such as antimicrobial, antifungal, antibacterial and interaction with DNA and RNA[15, 16]. Recently, we have reported that metal salophen complexes can act as catalyst for water oxidation reaction[17].

In view of the above stated features of metal salophen complexes, the purpose of the present work is to synthesis and examine some important structural properties of salophen complexes for their capability to be used in several fields such as precursors for preparation of metal oxide nanostructures, electrocatalytic (water oxidation), photovoltaic and catalytic applications for future works.

Here, we report on synthesis and spectral characterization of salophen ligand resulting from condensation reaction of salicylaldehyde and *o*-phenylenediamine and on Ni(II) complex **1**, Cu(II) complex **2** and Mn(II) complex **3** by treatment ligand with nickel, copper or manganese acetate salts, respectively. The antibacterial activity of the ligand and complexes have been investigated. Molecular modeling of a representative complex is also carried out.

MATERIALS AND METHODS

Materials

All chemical reagents, including *o*-phenylenediamine (99.0%), salicylaldehyde (98.0%), copper acetate monohydrate ($Cu(OAc)_2.H_2O$; 99.5%), nickel acetate tetrahydrate ($Ni(OAc)_2.4H_2O$; 98.0%), manganese acetate tetrahydrate ($Mn(OAc)_2.4H_2O$; 98.0%) and ethanol (EtOH; 99.7%), were purchased from Aldrich or Acros. All chemicals and solvents were used as received.

Spectroscopic measurements

^1H and ^{13}C-NMR spectra were recorded on a Bruker 500 MHz NMR spectrometer using TMS as internal standard and [d_6]DMSO as solvent. ESI-MS spectra were performed with an Agilent Technologies MSD SL Trap mass spectrometer with ESI source coupled with an 1100 Series HPLC system. FT-IR spectra were recorded on a Nicolet 5700 FT-IR instrument.

Elemental Analysis

Elemental analyses for CHNO were performed using a Vario EL cube [Germany elements (Elemental) analysis system].

Molar Conductivity

Molar conductivities of freshly prepared 1.0×10^{-3} mol/dm^{-3} DMSO solutions of the synthesized compounds were measured using Jenway 4010 conductivity meter.

Antibacterial Activity

The ligand and metal complexes were screened for their antibacterial activity against *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *carbapenem* & colistin resistant *Klebsiella pneumonia* by the agar diffusion method[18]. The concentration of the synthesized compound solution in DMSO was 300 µg/mL. A hot nutrient agar solution (20 mL) was poured into sterilized petri dishes and allowed to attain room temperature. The seed layer medium consisted of peptone (1.0 g), yeast extract (0.8 g), glucose (0.2 g), sodium chloride (0.6 g) and agar (0.2 g). It was melted and cooled to about 45 °C with gentle shaking. The previously grown subculture was added to the seed layer medium and mixed well. It was immediately raked into the petri dishes and allowed to attain room temperature. Then wells were made with a sterile cork borer and to these wells, the compound solution (0.01mL) was added and the plates were allowed to cool for an hour to facilitate diffusion. The plates were then incubated at 37 °C for 48 h. At the end of the incubation period the zones of inhibition around the wells were measured.

Preparation of salophen ligand (Slp)

The ligand, salophen was prepared according to the reported procedure [19]. 1 mM *o*-phenylenediamine solution in ethanol was added drop-wise to the 2 mM solution of salicylaldehyde in ethanol and then the mixture of the solutions was refluxed for 3 h at 85 °C. The precipitated Schiff-base ligand was filtered, washed with cold ethanol and finally recrystallized from hot ethanol giving the desired product, **Slp**.

Salophen ligand (Slp)

Orange Crystals; Yield 90%; **^{1}H-NMR ([d$_6$]DMSO):** 12.94 (s, 2H), 8.93 (s, 2H), 7.66 (dd, 2H), 6.93-7.50 (m, 10H). **^{13}C-NMR ([d$_6$]DMSO):** 164.53(C-OH), 160.96(C=N), 142.85, 133.92, 132.90, 128.31, 120.23, 119.97, 119.56, 117.09 (All are Ar.C). **FT-IR (KBr, cm^{-1}):** 3203-2400 (m, OH), 3051 (w, aromatic C-H), 1610 (s, C=N), 1190 (phenolic C-O). **Elemental Analysis:** Calculated- C, 75.93; H, 5.10; N, 8.86; O, 10.11%. Found- C, 76.04; H, 5.24; N, 8.90; O, 9.82%.

Synthesis of salophen Ni(II) complex, 1

The salophen Ni(II) complex was prepared as follows: 2 mM solution of $Ni(OAc)_2.4H_2O$ and 2 mM solution of salophen ligand in 50 mL ethanol were refluxed with vigorous stirring for 2 h. The reaction progress was monitored by TLC. The reaction mixture was then cooled to room

temperature and the obtained solid product was filtered, and washed with cold EtOH, Et_2O and dried [20, 21].

Salophen Ni(II) complex, 1

Yield 83%; **^{1}H-NMR ([d_6]DMSO):** 8.91(s, 2H), 8.16(q, 2H), 7.62(dd, 2H), 7.37(m, 2H), 7.32(m, 2H), 6.90(d, 2H), 6.68(t, 2H). **^{13}C-NMR ([d_6]DMSO):** 165.70(C=N), 157.08(C-O), 142.97, 135.66, 134.87, 128.08, 120.77, 116.59, 115.80, 100.17(All are Ar.C). **FT-IR (KBr, cm^{-1}):** 3063 (w, aromatic C-H), 1601 (s, C=N), 1194 (phenolic C-O). **ESI-MS (H_2O, *m/z*):** 372.1656 [{Ni($C_{20}H_{14}N_2O_2$)}H]$^+$. **Elemental Analysis:** Calculated- C, 64.40; H, 3.78; N, 7.51; O, 8.58%. Found- C, 64.62; H, 3.82; N, 7.53; O, 8.64%.

Synthesis of salophen Cu(II) complex, 2

0.5 mM solution of salophen ligand in ethanol (10 mL) and 0.5 mM solution of $Cu(OAc)_2.H_2O$ in water (1 mL) were mixed and refluxed with vigorous stirring for 3 h. The solution mixture was then cooled to room temperature and filtered. After filtration, the obtained solid product was washed thoroughly with water, ethanol and diethyl ether, then dried in vacuo to afford the desired product [22].
Yield 74%; **FT-IR (KBr, cm^{-1}):** 3065 (w, aromatic C-H), 1600 (s, C=N), 1195 (phenolic C-O). **ESI-MS (H_2O, *m/z*):** 377.0716 [{Cu($C_{20}H_{14}N_2O_2$)}H]$^+$.
Elemental Analysis: Calculated- C, 63.57; H, 3.73; N, 7.41; O, 8.47%. Found- C, 63.65; H, 3.78; N, 7.44; O, 8.52%.

Synthesis of salophen Mn(II) complex, 3

Owing to their air-sensitivity, the salophen Mn(II) complex was synthesized under argon with strict exclusion of air. To a 4 mM solution of salophen ligand in 40 mL of deaerated absolute EtOH was added a 8 mM solution of KOH dissolved in 10 mL of deaerated absolute EtOH through a cannula needle. To this resulting solution was added dropwise a 4 mM solution of $Mn(OAc)_2.4H_2O$ in 10 mL of deaerated absolute EtOH using a Teflon cannula. The solution mixture was stirred vigorously for 1.5 h at room temperature and refluxed for 5 h at 90℃. The solution mixture was then cooled to room temperature and the obtained yellow product was filtered, washed with deaerated EtOH and dried in *vacuo* [23].
Yield 68%; **FT-IR (KBr, cm^{-1}):** 3057 (w, aromatic C-H), 1606 (s, C=N), 1197 (phenolic C-O). **ESI-MS (H_2O, *m/z*):** 369.0103 [{Mn($C_{20}H_{14}N_2O_2$)}H]$^+$.
Elemental Analysis: Calculated- C, 65.05; H, 3.82; N, 7.59; O, 8.67%. Found- C, 65.11; H, 3.88; N, 7.62; O, 8.73%.

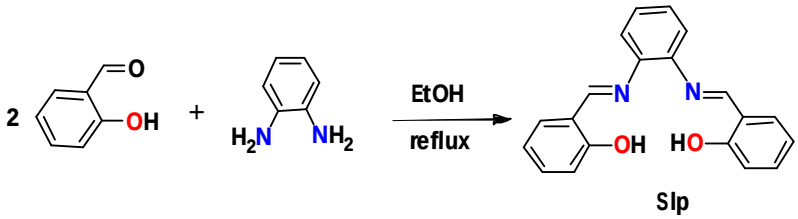
Molecular Modeling Studies

3D molecular modeling of a representative complex **2** was carried out using ChemDraw Ultra 12.0 software [24]. For suitability of observing over the different bond lengths and bond angles, the atoms in the complex in question are shown in numerical numbers.

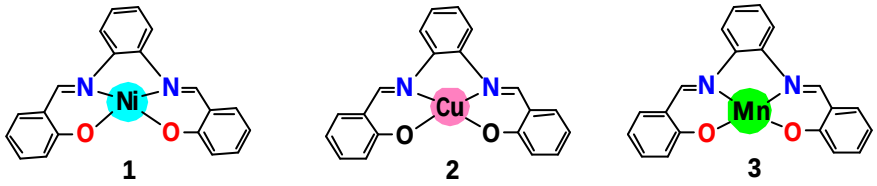
RESULTS AND DISCUSSIONS

Structural characterizations of the ligand and complexes

The ligand, **Slp** (Scheme 1) and the complexes **1-3** (Scheme 2) were prepared and characterized by elemental analysis, ^{1}H and ^{13}C-NMR spectroscopy, FT-IR spectroscopy, and ESI-MS spectroscopy.



Scheme 1: Preparation of Schiff base ligand, Salophen (Slp).



Scheme 2: Structure of the complexes studied in this work.

^{1}H and ^{13}C-NMR spectra of the prepared ligand confirm the formation of the ligand. ^{1}H-NMR spectrum of the ligand, **Slp** shows the OH proton and imine proton features at 12.94 and 8.93 ppm, respectively. ^{13}C-NMR spectra also support the proposed structure of the ligand showing the signals at 164.53 ppm (C-OH) and at 160.96 ppm (C=N). The OH proton peak in the ^{1}H-NMR spectra of the free ligand disappears in case of the complex **1** confirming that the OH group of the ligand has been deprotonated and coordinated to the metal, nickel.The imine proton signal (8.93 ppm) in the ^{1}H-NMR spectra of the free ligand has been shifted to higher field (8.88 ppm). Moreover, ^{13}C-NMR spectra of complex **1** also support the proposed structure. The FT-IR spectra of the ligand and complexes confirm the formation of ligand and complexes with the proposed structures (Scheme 2). By complexation, the broad O-H absorption bands of the salophen ligand in the region from 3203-2240 cm^{-1} are absent in the FT-IR spectra of the complexes **1-3**, confirming that the salophen ligand is deprotonated in the complexation and the oxygens are coordinated to the metal atom. In addition, the IR spectra of **1-3**, compared with the ligand, indicate that the ν(C=N) stretching band at 1610 cm^{-1} is shifted to lower energy by 4-10 cm^{-1} for salophen complexes, confirming that the ligand **Slp** is coordinated to the metal ions through nitrogen atoms of the azomethine groups. The electrospray mass spectrum of the salophen complexes (Figure 1) also supports the proposed structure of the complexes showing ions at mass-to-charge ratio (*m/z*) of 372.1656, 377.0716,

and 369.0103 matching the calculated values for the ions $[\{Ni(C_{20}H_{14}N_2O_2)\}H]^+$, $[\{Cu(C_{20}H_{14}N_2O_2)\}H]^+$ and $[\{Mn(C_{20}H_{14}N_2O_2)\}H]^+$ respectively.

Molar Conductivity

The molar conductivity values of all the synthesized compounds are tabulated in Table 1. The results confirm that all complexes are nonelectrolyte. Consequently, the ligand, **Slp** act as tetradentate and dianionic ligand with one N_2O_2 core when coordinated to the metal ion center (Scheme 1).

Table 1: Molar conductivity values for the ligand, Slp and complexes (10^{-3} M in DMSO).

Compound	Molar conductivity ($Cm^2\ \Omega\ mol^{-1}$)
DMSO	1.572
1	1.862
2	1.734
3	1.768

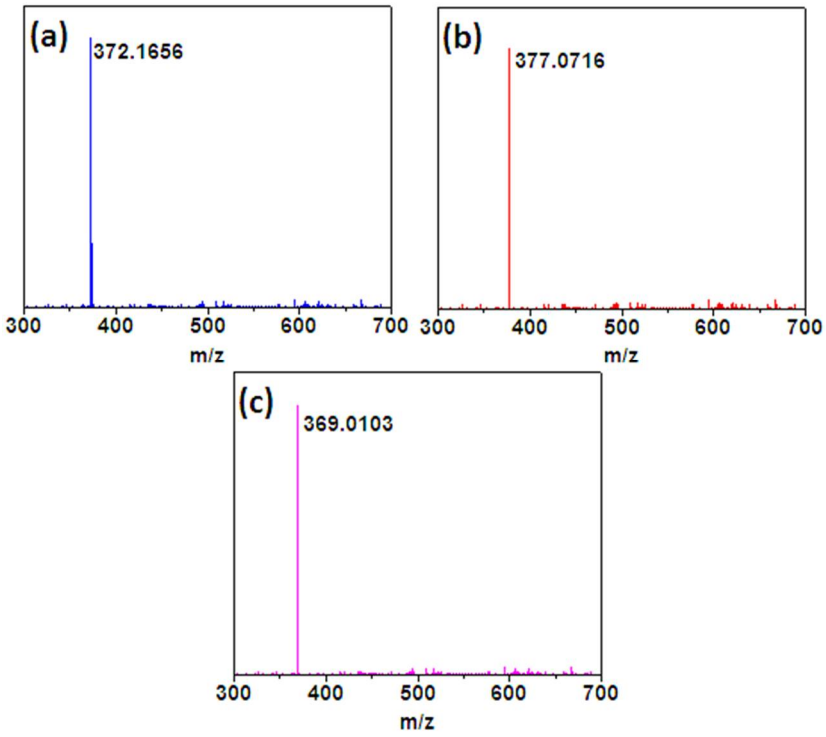


Figure 1: ESI-MS spectra of a 10^{-5} M solution of (a) 1, (b) 2, and (c) 3 in H_2O

Antibacterial Activity

The in *vitro* antibacterial activity is checked by agar well diffusion method using *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and carbapenem & colistin resistant *Klebsiella pneumoniae*. The activity results are presented as diameter of inhibition zone in Table 2. All the synthesized complexes have noteworthy antibacterial activity against S. aureus as a medically important Gram positive bacterium. Also, these complexes show the extreme antibacterial activity against carbapenem & colistin resistant *Klebsiella pneumoniae*. This biological effect is of high interest as the bacterium, is resistant to two most important therapeutic options for treatment of multi-drug resistant Gram negative bacteria, including polymyxins and carbapenems. Furthermore, the ligand is less active than its complexes.

Table 2: The antibacterial activity of the compounds, presented as diameter of inhibition zone (mm)

Compound	*P. aeruginosa*	*E. coli*	*S. aureus*	carbapenem & colistin resistant *K. pneumoniae*
Slp	10	9	11	9
1	20	18	22	19
2	23	21	27	25
3	19	17	20	18

3D Molecular Modeling and Analysis

Molecular modeling studies of a representative complex **2** were carried out because of the lack of single crystals to get structural information. All calculations were done using ChemDraw Ultra 12.0 software [24].

Table 3: Selected bond lengths in Å of the salophen Cu(II) complex, 2

Atoms	Actual bond lengths	Optimal bond lengths	Atoms	Actual bond lengths	Optimal bond lengths
N(2)-Cu(25)	1.3249	1.3030	N(2)-Cu(25)	1.3249	1.3030
C(22)-N(1)	1.2679	1.4560	C(22)-N(1)	1.2679	1.4560
N(1)-Cu(25)	1.3190	1.3030	N(1)-Cu(25)	1.3190	1.3030
C(18)-N(2)	1.2767	1.2600	C(18)-N(2)	1.2767	1.2600
C(23)-N(2)	1.2816	1.4560	C(23)-N(2)	1.2816	1.4560
C(10)-O(3)	1.3735	1.3550	C(10)-O(3)	1.3735	1.3550
O(3)-Cu(25)	1.8107	-	O(3)-Cu(25)	1.8107	-
C(13)-O(4)	1.3708	1.3550	C(13)-O(4)	1.3708	1.3550
O(4)-Cu(25)	1.8096	-	O(4)-Cu(25)	1.8096	-
C(17)-N(1)	1.2727	1.2600	C(17)-N(1)	1.2727	1.2600

Table 4: Selected bond angles in dgree of the salophen Cu(II) complex, 2

Atoms	Actual bond angle	Optimal bond angle	Atoms	Actual bond angle	Optimal bond angle
C(24)-C(23)-N(2)	131.4473	120.0000	O(4)-Cu(25)-N(1)	114.6847	-
C(22)-C(23)-N(2)	108.9108	120.0000	O(3)-Cu(25)-N(2)	114.2372	-
H(35)-C(18)-N(2)	114.2689	116.5000	O(3)-Cu(25)-N(1)	104.2009	-
C(12)-C(18)-N(2)	128.1751	123.5000	N(2)-Cu(25)-N(1)	105.4723	-
C(14)-C(13)-O(4)	119.6435	124.3000	C(9)-C(10)-O(3)	119.6593	124.3000
C(12)-C(13)-O(4)	122.5546	124.3000	C(5)-C(10)-O(3)	122.6269	124.3000
Cu(25)-O(4)-C(13)	110.4436	-	C(23)-C(22)-N(1)	105.5732	120.0000
Cu(25)-O(3)-C(10)	109.5753	-	C(21)-C(22)-N(1)	132.8638	120.0000
Cu(25)-N(2)-C(23)	100.0440	-	H(34)-C(17)-N(1)	117.1407	116.5000
Cu(25)-N(2)-C(18)	119.8553	-	C(5)-C(17)-N(1)	125.6689	123.5000
C(23)-N(2)-C(18)	111.5103	-	Cu(25)-N(1)-C(22)	102.4200	-
O(4)-Cu(25)-O(3)	110.5415	-	Cu(25)-N(1)-C(17)	119.6635	-
O(4)-Cu(25)-N(2)	107.7634	-	C(22)-N(1)-C(17)	127.9022	-

ChemDraw Ultra 12.0 permits to quick structure building, geometry optimization with minimum energy and molecular presentation. It has capability to handle transition metal and inner transition metal complexes [25, 26]. Energy minimization was repeated numerous times to get the global minimum [27]. Selected bond lengths and bond angles among all measurements of bond lengths and the bond angles are given in Table 3 and 4. Except for a few cases, the optimal values (most favorable) of both the bond lengths and the bond angles are given in the Tables along with the actual ones. In most of the cases, the actual bond lengths and bond angles are very close to the optimal values, and thus the proposed structure of the complex **2** and other complexes are acceptable. The energy minimization value for the Cu(II)-complex **2** is 146.6231 kcal/mol.

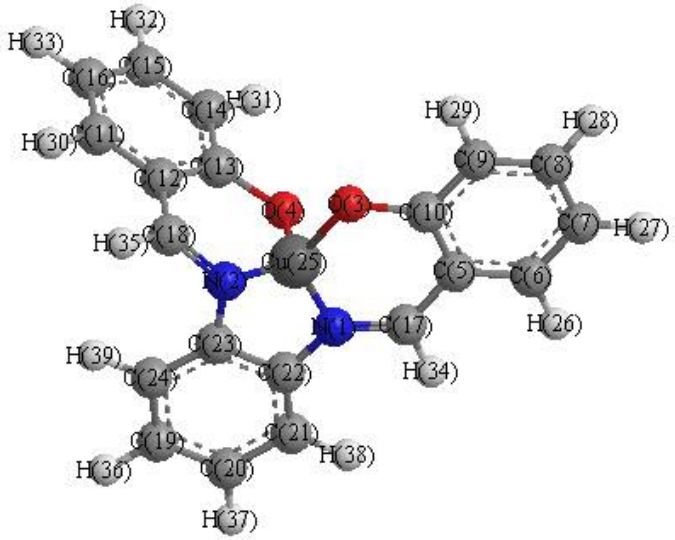


Fig 10 3D Structure Cu(II) salophen Complex, 2

CONCLUSION

In this study, nickel, copper and manganese complexes with salophen ligand were synthesized. All compounds were completely characterized and their antibacterial activity investigated. The investigation of antibacterial activity by agar well diffusion method showed all the complexes have strong antibacterial effect upon the studies bacteria. This study would pave the way for using of these type of complexes in several fields such as precursors for preparation of metal oxide nanostructures, electrocatalytic (water oxidation), photovoltaic and biological applications for future works. The proposed structures of the investigated complexes were supported by 3-D molecular modeling of complex **2** as a representative compound.

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