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SYNTHESIS, CHARACTERIZATION OF SCHIFF BASE DIVALENT MACROCYCLES DERIVE FROM 1, 2-DI(1H-INDOL-1-YL)ETHANE-1,2-DIONE AND THIOCARBOHYDRAZIDE WITH THEIR ANTIBACTERIAL EVALUATION

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ABSTRACT

The macrocycles [{ $M(C_{38}H_{28}N_{12}S_2)X$ } X_2] of Cu(II), Zn(II) and Ni(II) with Schiff base ligand ($C_{38}H_{28}N_{12}S_2$) obtained through the condensation of 1H-indol, diethyl oxalate and thiocarbodihydrazide. The newly formed compound have been characterized with the help of magnetic measurements, elemental analysis, condensation measurements and their structure configuration have been determined by various spectroscopic: Electronic, IR, ¹H NMR, ¹³C NMR, GCMS techniques. The electronic spectra of the complexes indicate an octahedral geometry of the center metal ion. These compounds were tested for their antibacterial potential against the bacteria: *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa*.

KEYWORD: Schiff base, Macrocycles, Biological Evaluation, Spectroscopic study.

1. INTRODUCTION

The area of inorganic chemistry, which most widely developed in the last few decades is mainly due to coordination chemistry and applies very particularly to the coordination compounds of transition metals. The chemistry of coordination compounds as always has been a challenge to the inorganic chemists as it has more branches now days. Coordination compounds play a very significant role in our lives; the study of them has contributed to the highest degree of understanding the chemical bond in inorganic chemistry. As whole classical coordination chemistry deals with the formation of adducts by metal in their higher oxidation states bonded to inorganic or organic ions or molecules. Interest in both basic and hi-tech research with these materials continues at a rapid pace.

Metals play a vital role in an immense number of extensively different biological processes. Some of these processes are quite specific in their metal ion requirements, in that only certain metal ions in specified oxidation states can accomplish the necessary catalytic structural requirement. Metal ion dependent processes are found throughout the life science and vary tremendously in their function and complexity. It is now appreciated that metal ions control a vast range of processes in Biological system. Many new and exciting developments in the field of biochemistry create interest out of inorganic chemists to court in the new area called

"Bioinorganic Chemistry". The popular method to synthesize the macrocyclic ligand is cyclo-condensation, such as (2+2), (3+3), (4+4).^[6,7] Literature reports reveal that free Schiff base ligands shows less or no biological activity as comparison to their complexes.^[1,2] Important characteristics that can be correlated with good antimicrobial activities are Lipophilicity and penetration of the complexes through the lipid membrane.^[3] The amide groups can bind with different metal ions via nitrogen and / or oxygen atoms. Compounds incorporating metal atoms are known as antitumor drugs such as cisplatin.^[4] In the present paper we report the structure and biological activity synthesized compound by condensation of thiocarbonodihydrazide with 1,2di(1H-indol-1-yl)ethane-1,2-dione and its Cu (II), Zn (II) and Ni (II) complexes. Results are reported on the bases of elemental analysis, conductance measurements, magnetic measurements and various spectroscopic studies.

2. EXPERIMENTAL

2.1. Reagents

The entire chemicals used, were of the analytical grade, diethyl oxalate, Indole and thiocarbohydrazide procured from s.d.-fine. Metal salts were purchased from Merck.

2.2. Synthesis of 1,2-di(1H-indol-1-yl)ethane-1,2-dione

1 H-indol was dissolved in ethanol and this solution was added diethyl oxalate in a 2:1 molar ratio containing few drop of concentrated HCl. The solution was refluxed for 3h. The cream crystalline product which formed was filtered off under vacuum and recrystallized from ethanol.^[5]

2.4. Synthesis of macrocyclic ligand

1,2-di(1H-indol-1-yl) ethane-1, 2-dione in ethanol (20 mL) was added to an ethanolic solution of thiocarbohydrazide (30 mL) containing a few drops of concentrated HCl. The reaction mixture was refluxed for 5 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure by rotavapour until a solid product was formed and it was washed with cold ethanol and dried under vacuum. $C_{38}H_{28}N_{12}S_{2}$ Melting point 151°C and Yield 70–75% (scheme 1): calcd. C 63.67, H 3.94, N 23.45,; found C 63.66, H 3.98, N 23.44. ¹ H NMR (300 MHz, DMSO-d₆) δ = 6.45-7.65 (m, 24H, Ar-H Indol), 8.13 (s, Ar-H, Carbonyl Phenyl), 10.15 (s, 4x1H, NH of Hydrazide). ¹³C NMR (300 MHz, DMSO-d₆) δ = 154.2 (C = N), 170.6 (C=O), 147.6, 145.9, 138.1, 135.5, 132.2, 130.1, 128.3, 112.4 (Ar-C). UV/vis (Nujol mul (nm)): $\lambda = 370, 420, 480.$ UV/vis (1× 10^{-4} mol, DMSO): $\lambda = 360, 390, 445$. IR (KBr): $v(N^2H)$ 3240, v(C=O) 1710, v(C=N) 1620, v(N-N) 1112, v(C-C) 750, v(C=C, aromatic) 1520, v(C-H, aromatic) 3030, v(NH, hydrazide) 3145 cm⁻¹.



Scheme I. Formation of Schiff base ligand

2.5. Synthesis of the Cu(II), Zn(II) and Ni(II) complexes

A solution of divalent metal salt (1.0 mmol) in methanol (8 mL) was added to a hot solution (75° C) of macrocyclic ligand (1.0 mmol) in ethanol (25 mL) and the reaction mixture was refluxed for 8 h. The solution was concentrated under vacuum. The precipitate was filtered off, washed with methanol and dried under vacuum over anhydrous CaCl₂ (68-75% yield) scheme 2.



Scheme II. Formation of Schiff base metal complex cation

2.5.1. Synthesis of the metal complex (1)

[Cu(C₃₈H₂₈N₁₂S₂)Cl₂] yield 71% (849.06): calcd. C 53.61, H 3.32, N 21.68, Cu 7.46; found C 53.12, H 3.28, N 21.15, Cu 7.92. Conductance Λ m: 69Ω⁻¹ cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =355, 420, 525, 720 and 1155. IR (KBr): v(N²H) 3272, v(C=N) 1640, v(C=O) 1710, v(N–N) 1120, v(C–C) 740, v(C=C, aromatic) 1530, v(C–H, aromatic) 3030, v(NH, hydrazide) 3145, v(M–N) 420, v(M–Cl) 320 cm⁻¹.

2.5.2. Synthesis of the metal complex (2)

[Cu(C₃₈H₂₈N₁₂S₂)(NO₃)₂] yield 78% (903.10): calcd. C 50.47, H 3.12, N 21.68, Cu 7.03; found C 50.48, H 3.15, N 21.66, Cu 7.04. Conductance Λ m: 74 Ω⁻¹ cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =255, 525, 720 and 1155. IR (KBr): v(H₂O) 3420, v(N²H) 3270, v(C=O) 1710, v(C=N) 1645, v(C-C) 760, v(C=C, aromatic) 1544, v(C-H, aromatic) 3020, v(NH, hydrazide) 3130, v(N-N) 1110, v(M-N) 420, v(M-O) 480 cm⁻¹.

2.5.3. Synthesis of the metal complex (3)

[Cu(C₃₈H₂₈N₁₂S₂)(OAc)₂] yield 75% (897.15): calcd. C 56.15, H 3.81, N 18.71, Cu 7.07; found C 56.18, H 3.84, N 18.69, Cu 7.08. Conductance Λ m: 79 Ω⁻¹ cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =260, 520, 724 and 1150. IR (KBr): v(H₂O) 3330, v(N²H) 3250, v(C=O) 1770, v(C=N) 1650, v(N–N) 1120, v(C–C) 760, v(C=C, aromatic) 1544, v(C–H, aromatic) 3030, v(NH, hydrazide) 3140, v(M–N) 420, v(M–O) 510 cm⁻¹. v_{sym}(OC(O)CH₃) 1549 (m), v_{asym}(OC(O)CH₃) 1366 cm⁻¹, (Δ v=190cm⁻¹).

2.5.4. Synthesis of the metal complex (4)

[Zn($C_{38}H_{28}N_{12}S_2$)Cl₂] yield 73% (850.06): calcd. C 53.50, H 3.31, N 19.70 Zn 7.66; found C 53.52, H 3.33, N 19.72, Zn 7.68. Conductance Λ m: 17 Ω^{-1} cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =260, 280, 320, 450, 700, 1150. IR (KBr): v(H₂O) 3370, v(N²H) 3260, v(C=O) 1735, v(C=N) 1670, v(N-N) 1145, v(M-N) 440, v(C-C) 755, v(C=C, aromatic) 1540, v(C-H, aromatic) 3040, v(NH, hydrazide) 3145, v(M-Cl) 320 cm⁻¹.

2.5.5. Synthesis of the metal complex (5)

[Zn(C₃₈H₂₈N₁₂S₂)(NO₃)₂] yield 72%. (904.10): calcd. C 50.36, H 3.11, N 21.64, Zn 7.22; found C 50.38, H 3.13, N 21.65, Zn 7.25. Conductance Am: 19 Ω⁻¹ cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =255, 710 and 1151. IR (KBr): v(H₂O) 3420, v(N²H) 3271, v(C=O) 1730, v(C=N) 1644, v(N–N) 1112, v(C–C) 754, v(C=C, aromatic) 1540, v(C–H, aromatic) 3040, v(NH, hydrazide) 3145, v(M–N) 420, v(M–O) 495 cm⁻¹

2.5.6. Synthesis of the metal complex (6)

[Zn(C₃₈H₂₈N₁₂S₂)(OAc)₂] yield 77% (898.15): calcd. C 56.03, H 3.81, N 18.67, Zn 7.26; found C 56.01, H 3.83, N 18.66, Zn 7.27, Conductance *A*m: 21 Ω⁻¹ cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ = 255, 451, 680 and 1144. IR (KBr): v(H₂O) 3310, v(N²H) 3250, v(C=O) 1720, v(C=N) 1655, v(N–N) 1122, v(C–C) 730, v(C=C, aromatic) 1530, v(C–H, aromatic) 3040, v(NH, hydrazide) 3130, v(M–N) 450, v(M–O) 520 cm⁻¹, v_{sym}(OC(O)CH₃) 1550, v_{asym}(OC(O)CH₃) 1360 cm⁻¹, (Δ v=188cm⁻¹).

2.5.7. Synthesis of the metal complex (7)

[Ni($C_{38}H_{28}N_{12}S_2$)Cl₂] yield 75% (844.07): calcd. C 53.92, H 3.33, N 19.86, Ni 6.93; found C 53.89, H 3.31, N 19.88, Ni 6.96.. Conductance Λ m: 11 Ω^{-1} cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =260, 652 and 1060. IR (KBr): v(H₂O) 3407, v(N²H) 3280, v(C=O) 1730, v(C=N) 1640, v(N-N) 1144, v(C-C) 744, v(C=C, aromatic) 1530, v(C-H, aromatic) 3045, v(NH, hydrazide) 3140, v(M-N) 450, v(M-Cl) 330 cm⁻¹.

2.5.8. Synthesis of the metal complex (8)

[Ni($C_{38}H_{28}N_{12}S_2$)(NO₃)₂] *Yield* 74%. (898.11): calcd. C 50.74, H 3.14, N 21.80, Ni 6.52; found C 50.76, H 3.16, N 21.78, Ni 6.51. Conductance Am: 12 Ω^{-1} cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ =255, 525, 720 and 1150. IR (KBr): v(H₂O) 3420 (br), v(N²H) 3270, v(C=O) 1688, v(C=N) 1630, v(N–N) 1130, v(C–C) 755, v(C=C, aromatic) 1530, v(C–H, aromatic) 3050, v(NH, hydrazide) 3135, v(M–N) 420, v(M–O) 480 cm⁻¹.

2.5.9. Synthesis of the metal complex (9)

[Ni($C_{38}H_{28}N_{12}S_2$)(OAc)₂] yield 66% (892.16): calcd. C 56.45, H 3.83, N 18.81, Ni 6.57; found C 56.44, H 3.85, N 18.82, Ni 6.59. Conductance Δ m: 14 Ω^{-1} cm² mol⁻¹. UV/vis (Nujol mul (nm)): λ = 265, 636, 1051. IR (KBr): v(H₂O) 3410, v(N²H) 3270, v(C=O) 1710, v(C=N) 1620, v(N–N) 1122, v(C–C) 751, v(C=C, aromatic) 1530, v(C–H, aromatic) 3040, v(NH, hydrazide) 3140, v(M–N) 450, v(M–O) 520 cm⁻¹ v_{sym}(OC(O)CH₃) 1560 (m), v_{asym}(OC(O)CH₃) 1360 cm⁻¹ (m) (Δ v=191cm⁻¹).

3. RESULTS AND DISCUSSION

3.1. Mass spectra

The FAB mass spectra of Cu (II), Zn (II) and Ni (II) Schiff base complexes have been recorded. The molecular ion (M^+) peaks obtained from various complexes are as follows (table 1):

3.2. IR Spectra

The IR spectral of the Schiff base ligand show a $_{V}(C=N)$ peak at 1610 cm⁻¹ and a medium intensity absorption band at 3180 cm⁻¹ which is attributed to the $_{\nu}$ (N–H) stretching vibration. The high intensity band at 1613-1632 cm⁻¹ which is attributed to the v(C=N) vibration. The various absorption band in the range ~1455-1570 cm^{-1} may be assigned due to $_{V}(C=C)$ aromatic stretching vibrations of the aromatic ring.^[6] The presence of the absorption bands at 1400-1445, 1280-1315 and 1020-1045 cm⁻¹ in the IR spectra of the nitrato complexes suggests that the nitrate groups are coordinated to the central metal ion in a unidentate fashion.^[7] The peak around 2140 cm⁻¹ may be assigned to (C=S). In IR spectra of the acetate complexes the appearance of three characteristic bands in the ranges 1555 - 1575 cm⁻¹, 1377 -1395 cm⁻¹ and 1795–1810 cm⁻¹ in the case of complexes was attributed to $v_{asym}(COO^{-})$, $v_{sym}(COO^{-})$ and uncoordinated (COO⁻), respectively, indicating the participation of the carboxylate oxygen in the complexes formation. The IR spectra of nitrato complexes exhibits bands at 1290–1310 cm⁻¹, 1050–1065 cm⁻¹ and 1435– 1450 cm^{-1[8]}, IR absorption band ~1355-1360 cm⁻¹ assigned the uncoordinated nitro group. The far infrared spectra show bands in the region 420-450 cm⁻¹ corresponding to $_{\nu}$ (M–N) vibration.^[9-11] The presence of bands in all complexes in the region 420-450 cm⁻¹ originate from (M-N) azomethine vibrational mode and identify coordination of azomethine nitrogen.^[12] The band present in the range $310-330 \text{ cm}^{-1}$ may be assigned due to $_{\nu}$ (M–Cl) vibration.^[9-11] The bands present in the region 235-260 cm^{-1} in all the nitrato complexes are assignable to $_{\nu}$ (M–O) stretching vibration.^[9,10]

3.3.¹H NMR

A survey of literature reveals that Schiff base have characterized by ¹H NMR and ¹³C NMR spectra to ensure ligand structure and purity in d_{6} -dimethylsulfoxide (DMSO- d_{6}) solution using Me₄Si (TMS) as internal standard. The ¹H NMR spectra of Schiff base ligand (HL) was recorded. The ¹H NMR spectra of the ligand shows broad signal at 9.4-12.1 ppm due to the presence of $-NH^{[13]}$ and 2.1-2.8 ppm due to the $-CH_2-$ (cyclic).^[14] The multiplets in the region 6.54-8.76 ppm may be assigned to aromatic proton.^[15-17]

3.4. Electronic spectral studies, magnetic measurements and molar conductance

The electronic spectra of Cu(II) complexes showed absorption band in the region 680-670 nm attributed to ${}^{2}T_{g} \leftarrow {}^{2}E_{g}$ transition indicative of distorted octahedral geometry^[18] The ESR spectrum of copper(II) complexes has been studied and depicted in. The g_{\parallel} and g_{\perp} values have been found to be 2.11149 and 2.13112, respectively. The g_{av} was calculated to be 2.11011. Cu(II) exhibits $g_{\parallel} < 2.3$, suggesting covalent characters of the copper–ligand bonding in this complex. The Cu(II) complexes shows reversed axial (compressed octahedral) with $g_{\parallel} < g_{\perp}$. The trend $g_{\parallel} < g_{\perp}$ showed that the electron is delocalised in d_{z}^{2} orbital of the ground state of Cu(II).

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Complexes	Mol. wt.	Molecular ion peak [M] ⁺	Important peak due to complex fragmentation			
$C_{38}H_{28}N_{12}O_2$	716.20	715.20	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21			
$[Cu(C_{38}H_{28}N_{12}S_2)Cl_2]$	849.06	848.06	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 778.13, 813.10			
$[Cu(C_{38}H_{28}N_{12}S_2)(NO_3)_2]$	903.10	902.10	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 778.13, 840.11			
$[Cu(C_{38}H_{28}N_{12}S_2)(OAc)_2]$	897.15	896.15	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 778.13, 837.14			
$[Zn(C_{38}H_{28}N_{12}S_2)Cl_2]$	850.06	849.06	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 779.14, 814.10			
$[Zn(C_{38}H_{28}N_{12}S_2)(NO_3)_2]$	904.10	903.10	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 779.14, 841.12			
$[Zn(C_{38}H_{28}N_{12}S_2)(OAc)_2]$	898.15	897.15	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 779.14, 838.14			
$[Ni(C_{38}H_{28}N_{12}S_2)Cl_2]$	844.07	843.07	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 773.15, 808.11			
$[Ni(C_{38}H_{28}N_{12}S_2)(NO_3)_2]$	898.11	897.11	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 773.15, 835.13			
$[Ni(C_{38}H_{28}N_{12}S_2)(OAc)_2]$	892.16	891.16	31.0, 75.0, 105.0, 116.0, 232.0, 259.1, 361.1, 463.1, 482.1, 596.1, 711.21, 715.2, 773.15, 832.15			

Table 1. FAB mass s	pectral data of the	e divalent Copper	. Zinc and Nickel c	complexes derived f	rom macrocyclic ligand
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In this case $(g_{\parallel} < g_{\perp})$ distortion occurs by compression.^[19] The parameter G, determined as $G = g_{\parallel} -2.0023/g_{\perp} -2.0023$, is found to be much less than 4 suggesting considerable interaction in the solid state (Hathaway et al., 1973). The magnetic moment value for this complex was found to be 1.48-1.63 B.M.

The absorption spectral bands of nickel(II) Complexes showed three spin allowed transitions: ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{2}g(F)$, ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{1}g(F)$, ${}^{3}A_{2}g(F) \rightarrow {}^{3}T_{1}g(P)$ appearing in the ranges 1145–1054, 706–695 and 461–443 nm, respectively consistent with a typical Ni(II) in an octahedral environment.^[20] The magnetic moment values for these complexes were found in the range 2.10–2.14 B.M.^[20] expected for octahedral nickel complexes.

3.5. Antibacterial activity

Antibacterial activities were evaluated using agar well diffusion method.^[21,22] The results of the bactericidal study of the synthesized compounds are displayed in Fig 1. The Schiff base ligand, its metal complexes, standard drug Imipenem and DMSO solution control were screened for their antibacterial activity against the bacteria *Staphylococcus aureus* and *Bacillus subtilis* (as gram positive bacteria) and *Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhi* (as gram negative bacteria),The walls of gram negative cells are more complex than those of gram positive cells. The zones of inhibition (ZOI) values obtained indicate that the ligand has moderate activity against *P. aeruginosa* and *E. coli* but no activity against *S. typhi*. Ligand showed a significant activity towards *B. subtilis* and *S. aureus*. Antibacterial activity of all the complexes towards gram positive and gram negative bacteria is quite significant. Antibacterial study reveals that, metal complexes have more biological activity than free ligand. Complex [Ni(C₃₈H₂₈N₁₂O₂)(OAc)₂] shows best antimicrobial activity against the given

microorganism. Further to it, the ligand showed moderate and the complexes moderate to high activities as compared to standard drug towards the all organism. The variation in the antimicrobial activity of different metal complexes against different microorganisms depends on their impermeability of the cell or the differences in ribosomes in microbial cell.^[23, 24]



Fig 1. Bactericidal screening data of the ligand and their corresponding metal complexes

^aExcellent activity (90-100% inhibition), Good activity (60-70% inhibition), Significant activity (30-50% inhibition), negligible activity (08-20% inhibition), ^bComplex 1 = [Cu(HL)Cl₂], 2 = [Cu(HL)(NO₃)₂], 3 = [Cu(HL)(OAc)₂], 4 = [Zn(HL)Cl₂], 5 = [Zn(HL)(NO₃)₂], 6 = [Zn(HL)(OAc)₂], 7 = [Ni(HL)Cl₂], 8 = [Ni(HL)(NO₃)₂], 9 = [Ni(HL)(OAc)₂], ^cImipenem = Standard drug.

4. CONCLUSION

The electronic spectral data is in the favor of a octahedral geometry of the complexes. New synthesized compounds were tested for antibacterial evaluation against some pathogenic strains and compared with standard drug. Antibacterial study reveals that, metal complexes have more biological activity than free ligand. Complex $[Ni(C_{38}H_{28}N_{12}S_2)(OAc)_2]$ shows best antibacterial activity against the given microorganism.

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