
Synthesis, Spectroscopic, Thermal Studies of Nickel(II) and Palladium(II) Complexes of Tridentate Ligand and Their DNA Cleavage Activity

Amna Qasem Ali* Abdusalam Matoog Hamil* Siang Guan Teoh**

*Chemistry department, Faculty of Science, Sebha University, Libya

**School of Chemical Sciences, U. Sains Malaysia, Minden-11800, Pulau Pinang, Malaysia

Abstract: Two novel complexes of Ni(II) and Pd(II) with Schiff base ligand derived from 5-chloro isatin with 4-phenyl-3-thiosemicarbazid have been synthesized in absolute EtOH. The structures of the isolated solid compounds have been characterized by elemental analyses and spectral (FT-IR and UV-vis.) measurements. The Schiff base ligand was further characterized by mass spectra. All the synthesized compounds were tested against supercoiled pBR322 DNA. It has been found that, the Schiff base ligand behaves as tridentate ligand forming chelates with 1:2 (metal:ligand) in case of Ni-complex and 1:1 (metal:ligand) in case of Pd-complex. Octahedral geometry was suggested for the Ni(II) chelate while square-planar geometry was suggested for the Pd(II) chelate. These compounds have been found to promote the cleavage of plasmid DNA pBR322 in the presence of H₂O₂.

Keywords: 5-chloro isatin; 4-phenyl-3-thiosemicarbazid; tridentate ligand; supercoiled pBR322.

Introduction

Thiosemicarbazones (hydrazine carbothioamides) are Schiff bases that can be synthesized by the condensation reaction of an aldehyde or a ketone with a thiosemicarbazide even in the absence of any catalyst either at room temperature or by heating for a few hours⁽¹⁾. Thiosemicarbazones are a class of small molecules that display numerous biological activities as antivirals and as anticancer therapeutics, as well as parasiticidal action against *Plasmodium falciparum* and *Trypanosoma cruzi*, the causative agents of malaria and Chagas's disease, respectively

⁽²⁻³⁾. Thiosemicarbazones have been intensively studied because of their inhibitory action on the DNA enzyme ribonucleotide diphosphate reductase, as well as their selectivity toward hormone-responsive cancers⁽⁴⁾. The deprotonated thiosemicarbazones usually coordinate to nickel, platinum, palladium and copper through donor atoms such as nitrogen, oxygen and sulphur in their bidentate form (N, S) or tridentate form (O, N, S) to form chelates⁽⁵⁾. The biological activities of certain thiosemicarbazones derivatives are related to their ability to form these chelates and to coordinate to metal centers

in enzymes ⁽⁶⁾. This coordination occurs through additional functional groups that are uncoordinated to their “primary” metal ion, suggesting that the biological activity may also depend on the non-coordinating groups ⁽⁷⁾. The current work describes the synthesis, spectroscopic characterization and thermal study of mono nickel(II) and palladium(II) complexes with tridentate ligand. The DNA cleavage activity of these compounds was reported.

Experimental

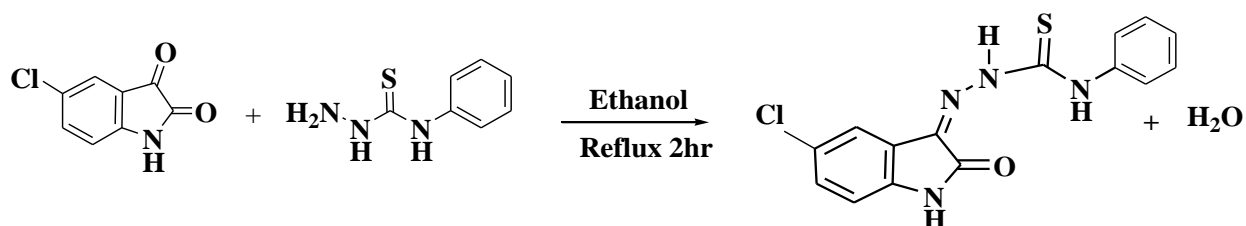
Materials and methods

The materials used in this study such as 5-Chloroisatin, 4-Phenyl-3-thiosemicarbazide, nickel (II) chloride hexahydrate and palladium (II) chloride were purchased from Aldrich Chemicals. Commercial grade solvents and reagents were used as supplied without further purification. Supercoiled (SC) pBR322 DNA and loading dye were purchased from Fermentas. Agarose (molecular biology grade), and ethidium bromide (EB) were from Sigma (St. Louis, MO, USA). The elemental analysis was carried out using Perkin-Elmer 2400 series-11 CHN/O

analyzer (Waltham, MA, USA). Infrared, electronic and nuclear magnetic resonance were recorded on PerkinElmer 2000, Perkin Elmer-Lambda 25, and Bruker 500 MHz spectrometer at room temperature using DMSO-d₆ as solvent and TMS as an internal standard, respectively. Thermal analysis was performed on 10-22 mg samples using a Mettler Toledo Star System. The samples were heated from 30 to 900 °C under nitrogen atmosphere flowing at 20 ml/ min. Mass spectra were obtained using LC / MSD Trap VL (Agilent Technologies).

Synthesis of Schiff base ligand [(Z)-2-(5-Chloro-2-oxoindolin-3-ylidene)-N-phenylhydrazinecarbothioamide].

The Schiff base ligand was previously synthesized and reported as a single crystal ⁽⁸⁾. Equimolar quantities of 5-chloro isatin and 4-phenyl-3-thiosemicarbazide were refluxed in ethanol for 2 h. The precipitate that formed during reflux was filtered and washed with cold ethanol (Scheme 1) and finally stored in a vacuum desiccator over P₂O₅.

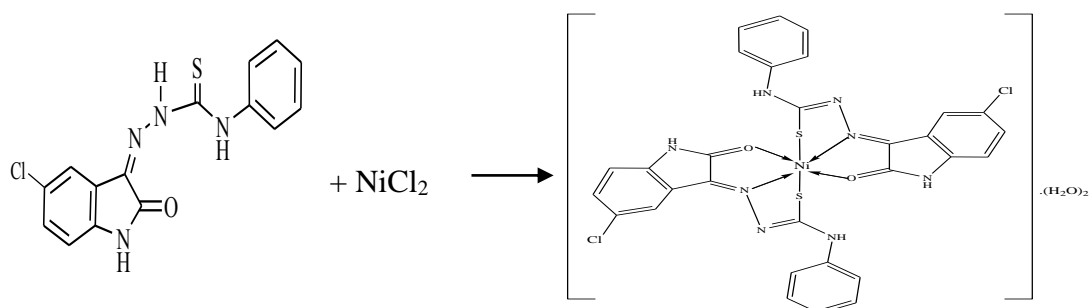


Scheme 1: Synthetic route and structure for the Schiff base ligand.

C₁₅H₁₁ClN₄OS: Orange crystals; Mwt.: 330.79; MP: 248.4 °C to 248.9 °C; yield: 97%; analytical calculated values: C (54.94%), H (3.41%) and N (16.55%); analytical results (experimental): C (54.46%), H (3.35%) and N (16.94%); selected IR data (KBr pellet, $\nu_{\max}/\text{cm}^{-1}$): 3318 to 3064 (NH), 1690 (C=O), 1622 (C=N), 1594 (C=C) and 1205/763 (C=S).

ynthesis of complexes: Synthesis of nickel(II) complex

The Schiff base nickel(II) complex was synthesized by refluxing the reaction mixture of hot ethanolic solutions (30 ml each) of nickel(II) chloride (NiCl₂·6H₂O) (0.01 mol) and Schiff base ligand (0.01 mol) for 2 h. The precipitate that formed during reflux was filtered and washed with cold ethanol (Scheme 2) and finally stored in a vacuum desiccator over P₂O₅



Scheme 2: Synthetic route and structure for the nickel complex.

C₃₀H₂₄Cl₂NiN₈O₄S₂: Green powder; Mwt.: 754.29; MP: >300 °C; yield: 72%;

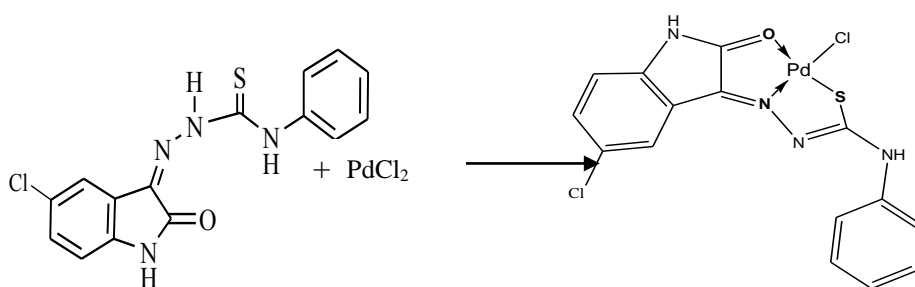
Analytical calculated values: C (47.77%), H (3.21%), N (14.86%) and Ni (7.178%); analytical results (experimental): C (47.87%), H (3.10%), N (14.93%) and Ni (7.40%); selected IR data (KBr pellet, $\nu_{\text{ma}}/\text{cm}^{-1}$): 3375 to 3062 (NH), 1669 (C=O), 1615 (C=N), 1595 (C=C) and 750 (C-S).

Synthesis of palladium(II) complex

The Schiff base palladium(II) complex was synthesized by refluxing the reaction mixture of hot ethanolic solutions (30 ml each) of palladium (II) chloride (PdCl₂) (0.01 mol) and Schiff base ligand (0.01 mol) for 2 h. The precipitate that formed

during reflux was filtered and washed with cold ethanol (Scheme 3) and finally stored in a vacuum desiccator over P₂O₅.

C₁₅H₁₀ClPdN₄OS (PdL1): Brown powder; Mwt.: 471.66; MP: >300 °C; yield: 88%; analytical calculated values: C (38.20%), H (2.14%), N (11.88%) and Pd (22.56%); analytical results (experimental): C (38.53%), H (2.47%), N (12.05%) and Pd (22.41%); selected IR data (KBr pellet, $\nu_{\text{ma}}/\text{cm}^{-1}$): 3308 to 3018 (NH), 1646 (C=O), 1610 (C=N), 1553 (C=C) and 747 (C-S).



Scheme 3: Synthetic route and structure for the palladium complex.

DNA cleavage studies

Cleavage experiments of supercoiled pBR322 DNA (0.5 $\mu\text{g}/\mu\text{l}$) were

performed at pH 7.2 in Tris-HCl/NaCl (5:50 mM) buffer. Oxidative DNA cleavage was monitored by treating

pBR322 DNA with varying concentrations of Schiff base ligand (1.0 to 6.0 mM) and Ni(II) or Pd(II) complexes (0.1 to 1 mM) and H₂O₂, followed by dilution with Tris-HCl/NaCl (5:50 mM) buffer to a total volume of 20 μ l (Lanes 4 to 12). To investigate the mechanism of DNA cleavage promoted by these compounds, the experiment was carried out by adding scavenger for reactive oxygen species (ROS), DMSO to compound-DNA mixture (lane 3). The samples were incubated for 2 h at 37 °C. A loading dye was added, and electrophoresis was carried out at 50 V for 1 h in Tris-HCl buffer using 1% agarose gel. The resulting bands were stained with EB before being photographed under UV light.

Results and discussion

The nickel(II) and palladium(II) complexes were obtained in good yield from the reaction of nickel(II) or palladium(II) with Schiff base ligand in 1:1 M and 1:2 (M:L in case of nickel complex) ratio in the ethanol medium with reflux for 2 h. These complexes were slightly soluble

in common organic solvents, but soluble in DMF and DMSO.

Spectroscopic properties

IR studies

IR spectrum of Schiff base (Fig. 1) showed absorption band at 1622 cm⁻¹ can be assigned to (C=N) which confirms the formation of the Schiff base. The peak at 1594 cm⁻¹ may be assigned to (C=C) as reported for similar compounds ⁽⁹⁾. The peak at 1141 cm⁻¹ regions resulting from ν (N-N) stretching vibration band. The Schiff base contain a thione group (C=S) with protons adjacent to it. Although it has been noted that the thione group (C=S) is relatively unstable in the monomeric form and tends to convert to a stable C-SH single bond. Absence of any bands in the 2800-2550 cm⁻¹ region confirms the lack of —SH stretching frequencies in the molecule. It reveals the presence of only the thione tautomer in the solid state (strong bands at 1205 / 763 cm⁻¹). However, equilibrium with the thiolo tautomeric form may be established in solution ⁽¹⁰⁾.

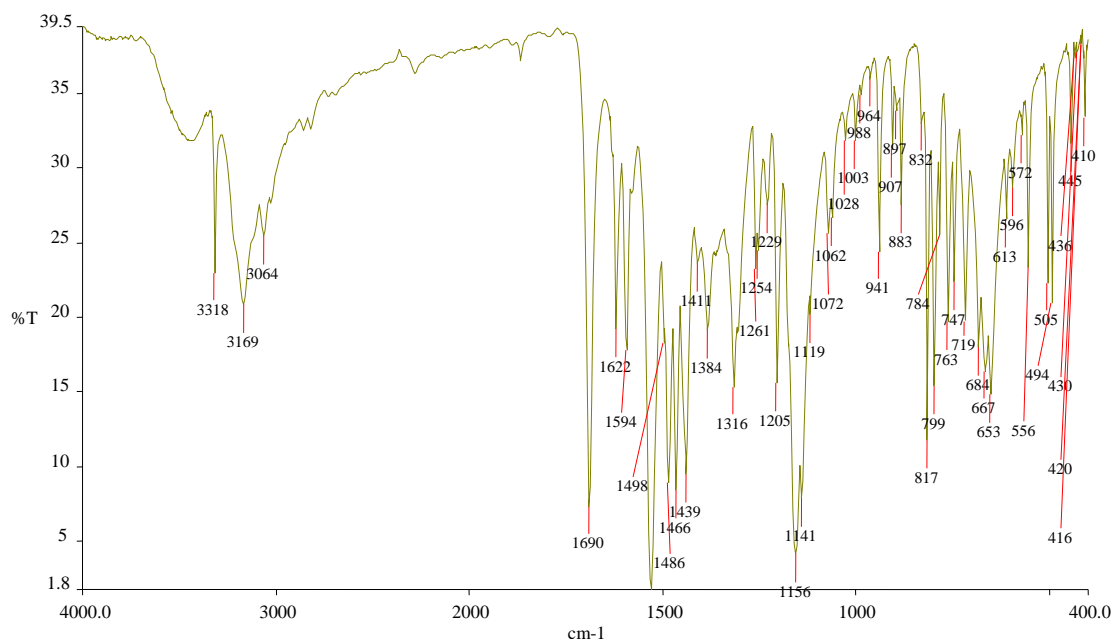


Fig. 1: FT-IR spectrum [(Z)-2-(5-chloro-2-oxoindolin-3-ylidene)-N-phenylhydrazinecarbothioamide] in KBr.

The characteristic IR bands recorded for the free ligand differ from those of the related complexes and provided significant indications of the bonding sites of thiosemicarbazone ligand. In comparison with the spectra of the Schiff base, the Ni-complex (Fig. 2) and Pd-complex (Fig. 3) exhibited the band of $\nu(\text{C}=\text{O})$ within $1646\text{--}1669\text{ cm}^{-1}$, showing a shift of the band to lower wavenumbers. This finding indicates that the carbonyl oxygen is coordinated to the metal ion. The

band of $\nu(\text{C}=\text{N})$ within $1610\text{--}1615\text{ cm}^{-1}$ in the metal complexes shows a shift of the band to lower wavenumbers, which indicates that the nitrogen atom of the azomethine group is coordinated to the metal ion. This finding is further supported by the band at around $747\text{--}750\text{ cm}^{-1}$ in the metal complexes because of $\nu(\text{C}\text{--}\text{S})$ ⁽¹¹⁾. Thus, the IR spectral results of the complexes provide strong evidence for the complexation of Schiff base with metal ions in tridentate mode.

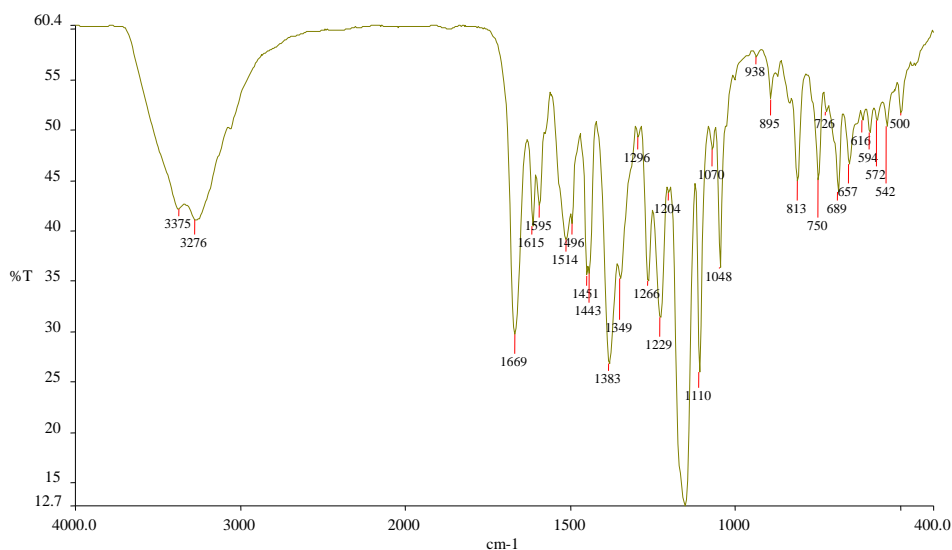


Fig. 2: FT-IR spectrum of Bis[2-(5-chloro-2-oxoindolin-3-ylidene)-*N*-phenylhydrazinecarbothioamidato- κ^3O, N^2, S]nickel(II) dihydrate in KBr.

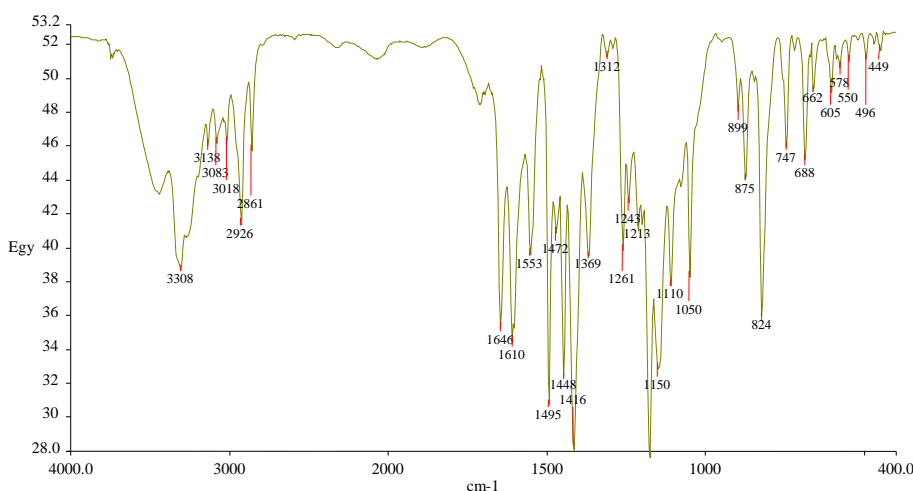


Fig. 3: FT-IR spectrum of chloro{*N'*-[5-chloro-2-(oxo- κO)-1, 2-dihydro-3H-indol-3-ylidene]-*N*-phenylcarbamohydrazone-thioato- κ^2N', S } palladium(II) in KBr.

UV-vis. studies

The UV-vis. spectra of the complexes recorded in DMSO solution show similar pattern suggesting that the

complexes retain their structure in solution. The electronic spectrum of free ligand (Fig. 4) consist of an intense bands centered at 330 nm attributed to $n-\pi^*$

transitions of the azomethine group. There is another intense band at xxx nm related to $\pi-\pi^*$ transitions of phenyl rings ⁽¹²⁾. These transitions are also found in the spectra of the complexes, but they shifted

to the lower frequencies. The spectrum of nickel complex (Fig. 5) showed three low intensity bands in visible region, 600 and 485 nm assigned to d-d transitions, typical for distorted octahedral complexes ⁽¹³⁾.

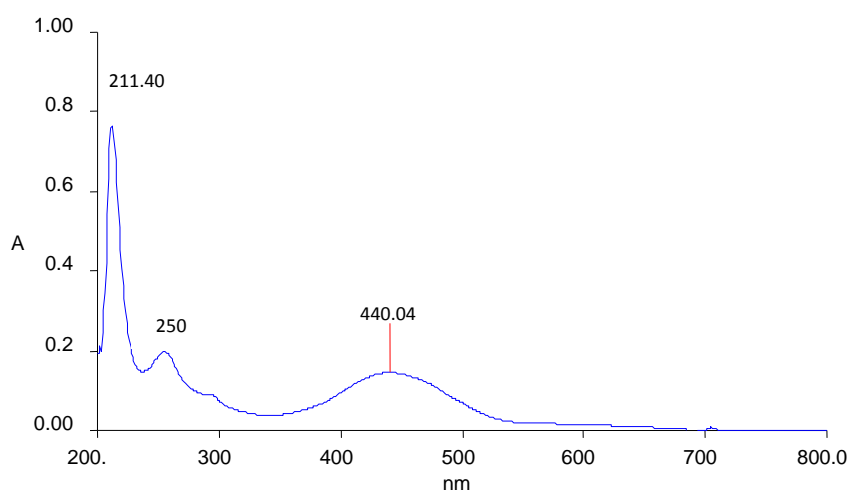


Fig. 4: Electronic spectrum of [(Z)-2-(5-chloro-2-oxoindolin-3-ylidene)-N-phenylhydrazinecarbothioamide] in DMSO.

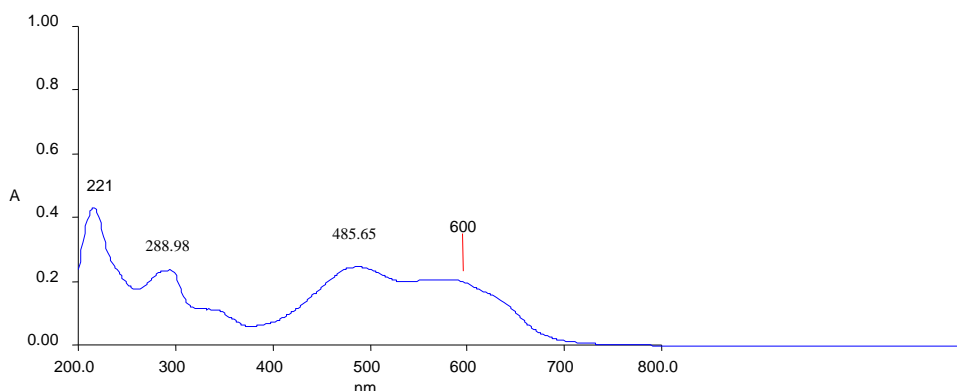


Fig. 5: Electronic spectrum of Bis[2-(5-chloro-2-oxoindolin-3-ylidene)-N-phenylhydrazinecarbothioamidato- κ^3O, N^2, S]nickel(II) dihydrate in DMSO.

The electronic spectrum of palladium (II) complex (Fig. 6) showed bands in the region 220-468 nm. The appearance of bands below 470 nm suggests a square planar geometry around the Pd(II) in the complex. The band at 271nm has been

assigned to intra ligand transitions and the band appearing at of 368 nm has been assigned to LMCT (S d) transitions. The band at 468 nm is due to MLCT (metal to ligand charge transfer)⁽¹⁴⁾.

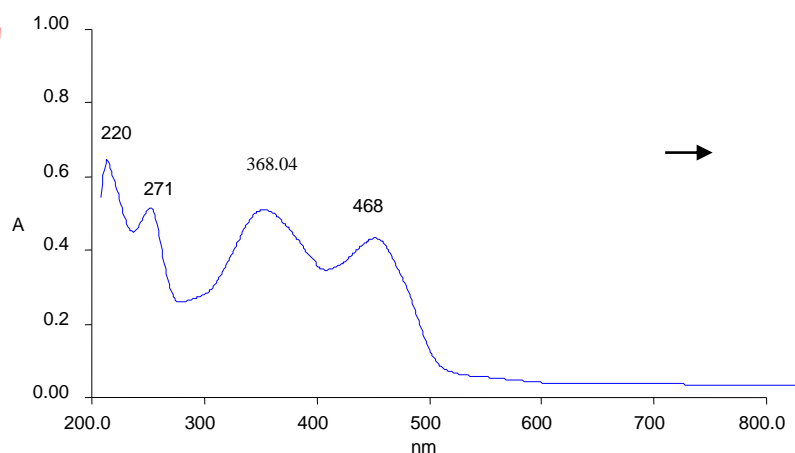


Fig. 6: Electronic spectrum of chloro{*N'*-[5-chloro-2-(oxo- κO)-1, 2-dihydro-3H-indol-3-ylidene]-*N*-phenylcarbamohydrazonothioato- $\kappa^2 N', S$ } palladium(II) in DMSO.

MS studies

The ESI-mass spectrum of the Schiff base, which was recorded in negative mode, exhibit peak at m/z : 329, thus indicating the presence of $[M-H]^-$. The

major fragmentation pathway involved the cleavage of NH-CS bond; this can be confirmed by the presence of peaks at m/z : 194.

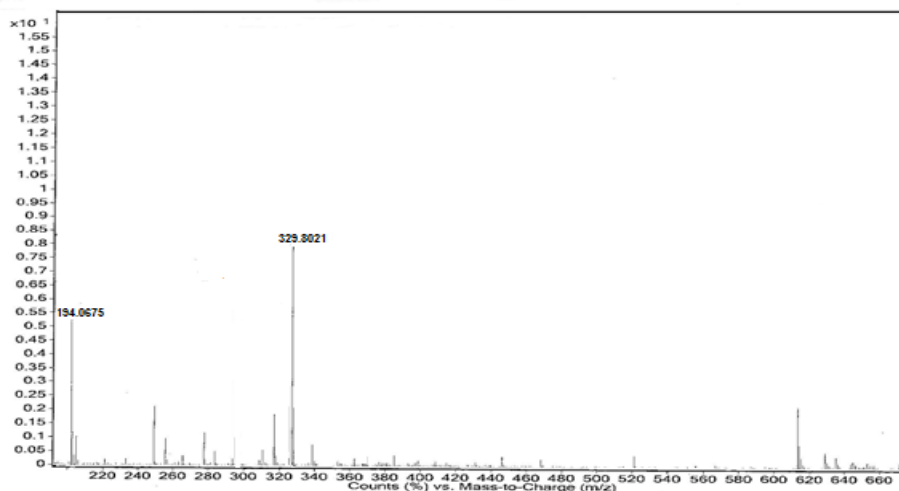


Fig. 7: ESI-mass spectrum (LC / MSD) of [(Z)-2-(5-Chloro-2-oxoindolin-3-ylidene)-N-phenylhydrazinecarbothioamide] .

Thermogravimetric analysis of the complexes:

Thermogravimetric analysis of the complexes $C_{30}H_{24}Cl_2N_8NiO_4S_2$ and $C_{15}H_{10}Cl_2N_2OPdS$ was measured from the ambient temperature up to 800°C using heating rate of 10 °C /min. The thermogravimetric analysis data of the complexes are listed in table 1, and their curves are shown in the figures (8 and 9). The thermogram curve of the Ni(II) complex (Fig. 8) shows a mass-loss of 4.77% and found mass loss of 5.82% corresponding to the presence of two hydrated water molecules at 0–

220 °C. Whereas, this complex does not contain coordinated water molecules. In the range of 220 - 450 °C, the used ligand decomposes as carbonate or oxalate. At temperature above 450 °C, the constant line represents the metal oxide (NiO) which appeared at 13.67% in comparison with the calculated value of 11.20%. In the Pd(II) complex (Fig. 9), there is no water molecules. The ligand decomposed as carbonate or oxalate.⁽¹⁵⁻¹⁶⁾ At temperature above 450 °C. The metal oxide (PdO) is observed at mass loss of 27.45% which is in agreement with calculated value of 25.92%

Table (1): Thermogravimetric analysis data of Ni(II) and Pd(II) complexes.

Complexes	weight loss% of hydrated water	No. of water molecules	Temp °C	Temp. °C of Schiff base decomposition	Weight loss% of metal oxide	Temp °C
[Ni(L) ₂](H ₂ O) ₂	4.77 (5.82)	2	0 - 220	220 - 450	13.67 (11.20)	>450
[PdL]	-	-	-	476-539	27.45 (25.20)	>539

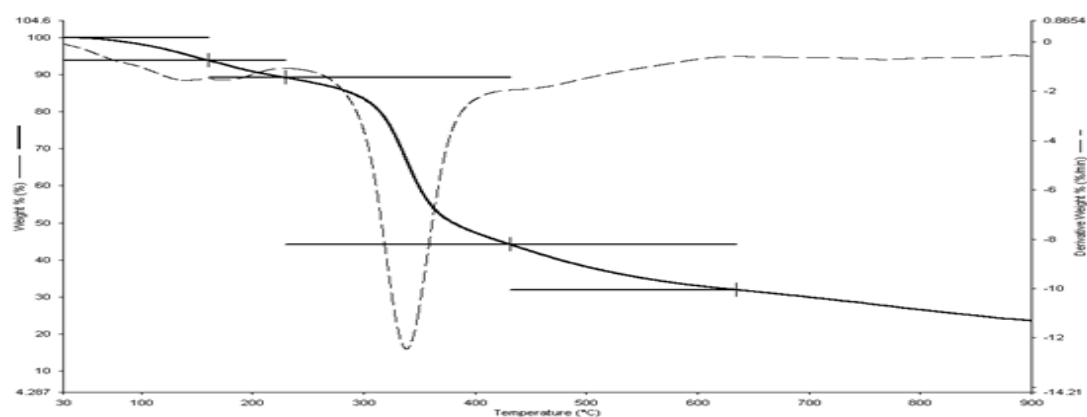


Fig. 8: Thermogravimetric analysis of Ni(II) complex.

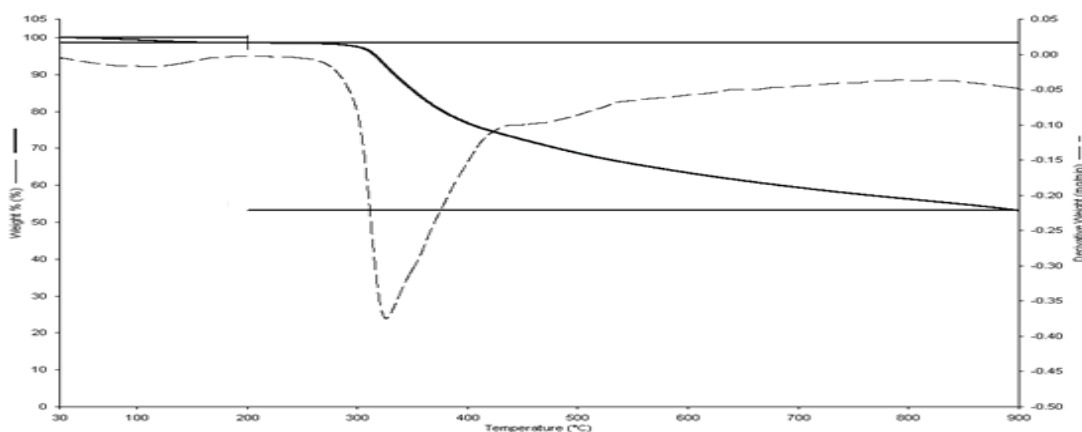


Fig.9: Thermogravimetric analysis of Pd(II) complex.

DNA cleavage studies

The degree to which the compounds could function as DNA cleavage agent was examined using supercoiled pBR322 DNA (0.5 $\mu\text{g}/\mu\text{l}$) as the target. The efficiency of cleavage of these compounds was investigated through agarose gel electrophoresis using different concentrations of compounds in 1% DMSO/5 mM Tris-HCl/50 mM NaCl buffer at pH 7.2, with and without H_2O_2 , and with 2 h incubation. The activity of the compounds was estimated by the conversion of DNA from Form I to Forms II and III. The fastest migration is detected

in the supercoiled form (Form I). If only one strand is cleaved, the supercoils relax to convert into a slower-moving form (Form II). If both strands are cleaved, a linear form (Form III) is produced, which migrates between Forms I and Form II⁽¹⁷⁾. This experiment was evaluated in the presence of H_2O_2 as an oxidizing agent. The control experiment did not show any apparent cleavage of DNA (lane 2). In the presence of the compounds [Schiff base ligand, Ni(II) and Pd(II) complexes] at different concentrations (lanes 4 to 12), the plasmid DNA was converted from Form I to Forms II and Form III at 3.5 mM (lane 7 for Schiff base ligand; Fig. 10).

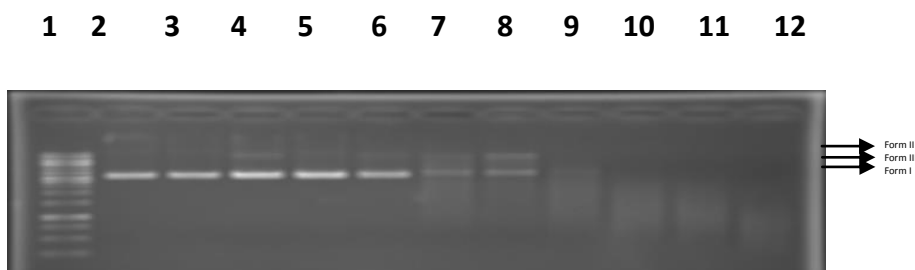


Fig. 10: Cleavage of supercoiled pBR322 (0.5 $\mu\text{g}/\mu\text{l}$) at different concentrations of Schiff base ligand in Tris-HCl buffer pH (7.2) for 2 h at 37 °C. Lane 1: DNA ladder; lane 2: DNA + H_2O_2 ; lane 3: DNA + Schiff base ligand + DMSO; lane (4-12): DNA with increasing the concentrations of Schiff base ligand (1-6 mM) + H_2O_2 + Buffer.

The DNA supercoiled was converted from Form I to Form II at 0.1 mM [lane 4 for Ni(II), (Fig 11) and Pd complexes].

The supercoiled DNA was completely degraded at (4.5 mM, lane 9 for Schiff base and at 0.2 mM, lane 5 for Pd(II) complex; Fig. 12).

To investigate the mechanism of DNA cleavage promoted by these compounds, the reactions were allowed to proceed in the presence of DMSO (lane 3) as hydroxyl radical scavengers ⁽¹⁸⁾. The addition of hydroxyl radical scavenger

completely inhibits DNA cleavage activity (Schiff base ligand and Pd(II) complex, lane 3), which is induced by these compounds (except for Ni(II) complex). This observation suggests the involvement of the hydroxyl radical in the cleavage, thereby confirming the oxidative pathways of these compounds toward DNA ⁽¹⁹⁻²⁰⁾. The results revealed that the Pd(II) complex has more cleavage activity than the other compounds; probably this may be due to the presence of Pd ion

1 2 3 4 5 6 7 8 9 10 11 12

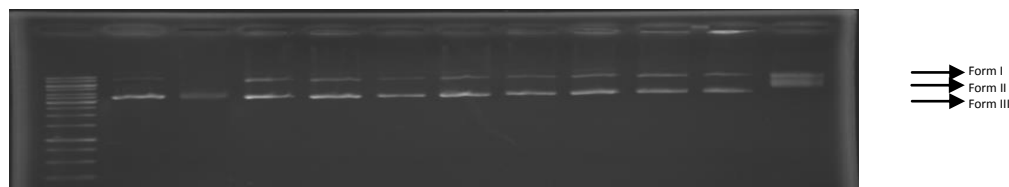


Fig. 11: Cleavage of supercoiled pBR322 (0.5 µg/µl) at different concentrations of Ni(II) complex in Tris-HCl buffer pH (7.2) for 2 h at 37 °C. Lane 1: DNA ladder; lane 2: DNA + H₂O₂; lane 3: DNA + Ni(II) complex (1 mM) + DMSO; Lanes: (4-12), DNA with increasing the concentrations of Ni(II) complex (0.1 to 1 mM)+ H₂O₂ + Buffer.



Fig. 12: Cleavage of supercoiled pBR322 (0.5 $\mu\text{g}/\mu\text{l}$) at different concentrations of Pd(II) complex in Tris-HCl buffer pH (7.2) for 2 h at 37 $^{\circ}\text{C}$. Lane 1: DNA ladder; lane 2: DNA + H_2O_2 ; lane 3: DNA + Pd(II) complex (1mM) + DMSO; Lanes: (4-12), DNA with increasing the concentrations of Pd(II) complex (0.1-1mM) + H_2O_2 + Buffer.

Conclusion

Two novel octahedral nickel(II) and square planar palladium(II) complexes, with a tridentate Schiff base ligand were synthesized and characterized using elemental analysis and various spectroscopic techniques. Results of gel electrophoresis experiments indicate that

these compounds can induce cleavage of plasmid DNA. Cleavage of DNA by these compounds has been found to be concentration dependent. All compounds show nuclease activity in the presence of oxidant, which may be due to free radical reaction (OH^*) with DNA.

Abbreviations

CT-DNA	Deoxyribonucleic acid sodium salt from calf thymus
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
EB	Ethidium bromide
IR	Infrared

ESI-MS	Electrospray ionization mass spectroscopy
NMR	Nuclear Magnetic Resonance
pBR322 DNA	Is a 4361 bp double-stranded closed circular medium copyplasmid DNA commonly used for cloning.
TMS	Tetramethylsilane
UV-Vis Ultraviolet-Visible	

الملخص العربي متضمنا العنوان والاسماء

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