An-Najah National University

Faculty of Graduate Studies.

Syntheses, Spectral, DNA Binding Studies of New Family of Copper (II) / Pentadentate SNNNS Schiff's Bases Complexes

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Dedication

Dedicated To

My Affectionate Mom

Brothers and Sisters.

Special Dedication To

My Husband, Mahmoud

With my Respect and Love,

To all People and Muslims in the world.

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First of all, I thank Allah for giving me the strength and the patience that I needed to stay on the path of learning and to finish my thesis. I would like to express my deep appreciation and respect to Prof. Ismail warad (Advisor) and Prof. Mohammad Al-Nuri (Co-advisor) for their direct supervision, fruitful discussion, encouragement and help throughout the course of this work.

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الإقرار

أنا الموقعة أدناه مقدم الرسالة التي تحمل العنوان

Syntheses, Spectral, DNA Binding Studies of New Family of Copper (II) / Pentadentate SNNNS Schiff's Bases Complexes

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The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degrees or qualifications.

Student's Name: **اسم الطالبة: هديل صادق صالح صبح**

Signature **التوقيع:**

Date **التاريخ: 2016/11/17**

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Syntheses, spectral, DNA Binding Studies of New Family of Copper (II) / Pentadentate SNNNS Schiff's Bases Complexes

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Abstract

This research focuses on new type of pentadentate ligand[N_3S_2], which received great interest as a chelating ligand in coordination chemistry, and synthesis of its Cu(II) complexes.

In part one, new pentadentate Schiff bases (E)-N1-((5bromothiophen-2-yl) methylene)-N2-(2-((E)-((5-bromothiophen-2yl) methylene) amino) ethyl)-ethane-1,2-diamine was prepared through one step reaction by mixing of 5-bromothiophene-2-carbaldehyde with diethylenetriamine without solvent.

The characteristics of the ligand were determined by several techniques like: UV-Vis, MS, DFT, EA, SEM, EDS, NMR, IR and TG/DTG.

The Cu(II) complexes **1** and **2** with general formula $[CuN_3S_2]X_2$ where X: (Cl, Br) were prepared by mixing the ligand with CuX_2 salt, X = Br, Cl. These complexes showed square pyramidal structure around the Cu(II) center. Several analytical techniques were performed for these complexes: Solvatochromism, TG/ DTG UV-Vis, MS, DFT, EA, SEM, EDS, NMR, IR and CV.

In part two, another new pentadentate ligand (E)-N1-((5-bromothiophen-2-yl) methylene)-N2-(2-((E)-((5-bromothiophen-2-yl) methylene) amino) ethyl) ethane-1,2-diamine was prepared by the same procedure , mixing of 5 -bromothiophene-2-carbaldehyde

with dipropylenetriamine, the product was characterized by : UV-Vis, MS, DFT, EA, SEM, EDS, NMR, IR,and TG/DTG.

Complexes **3** and **4** were formed through mixing N_3S_2 with Cu(II) salt, the properties of the complexes were determined by TG/ DTG UV-Vis, MS, DFT, EA, SEM, EDS, NMR, IR and CV.

The CT-DNA binding affinity of complexes **1** and **2** were evaluated by two methods: absorption spectroscopy, titration in both UV and visible regions, viscosity technique was also performed to support the results.

Chapter One
Introduction

Introduction

1.1 Coordination Chemistry:

Coordination chemistry is the most important part of inorganic chemistry which focuses on the study of the properties of various elements and their complexes [1].

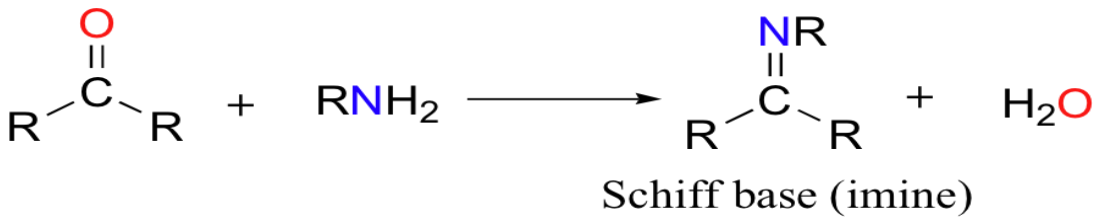
Coordinated complexes were known long time ago. Many studies and research were done about such complexes and their applications in various fields as in: dyes, mineral extraction, toxicology, inorganic chemistry, microelectronics, catalysis, ceramics, etc [2].

Transition metals played an important role in their metal complexes applications, as in industrial fields as well as biological fields [3, 4].

Hemoglobin is considered to be very important example for coordination chemistry in our bodies where Fe^{+2} coordinates to morphine and histamine [5].

1.2 Schiff Bases Ligand

Schiff bases are fundamental and attractive types of organic compounds, which have been obtained and worked out for the first time in 1864 by Hugo Schiff, which have been synthesized in two-steps reaction, condensation of primary amines with carbonyl groups followed by dehydration [6]. As shown in scheme **1**



Scheme 1: General Procedure of Synthesis of Schiff Base.

1.3 Chemistry of Schiff Bases Ligand:

Schiff bases, as previously mentioned, are organic compound that have been prepared through condensation of primary amines with carbonyl groups to produce an imine or azomethine group with the general formula RHC = N-R1, where R and R1 is alkyl, aryl, cycloalkyl, or heterogeneous groups, through this procedure. The carbonyl group (> C = O) was converted to (>C=N) as it exists in imine or azomethine group.

In general, Schiff bases which have aryl substituent are more stable than those with alkyl group.

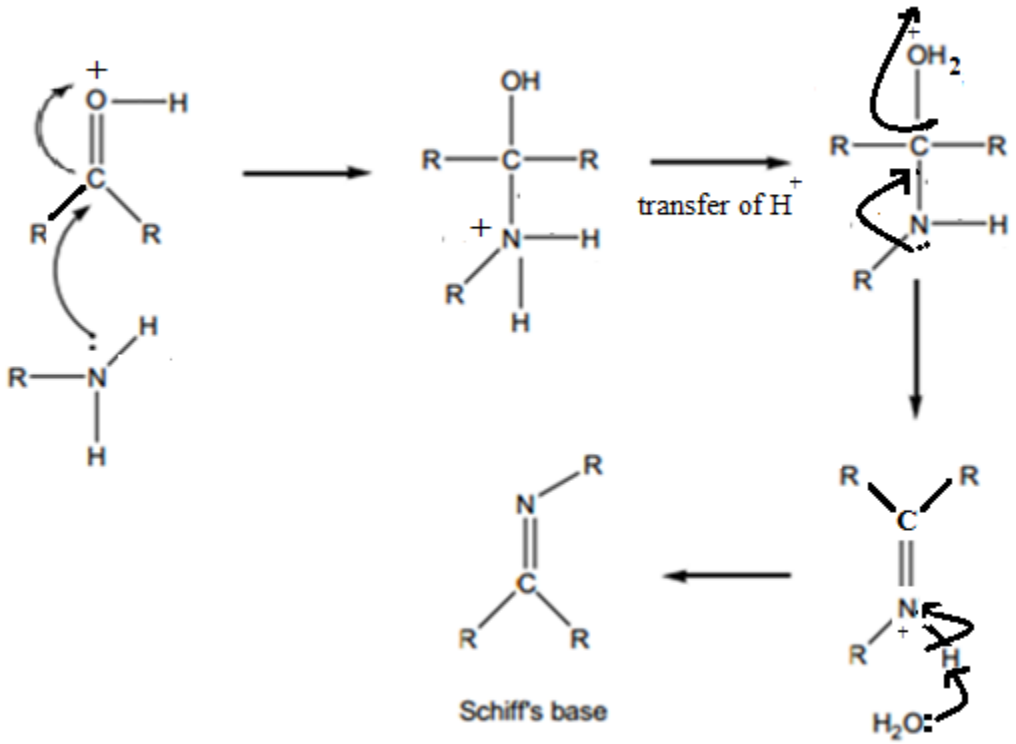
Moreover, the presence of the lone pair of electrons on nitrogen atom in the azomethine group makes the Schiff bases playing important role in biology and coordination chemistry. In fact, Schiff bases act as monodentate and polydentate chelating agents [7, 8].

1.4 The Mechanism of Schiff Base Formation and Hydrolysis:

Schiff bases are made in two - step reaction where a primary amine reacts with a carbonyl group (aldehyde or a ketone) under acidic or basic conditions [9].

The mechanism includes two steps: addition and elimination and if the reaction was carried in acidic medium, the acid must be diluted because amines are basic compounds so if the amines become non-nucleophilic, the carbinolamin cannot form. Thus, the best conditions for such reaction must be mild acidic [10].

The first step for this reaction is that the amine reacts as (nucleophile) with aldehyde or ketone as an (electrophile) to form carbinolamine then the next step is the departure of water molecule as shown in scheme 2.



Scheme 2: Mechanism of Schiff Bases Formation

The physical and chemical properties of Schiff bases can be determined by several techniques (IR, NMR, UV- visible spectroscopy, TG/ DTG, MS, DFT, EA, SEM, EDS and CV measurements) [9].

1.5 Novelty of Schiff Bases Ligand:

The synthesis of Schiff bases is an excellent method for preparing ligands, that play important roles in coordination chemistry

especially in stabilization of metal complexes and the ability to have tremendous biological activities as: antibacterial, antitumor, and anti fungal [10].

1.6 Types of Schiff Bases Ligands:

There are many kinds of Schiff bases that have been studied in different fields such as: monodentate with one donor atom, bidentate with two donor atoms, tridentate with three donor atoms, tetra dentate ligands with four donor atoms, pentadentate with five donor atoms, and hexadentate with six donor atoms. Such ligands are having ability to coordinate to metal atoms and form complexes [11].

As an example of such Schiff bases ligands the one with N, N, S donor atoms which were easy to prepare and were found to have biological activities and chemical reactivity [11, 12].

In our present work, N_3S_2 ligand is of pentadentate type that has been synthesized from triamine and 5-bromothiophene-2-carbaldehyde [13] as shown in Figure 1.1

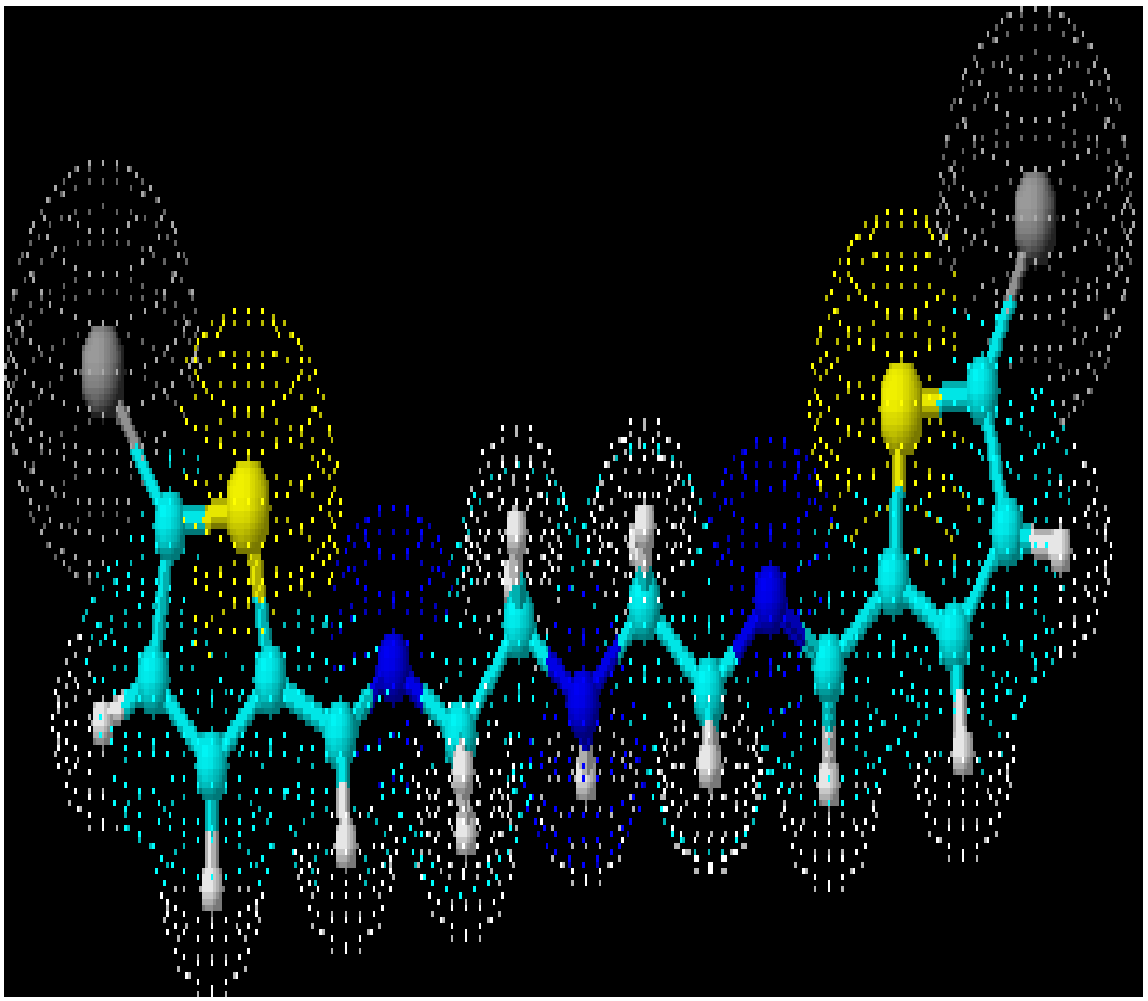


Figure (1.1): N_3S_2 Model Structure

Figure **1.1** showed the N_3S_2 model with the presence of a nitrogen and sulfur donor atoms in the backbone of the ligand made it polychelate mode ligand, very stable complexes with high reactivity toward CT-DNA binding were made available [14-16].

1.7 Complexes of Schiff Bases and Their Application:

Schiff bases have special characteristics that qualify them to act as ligands to form unique complexes in sensitivity, selectivity, flexibility and stability toward number of metals especially Cu(II).

The metal complexes of Schiff base, which were studied by azomethine group (>C=N–) have wide applications in industrial, chemical, biological and medicinal fields as: food industry, dye industry analytical chemistry, material science, agrochemical, corrosion inhibitor, catalysis, crystal synthesis, antibacterial, antifungal, antidiabetic, antitumor, antiproliferative, anticancer, and herbicidal [8,18 -20].

1.8 Biological Activity of Schiff Base Complexes:

The presence of positive charge on the metal of the complex due to electron deficiency allow them to have high solubility in polar solvents and high reactivity for binding and reacting with electron rich biological molecules [21].

Moreover, other properties for metal ion complexes of Schiff base are cationic properties, reactivity, redox chemistry photochemical reactivity, in addition to inhibition of growth of DNA on the living organisms [22].

1.9 Novelty of Copper (II) and its Application in DNA Binding:

Copper is considered to play vital role in processes occurring in the human body, and this has importance in pharmacological industries [23]. Copper participates in the function of many enzymes and hormones in our body. Therefore, copper has its tremendous role in biological activities and it has been studied for chemotherapeutic remedy as antibacterial drugs, antifungal, and anti- cancer remedy [23, 24].

The complex of Cu(II)-ligand, synthesized from ethylenediamine and 5-bromothiophene-2-carbaldehyde, has anti cancer activity due to its ability to binding with DNA and inhibits its growth [23, 24]. Copper (II) complexes participate in many catalytic processes in living organisms through electron transfer reactions of Cis-platin, as the most active anticancer drugs. But unfortunately, Cis-platin has limited usage due to its side-effects.

Therefore, it is very important to find other drugs as substitutes that have good DNA binding ability with less toxicity [25].

Accordingly, we need to work on copper as the active element in this area. Cu (II) complexes having tendency to bind with DNA in either electrostatic atraction or covalent bonds which makes the DNA more stable. Such binding of the Cu(II) complexes inhibit the DNA growth and reduce the size of cancer cells, increasing the duration of the hosts and delaying of metastasis [26,23].

In this research, the synthesis of new type of pentadentate ligand from ethylenediamine and 5-bromothiophene-2-carbaldehyde and its Cu complexes have been reported from $CuBr_2$, $CuCl_2$, by using ultrasonic waves.

Such coordination was studied by (IR, UV-Visible, T.G/DTA, EA, MS, NMR, and CV). Biological studies on CT-DNA binding were evaluated.

Objectives

1. Two new families of pentadentate SNNNS Schiff's bases and their CuX_2 complexes {X= Cl, Br) were prepared.
2. Several physical measurements such as: [IR, UV-Visible, T.G/DTA, EA, MS, NMR, SEM, EDS and CV] were investigated in order to characterize and optimize the synthesis of compounds.
3. Intrinsic binding constant K_b of the complexes bind to CT-DNA was evaluated using both uv_vis absorption and viscosity methods.

Chapter Two

Experimental Part

Materials and Instrumentation

The chemicals and the solvents were purchased from Sigma Chemical Co. and used without further purification. TLC was performed for testing the purity of the synthesized compound when needed. Elemental analyses were carried out on Elementar-Vario EL analyzer. TG/DTG curves a TGA-7 were recorded by Perkin-Elmer thermogravimetric analyzer. Perkin-Elmer Spectrum 1000 FT-IR Spectrometer for IR. TU-1901double-beam UV–visible spectrophotometer for UV-Vis. Spectroscopy. All electrochemical experiments were carried out at room temperature under argon with a three-electrode cell Volta lab 80 potentio-state PGZ402 with Pt-electrode (Metrohm, A = 0.0064 cm^2) was used as working electrode. Platinum wire spiral with diameter 7 mm was used as a counter electrode.

Synthesis of the Ligand: N-[(1E)-(5-bromothien-2-yl) methylene]-N'-(2-{[(1E)-(5-bromothien-2-yl)methylene]amino}ethyl)ethane-1,2-diamine [N3S2]

5-bromothiophene-2-carbaldehyde (0.026 mol) was added to diethylenetriamine (0.013 mol) directly without solvent, the reaction mixture was stirred for 30 min. at room temperture until the mixture became viscous, rising in temperature and the viscosity of the reaction mixture ensured the processing of condensation reaction. Dichloromethane (10 ml) was added to the mixture until complete solubility was achieved. Then the reaction mixture was sealed and left for 1 h under stirring. A colorless oily product was obtained after evaporation of the dichloromethane solvent.

Yield 85%, at RT the product is colorless oil; Molecular formula $C_{14}H_{15}Br_2N_3S_2$. ^{1}H NMR (250 MHz, $CDCl_3$): (ppm) 2.4 (t, 4H, -HNC$\underline{H_2}$$CH_2$N=CH-), 3.9 (t, 4H,-HN$CH_2C\underline{H_2}$N=CH-), 4.3 broad (s, 1H,HN only on free dissolved sample), 6.7 (d, 2H, thiophene), 7.6 (d, 2H, thiophene), 8.2 (s, 2H, –HC=N-).^{13}C NMR: (ppm) 15.8 (s, 2C, -HN$\underline{C}$$H_2CH_2$N=CH-), 61.1 (s, 2C,-HN$CH_2\underline{C}H_2$N=CH-), 125.6, 130.0, 140.0, 143.0 (d, 8C, thiophene), 156.1 (s, 2C, –HC=N-).[M^+] = 446.2 *m/z*. UV–Vis in EtOH: 240, 280 nm. IR: 3320 cm^{-1} $_{N–H}$, 3020 cm^{-1} $_{C–H\ thiophene}$, 2960-2770 cm^{-1} $_{C\text{-}H\ aliphatic}$, 1675 cm^{-1} $_{C=N}$.

Synthesis of Complexes 1-4

Solution of N_3S_2 (0.18 mmol) in 5 mL ethanol was added to the Cu(II) salt (0.17 mmol) dissolved in 20 mL freshly distilled ethanol, both the color change (brown to blue) and temperature rizing were detected directly upon addition. The product complexes were less soluble in ethanol and started to precipitate. By vacuum reduction of solution volume, most of the blue Cu(II) complex was precipitated, which was filtered and washed well with cold ethanol and ethyl acetate.

Complex 1

Yield 90%, m.p. = 204 °C. MS m/z 507.2 [M^{+2}] Anal. Calc. for [$C_{14}H_{15}Br_2CuN_3S_2$]Cl_2 Calculated: C, 28.81; H, 2.59.Found C, 28.66; H, 2.45%. Conductivity in water: 185 (µS/cm). IR (KBr, νcm^{-1}): 3360 (ν_{H2O}), 3250 (ν_{H-N}), 3010(ν_{C-H})thiophene, 2930 (ν_{C-H}), 1655 ($\nu_{C=N}$), 1590 (ν_{N-H}), 1150 (ν_{N-C}), 520 (ν_{Cu-N}). UV–Vis in water: 250 (2.2 x 10^4 $M^{-1}L^{-1}$) and 615 nm (2.8 x 10^2 $M^{-1}L^{-1}$).

Complex 2

Yield 92%, m.p. = 220 °C. MS m/z 507.2 [M^{+2}] for [$C_{14}H_{15}Br_2CuN_3S_2$] Br_2 Calculated: C, 25.00; H, 2.25%. Found C, 24.88; H, 2.10%. Conductivity in water: 210 (µS/cm). IR (KBr, νcm^{-1}): 3360 (ν_{H2O}), 3280 (ν_{H-N}), 3030(ν_{C-H})$_{thiophene}$, 2910 (ν_{C-H}), 1658 ($\nu_{C=N}$), 1580 (ν_{N-H}), 1180 (ν_{N-C}), 510 (ν_{Cu-N}). UV–Vis in water: 260 (2.3 x 10^4 $M^{-1}L^{-1}$) and 625 nm (2.2 x 10^2 $M^{-1}L^{-1}$).

DNA Binding Experiments

The experimental titration absorption spectra were carried out in Tris–HCl buffer (5 mM Tris–HCl/50 mM NaCl buffer of pH 7.2) with Cu(II) complex concentration = 5.0 x 10^{-5}M (for complex **1**) and1.0 x 10^{-5}M (for complex **2)** constant throughout the experiment. The CT-DNA concentrations varied between 0 and 5.0 ×10^{-5} M (for complex **1**) and 0 and 1.0 ×10^{-3} M (for complex **2**) by keeping the total mixture volume constant to 10.0 mL. The resulting mixed solution of Cu(II)/CT-DNA stands to equilibrate 10 min at room temperature for each trial before being subjected to uv_vis absorption measurements [35-39].

Viscosity Experiments

Viscosity experiments were performed on Ubbelodhe viscometer at 25.0 (±0.1) ^{o}C. Flow time was measured with stop watch for different concentrations of complexes (0, 2.5x10^{-5}, 6.25x10^{-5}, 8.75x10^{-4} 1.12x10^{-4} and 1.37x10^{-4}) and fixed concentration of DNA = 5.0 x 10^{-4} M in in Tris–HCl buffer. Each sample was measured three times and an average flow time was calculated. Data were presented as $(\eta/\eta^{o})^{1/3}$ versus binding ratio [Cu]/[DNA] [35-41], where η is the viscosity of DNA in the presence of compound, and η^{o} is the viscosity of pure DNA solution.

Chapter Three

Results and Discussion

Part I

Physicochemical, syntheses and coordination behavior of pentadentate N_3S_2 ligand derived from diethylenetriamine: mononuclear dicationic Cu(II) complexes, spectral, DFT-Computational, solvatochromism, thermal and electrochemical

Introduction

Multidentate ligands are used frequently in organometallic area because of their poly bonding ability and are regarded suitable toward complexation with several metal ions [1-3]. A system with multidentate ligands is a critical point for the success of coordination projects. One of the famous multidentate ligands is Schiff base type which has attracted researcher's attention mainly due to their ability to coordinate metals *via* several sites which stabilize the structures around the metal center [3-8]. In general, Schiff base-transition metal complexes have been broadly investigated because they can coordinate with metal ion centers by one or more sites that lead to synthesis of several types of complexes with different metals centers, stereochemistry and broad range of applications [8-10]. Recently, several reports showed that such ligands and their complexes were interesting for designing new drugs with high biological activities as anti-cancer, enzyme inhibition, anti-malarial, antifungal, antibacterial and anti-inflammatory activity [8-16].

Copper element is very essential in bodies, plays critical roles in biological activities that contain electron transfer reactions. Actually, Cu(II) complexes with, {S, O, N} donor chelators are excellent anti-cancer agents because of their strong DNA binding ability [4-10]. Due to high selectivity and permeability of the copper(II) to cell membranes of the cancer cells, copper is considered to be one of the most effective anti-tumor agents with low cost and side effects [7-16]. Thus, huge numbers of such complexes with several ligand types have been prepared and evaluated against cancer

cells [12-24]. Pentadentate Schiff bases ligands have received less attention compared to mono, di, tri-and tetra-dentate type, due to their difficult synthesis and unexpected multimode of coordination behavior [15-24].

Accordingly, several coordination modes of N_3S_2 pentadentate ligand derived from thiophene and their structural aspects are interesting as well as CT-DNA- binding affinity applications of their Cu(II) complexes, and this work reports the synthesis of two mono nuclear copper(II) complexes obtained with new pentadentate N_3S_2 ligand, CT-DNA binding affinity of such complexes was evaluated.

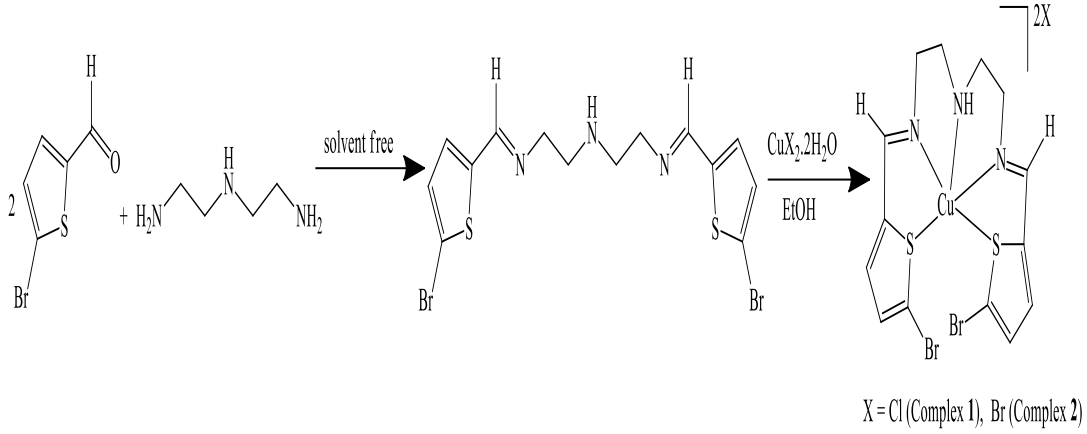
Results and Discussion

Synthesis

Solvent-free condensation of 5-bromothiophene-2-carbaldehyde and diethylenetriaminein a 2:1 M ratio, furnished new pentadentate Schiff base(E)-N1-((5-bromothiophen-2-yl)methylene)-N2-(2-((E)-((5-bromothiophen-2-yl)methylene)amino)ethyl)ethane-1,2-diamine(N_3S_2) ligand in an open atmosphere in a very good yield, as shown in Scheme 1. The desired Cu(II) complexes were made available by mixing equivalent amounts of N_3S_2 ligand with the hydrated CuX_2 salt at room temperature in ethanol. The formation of complex **1** and **2** was confirmed by color change (from brown to blue) and temperatures rise. The isolated complexes were spectrally and thermally analyzed.

The complexes have excellent solubility in polar solvents as water, DMSO and DMF, and poor solubility in alcohols like ethanol, which indicates that the complexes are ionic. The molar conductivity of the aqueous complexes solutions was 185-210 µS/cm which is within the range of [1:1] electrolyte. Structures of the N_3S_2 ligand and its complexes were experimentally analyzed by using: EA, MS, FT-IR, CV, NMR, UV-vis, SEM, EDS and TG/DTG physical analyses. The DFT theoretical calculations of free ligand was performed using Gaussian 09 program. The analysis of the complexes revealed the construction of square pyramidal complexes of types $[Cu{:}N_3S_2]X_2$. Mass spectrometry, the conductivity and water solubility of

the complexes supported their dicationic mononuclear salt nature, as illustrated in Scheme 3.



Scheme 3. Synthesis of the N_3S_2 Ligand and its Desired Cu(II)Complexes.

Optimized Structure of N_3S_2

Since the ligand is oily in its nature at room temperature, it was not possible to collect stable and suitable crystal for X-ray diffraction measurement. Therefore, the structure of ligand was subjected to DFT-B3LYP levels optimization process. The optimized structure along with atoms numbered is shown in Fig. 3.1. The ligand optimized molecular structure revealed that E, E isomers around both C=N groups as kinetically favored isomer with less internal steric repulsion effect, which forced the S-heterocyclic rings to be in the same plane that creates semi-vacant site center suitable to be occupied by metal ions. The presence of two conjugated aromatic rings to two C=N groups left N-H bond with higher acidity for ligand [4-10].

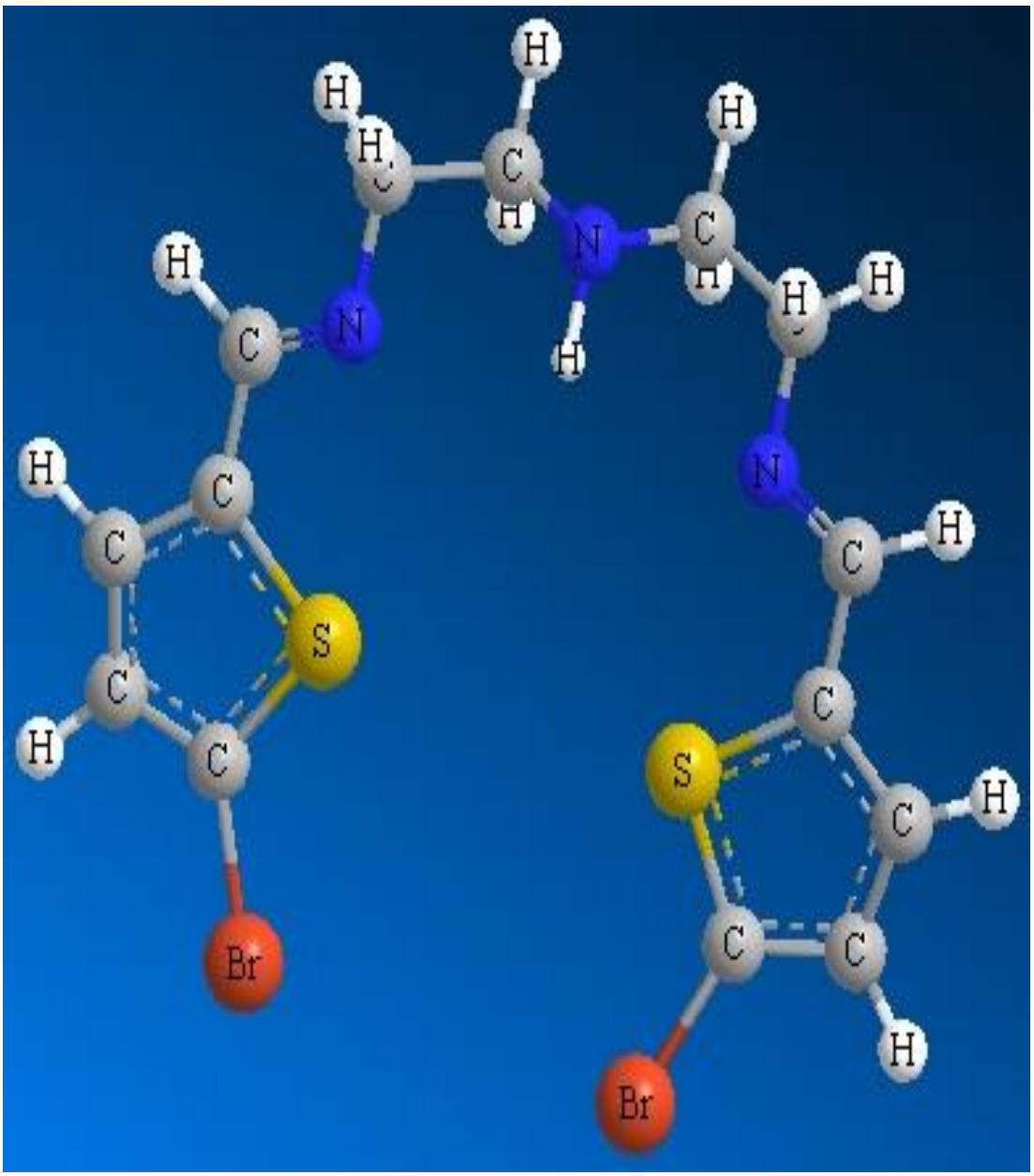


Fig. (3.1): DFT Optimized Molecular Structure of Desired N_3S_2 Schiff Base Ligand.

Mass Spectrometry and Elemental Analysis

The elemental analysis of N_3S_2 ligand and its Cu(II) complexes were compared with the proposed molecular formula. For the N_3S_2: Calcd. form $C_{14}H_{15}Br_2N_3S_2$: C, 37.43; H, 3.37%. Found: C, 37.25; H, 3.21%). EI-MS of the ligand is agrees with its assigned structure [M^+] *m/z* = 446.2[M^+] and 448.2 [M^++2], (446.9 theoretical) as seen in Fig.(3. 2a).

The ESI-MS data of the desired complexes are consistent with their proposed formula weight and supported their monomeric dicationic structural formula. The mass to charge (m\z) theoretical value of complex **2** showed *m/z* = 509.2 [M^+], the same complex revealed experimentally molecular ion peaks [M^++1] at 510.2 and [M^++2] at 511.1.Such results confirm the dicationic mononuclear nature of the complex, as well as its molecular formula, as seen in Fig.(3. 2b).

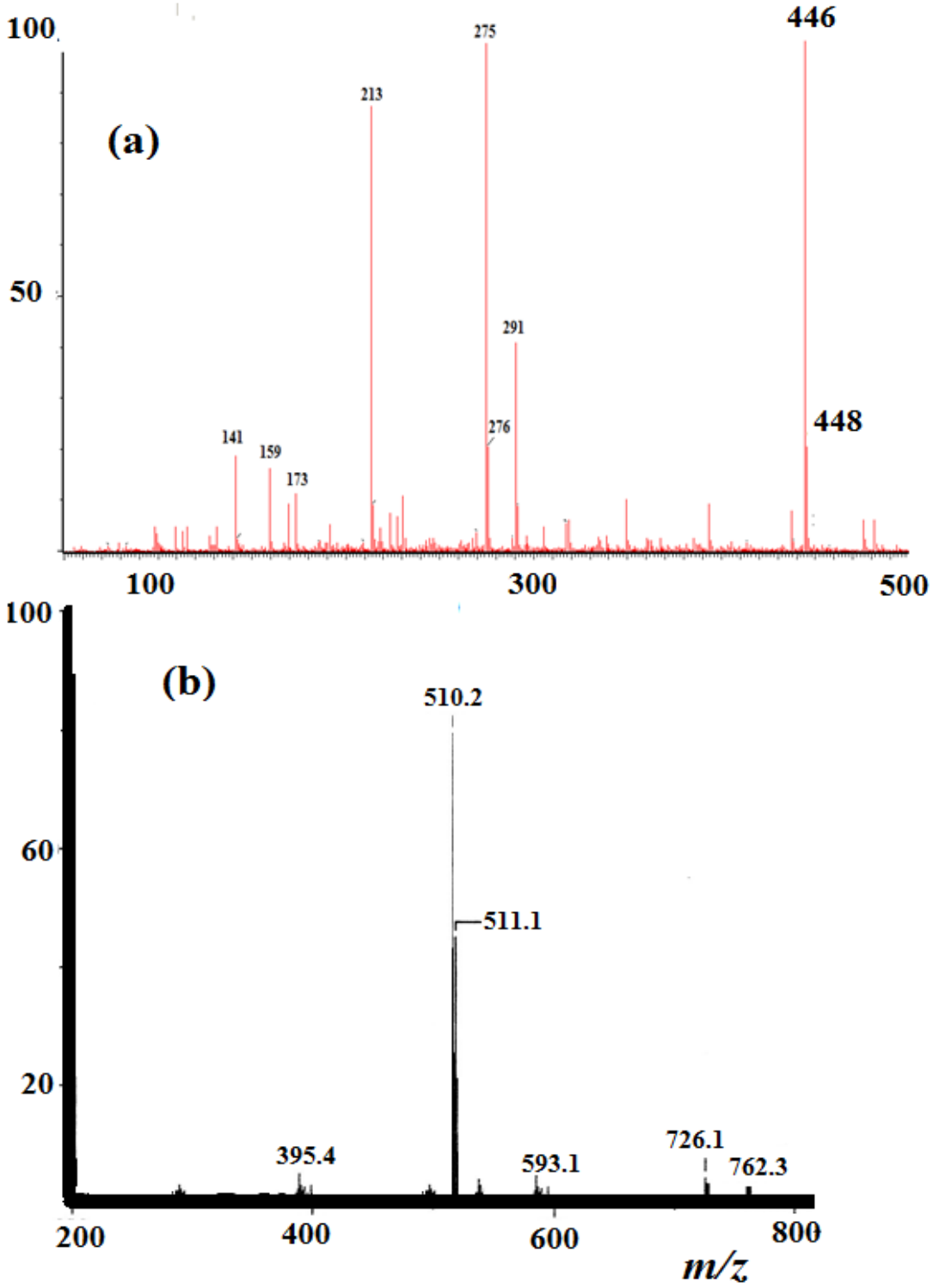


Fig. (3.2): (a) EI-MS Spectrum of the N_3S_2 Ligand and (b) ESI-MS Spectrum of Complex **2**.

^{1}H and ^{13}C-NMR Spectra of the Ligand

The ^{1}H-NMR of N_3S_2 ligand was experimentally performed in $CDCl_3$ and illustrated in Fig. (3.3a), and the theoretical calculation was shown in Fig. (3. 3b). Meanwhile, the comparison between theoretical and experimental ^{1}H NMR was plotted in Fig. (3.3c). Typical ^{1}H NMR spectrum showed two sharp triplet signals at δ 2.4 and 2.9 ppm due to =$NCH_2C\underline{H_2}NHC\underline{H_2}CH_2N$=and =$NC\underline{H_2}CH_2NHCH_2C\underline{H_2}N$=, respectively. No signal of NH proton was detected due to the D/H rapid exchange parallel to the $CDCl_3/CHCl_3$ signal at 7.2 ppm formation.The signal of N-H appears as broad singlet at 4.3 ppm in a freshly dissolved ligand.This result is in consistent with the acidity of NH theoretical calculation. The thiophene protons were cited as two multiple signals at δ 6.7 and 7.6 ppm, azomethine proton N=CH was detected as singlet at 8.2 ppm.

The theoretical ^{1}H-NMR calculation illustrated several peaks belonging to the aliphatic, resonated and azomethine protons of the prepared ligand which is consistent with the experimental spectrum. For comparative reason, the theoretical ^{1}H-NMR was plotted against the experimental one, as shown in Fig. (3.3c), Figure 3.3c revealed matched-linear relation between theoretical and experimental ^{1}H-NMR, that reflects a high degree of consistency.

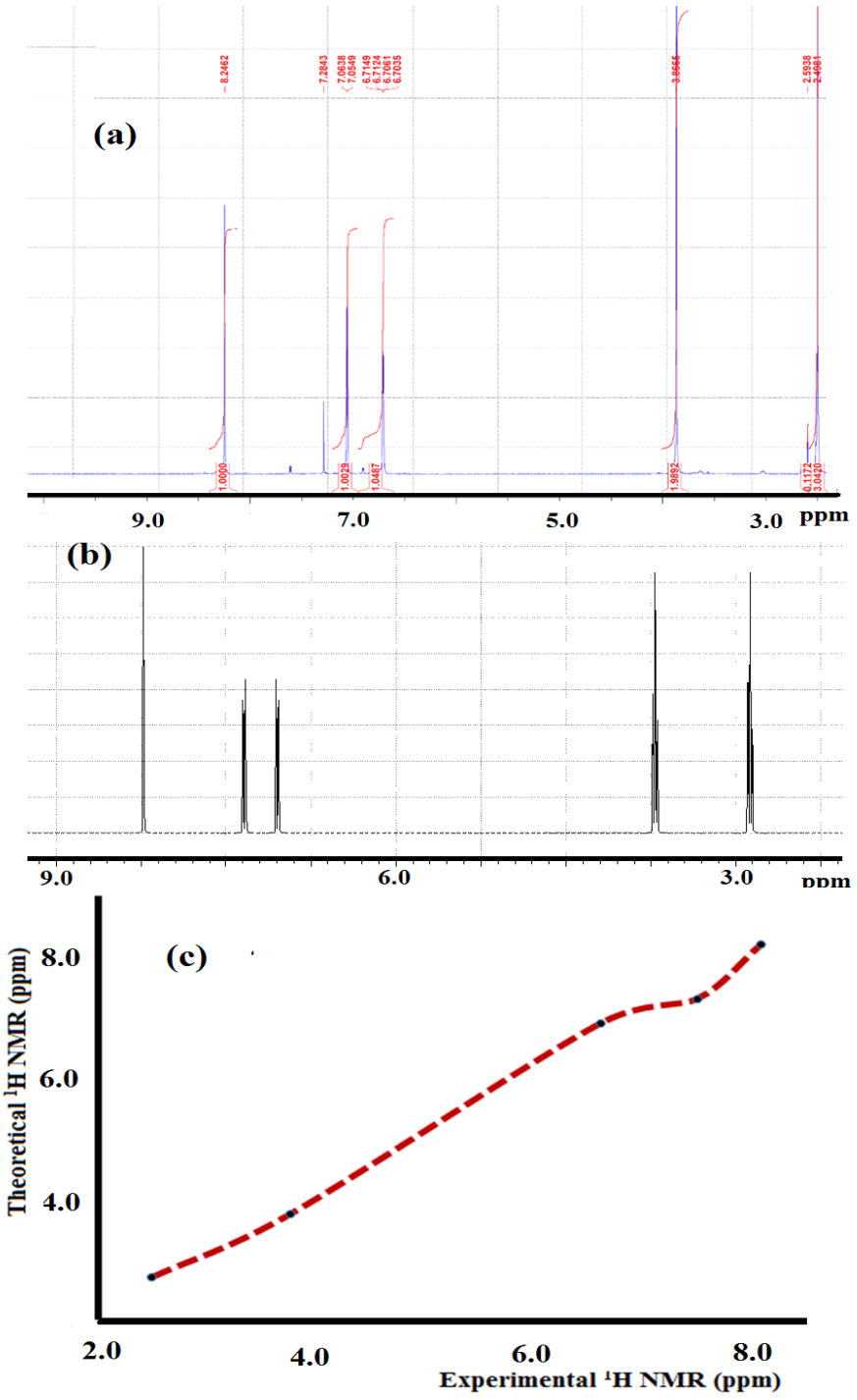


Fig. (3.3): ^{1}H NMR Spectra of Desired Ligand (a) Experimentally in $CDCl_3$ at RT, (b) Theoretically (c) Experimentally in Comparison to The theoretically Obtained.

The ^{13}C NMR spectrum of the desired ligand was shown in Fig. (3.4). Which revealed two signals at δ 15.0 ppm (CH_2NH) and 61.1 ppm (CH_2N=).The four aromatic carbons appeared at δ 125.6, 130.0, 140.0, 143.0 ppm. The signal of azomethine carbon atom (N=CH) appeared at 156.0 ppm .

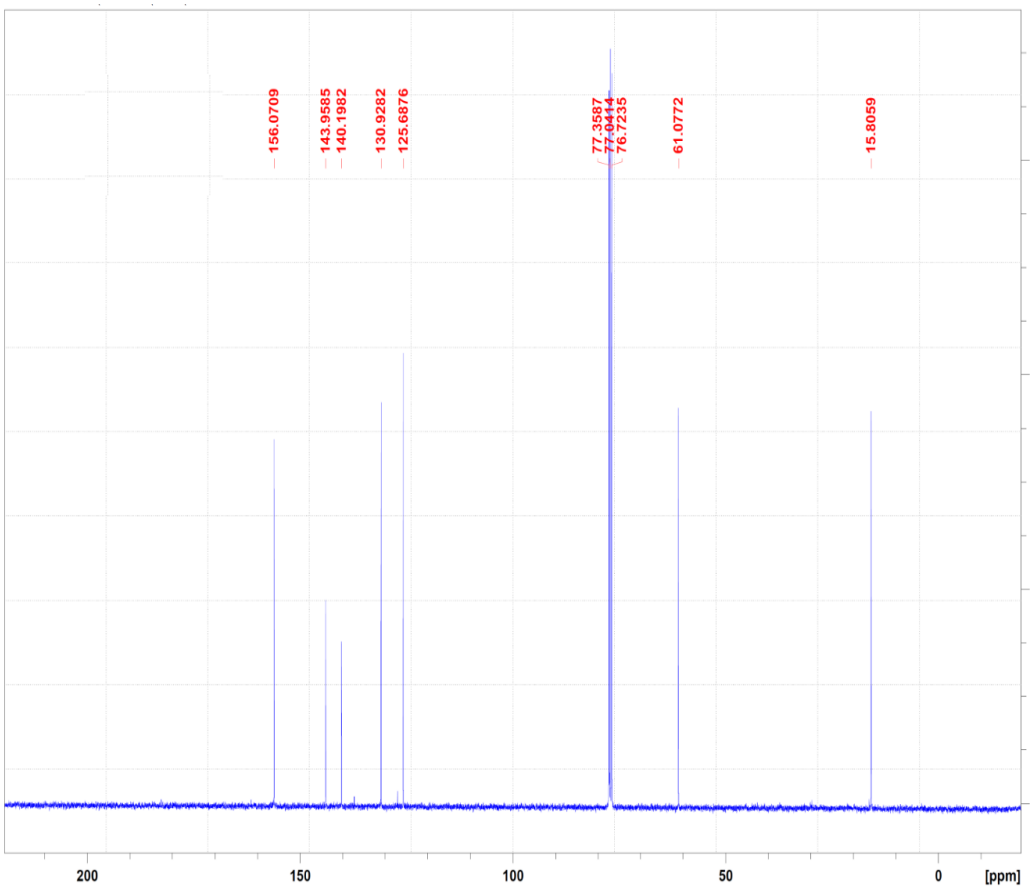


Fig. (3.4): ^{13}C NMR Spectrum of N_3S_2 Ligand Dissolved in $CDCl_3$ at RT.

FT-IR and DFT-IR Spectral Analysis

FT-IR spectroscopy was utilized to monitor the condensation reaction during the ligand formation. The FT-IR of the starting materials 5-bromothiophene-2-carbaldehyde and N1-(2-aminoethyl) ethane-1,2-diamine were recorded before and after condensation as illustrated in Fig.

(3.5). The ligand formation was confirmed by two major changes: the primary N-H stretching vibration in diethylenetriamine at 3340 and 3270 cm^{-1} Fig.(3.5a) was reduced to one single peak at 3240 cm^{-1}, due to the ligand secondary amine formation Fig.(3.5b). Stretching vibrations belongs to C=O of carbaldehyde at 1742 cm^{-1} was reduced by ~ 60 cm^{-1} due to the C=N- (1688 cm^{-1}) ligand group formation as shown in Fig.(3.5 c).

DFT-IR theoretical calculation was also carried out for the free ligand, as seen in Fig.(3.5d). The DFT-combinatorial calculation was performed for a free molecule in gaseous state meanwhile; experimental calculation was done for the molecule in solid state. It was found that experimental results are smaller than theoretical calculations [25-27].

The theoretical and experimental FT-IR spectra are illustrated in Fig.(3.5c) and (3.5d) which show a high degree of agreement.

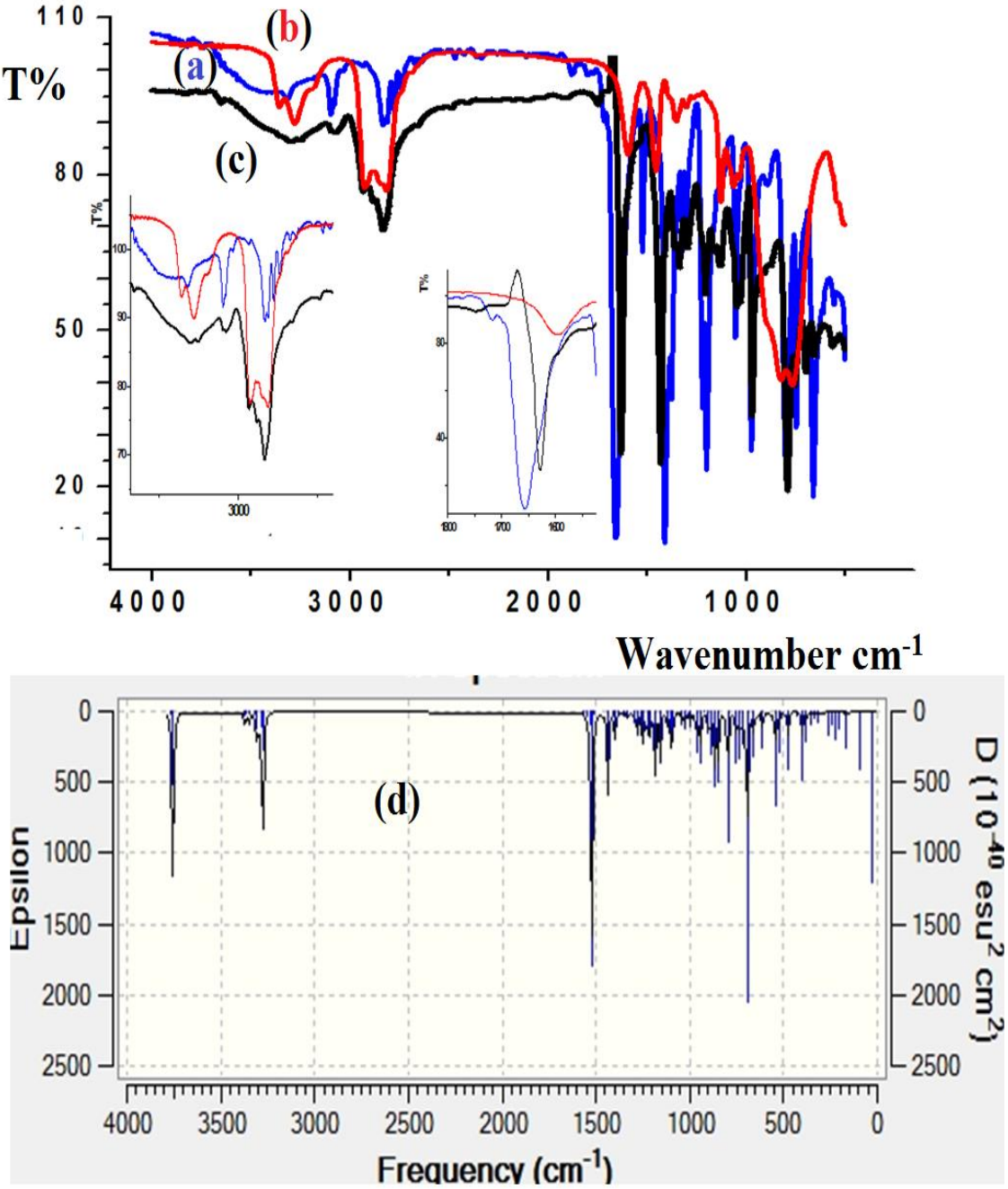


Fig. (3.5): IR Spectra of: (a) 5-Bromothiophene-2-Carbaldehyde, (b) Diethylenetriamine and (c) N_3S_2 Ligand, and (d) DFT- IR Theoretical Calculation of N_3S_2 Ligand.

The IR spectra of the synthesized complexes showed high similarity with IR-spectra of free ligand with slightly down chemical shifts, as seen in Fig.(3.6). Figure 3.6 showed the IR differences for both the ligand and

complex **1**. In the complex, water peaks vibrations appear at ~ 3425$\nu_{(O-H)}$/1422$\nu_{(bend)}$ indicates the presence of uncoordinated water molecules in complex **1** lattice and not in the ligand. Since the complex is water- soluble and the ligand is water –insoluble, $\nu_{(N–H)}$ which absorbs at 3320 cm^{-1} in the ligand was shifted to lower absorption 3250 cm^{-1} in the complex. Such result confirms the coordination of N-H proton with copper center. In addition, $\nu_{(C=N)}$vibration of complex was reduced by ~ 23 cm^{-1} (from 1688 cm^{-1} to 1665 cm^{-1}) due to C=N→ Cu(II) bond formation. The most important part in IR study, is the presence of a sharp peak at 510 cm^{-1}(only in the complex spectrum) due to $\nu_{(Cu-N)}$ vibrations, which support the formation of new N→Cu(II) bond.

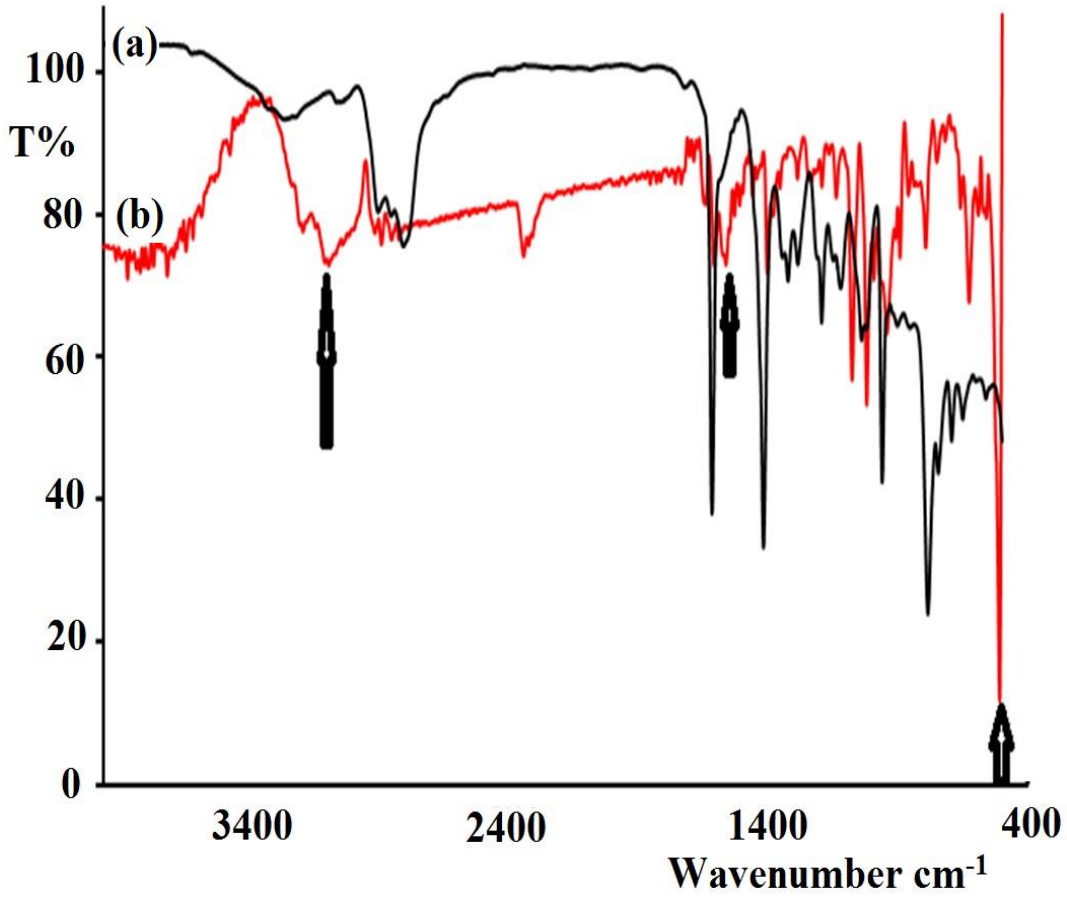


Fig. (3.6): IR Spectra of: (a) N_3S_2 Ligand and (b) Complex **2**

Ligand Frontier Molecular Orbital Calculation

The evaluation of HOMO/LUMO energies are beneficial to estimate the chemical behavior of the desired ligands. HOMO/LUMO energy gap calculation controls many of the chemical reactivity descriptors such as: hardness, electrophilicity, quantum chemistry terms, chemical potential, electronegativity and local reactivity [25-28]. The nuclophilicity of the molecule, for example, was evaluated by the ability of ligand to donate electrons which is associated with HOMO energy level, while electron affinity is characterized by LUMO. The pictorial shapes of the HOMO /LUMO orbital of the ligand in the gaseous phase is shown in Fig.3.7. The HOMO is located at -0.19224eV while the LUMO is located at -0.05605 eV with 0.13619eV energy gap. The calculated energy gap value revealed the easiness of HOMO to LUMO electron transfer. Such results reflect the fact that HOMO behaves as predominate molecular orbital which is consistent with the nature of the pentadentate ligands as strong nucleophiles [22-31]. Several parameters related to HOMO/LUMO energy gap value were theoretically calculated and illustrated as shown Table 1.

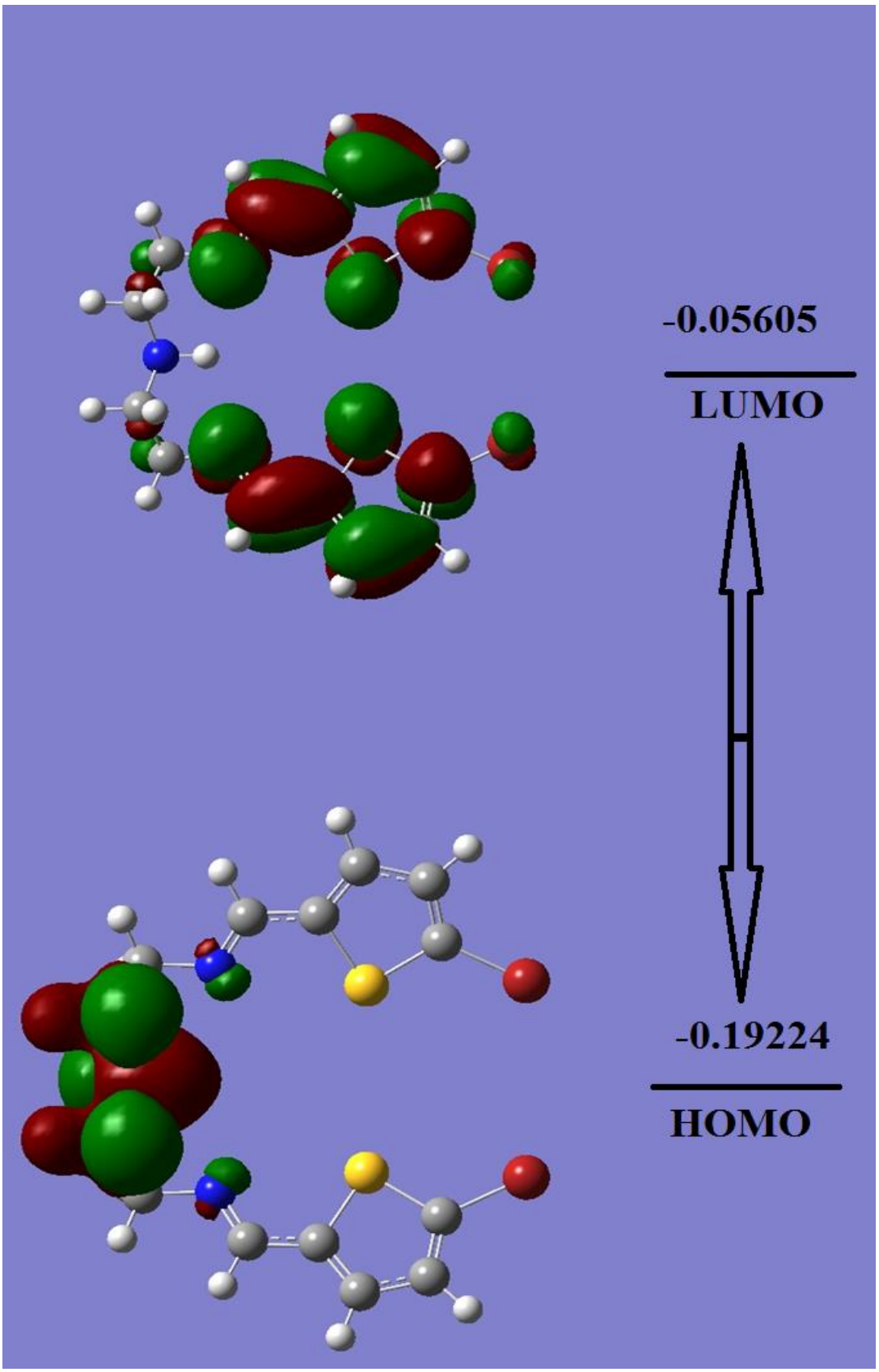


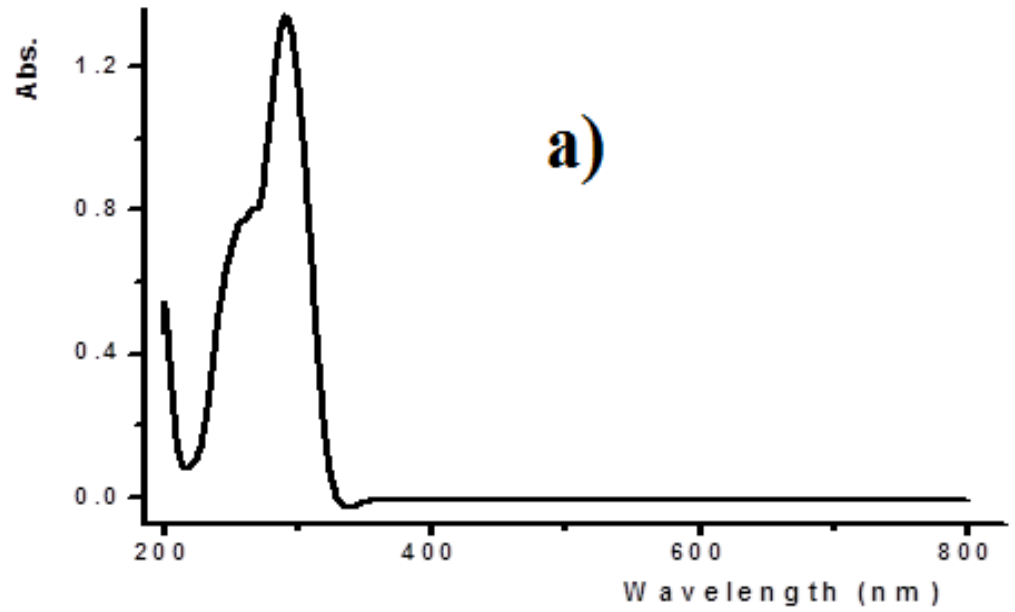
Fig. (3.7): HOMO and LUMO Molecular Orbitals Plots of N_3S_2 Ligand.

Table (3.1): Calculated Energy Values by B3LYP/3-21G.

Basis set	B3LYP/3-21G
E_{HOMO}	-0.19224
E_{LUMO}	-0.05605
Chemical potential (μ)	-0.24829
Dipole moment	2.49140
Chemical hardness (η)	0.06808
Electronegativity (*X*)	0.24829

UV-Vis. Spectral Analysis of the Ligand

The electronic absorption behavior of N_3S_2 ligand and its complexes are measured at room temperature in ethanol and in water, respectively. The absorption bands of the ligand are assigned also by TD-DFT/B3LYP/3-21 theoretical calculation. The spectrum of the N_3S_2 demonstrats high intense transitions at λ_{max} = 240 (sharp) and 280nm (3.0 x $10^4 M^{-1}L^{-1}$) which is associated to π-π* electron transition, as seen in Fig.(3.8a). Time-dependence DFT UV–vis spectra absorption maximum was found to be 275 nm (sharp) and a broad signal at ~ 1100 nm (out of range > 800nm), as seen in Fig.(3.8b). UV-Vis. Theoretical calculations of molecular orbital geometry revealed the visible absorption maximum of N_3S_2 ligand which corresponds to the electron transition from HOMO to LUMO. A good match between the theoretical-TD-DFT compared with experimental UV-measurement analysis was obtained with slight ~5 nm shift due to solvent effect [26-30].



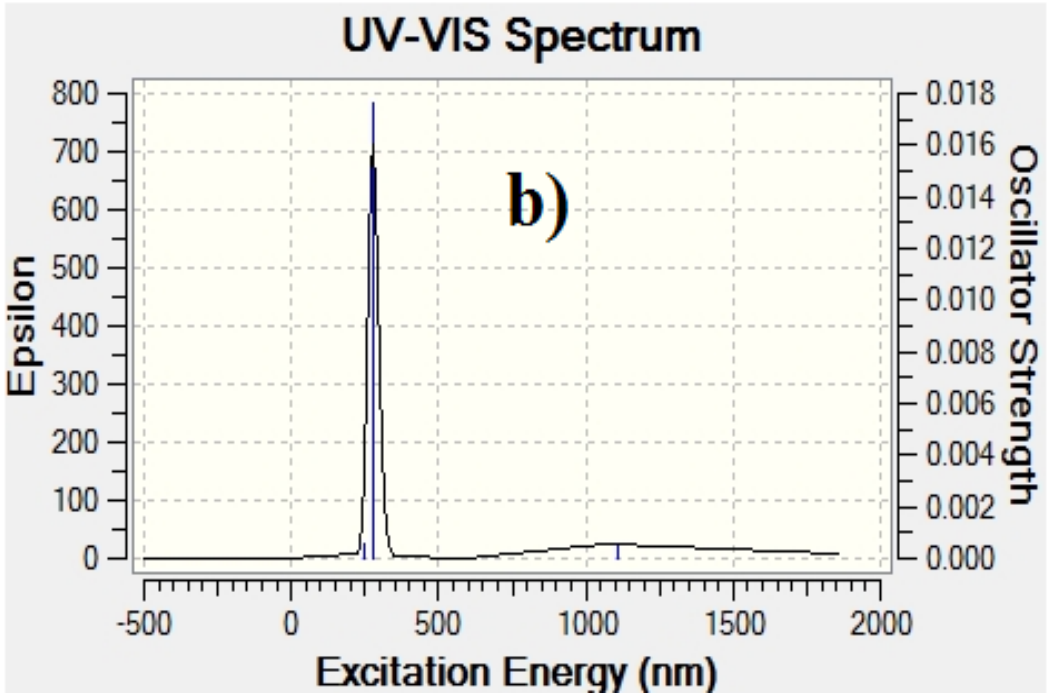


Fig. (3.8): UV-Vis. Spectroscopy Spectra of the Ligand a) Experimentally (in Ethanol at RT), and b) TD-DFT/B3LYP/3-311 Theoretically (in Gaseous State).

In water, complex **1** and **2** revealed similar electronic spectral behavior, the signals of π-π* electron transition was shifted from 280 nm (fee ligand) down to ~ 250 nm in complexes, due to the coordination of the ligand with Cu(II) center. Additionally, broad band's appearing in the visible regions 600-640 nm upon complexation which is not recorded in free ligand nor in CuX_2 starting material spectra. Such visible band revealed the blue color N→Cu(II) complexes formation. The blue color absorption assigned to d - d electron transition which belongs to the square pyramidal geometry around Cu(II) complex centers, as illustrated in Fig.(3.9) (for complex **1**).

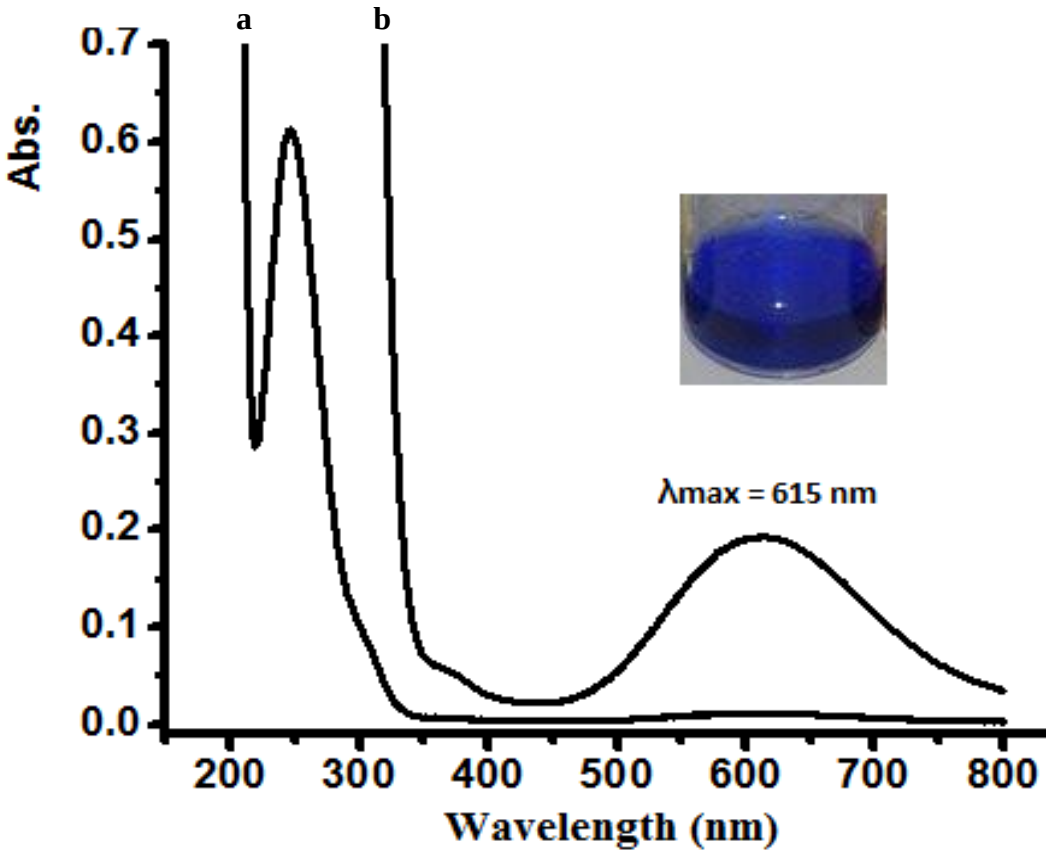


Fig. (3.9): UV–Vis Spectra of Complex Dissolved in Water at RT (a) 5 x 10^{-5}M and (b) 5 x 10^{-4} M Concentrations.

Solvatochromism of Complex 2

Water (H_2O), ethanol (EtOH), dimethylformamid (DMF), and dimethylsulfoxid (DMSO) are solvents that served to evaluate the solvatochromism phenomenon which is limited up to the solubility of the desired dicationic complexes. The vis. spectra of complex **2** in such solvents revealed broad band between 600-800 nm. due to Jahn–Teller effect expected in Cu(II) center (with d^9 and five coordination number) such complexes revealed relevant positive λ_{max} shifts when the polarity of solvents increased.

The visible spectrum of complex **2** shifted depending on the solvents donor number polarity, as seen in Fig.(3.10.I). Bathochromic shifts were recorded due to the direct coordination of the polar solvents on to the vacant sites of the five coordination Cu(II) center with different strengths, which agrees with the mechanism of solvatochromism behavior of such complexes [32-34].

Accordingly, the λ_{max} values of complex **2** in different solvents increased linearly when Gutmann's donor number (DN) of the selected solvents increased. The linear trend of λ_{max} of complex **2** against DN is presented in Fig.(3.10.II)

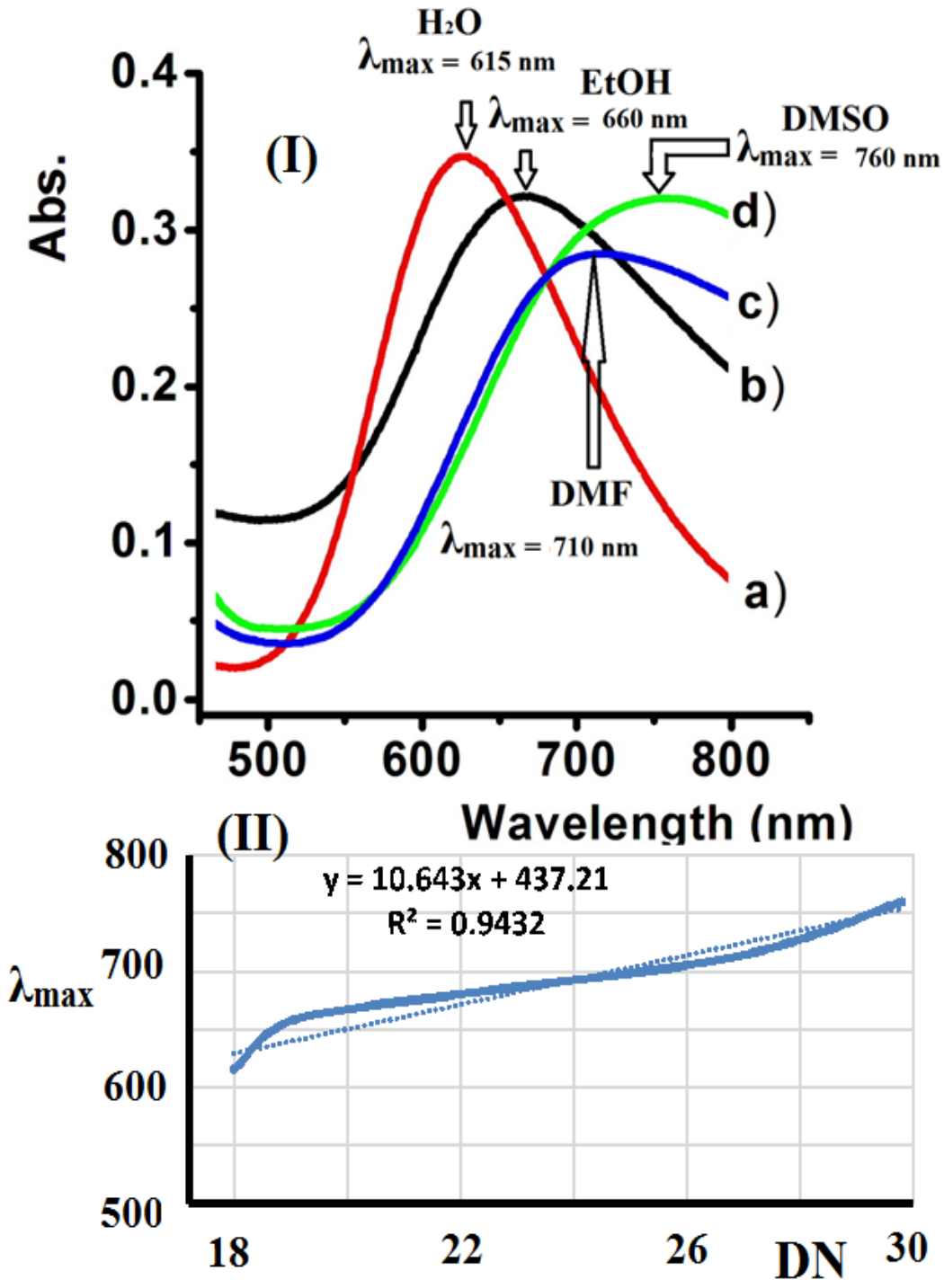


Fig. (3.10): (I) Absorption Spectra of Complex **2** Dissolved in Selected Solvents, (II) Dependence of λ_{max} of Complex **2** on the Solvent Gutmann's Donor Number Values (DN).

Thermal Analysis Investigation

The thermal behavior of N_3S_2 ligand and complex **2** have been performed by TG\DTG in a range of 0–900 °C temperature in an open atmosphere as illustrated in Figure (3.11).

Fig. (3.11a) showed TG curve of N_3S_2 ligand**,** which displays a noticeable thermal stability up to 140 ˚C. Representative decay started from 140 °C and ended at ~260°C.The ligand was totally decomposed to light gases species like: SO_2, NO_2, CO_2, in a broad step (with ~100% Wt. lost). No intermediate degradation steps, or residue were recorded, and the compound processed with simple one step thermal decomposition mechanism.

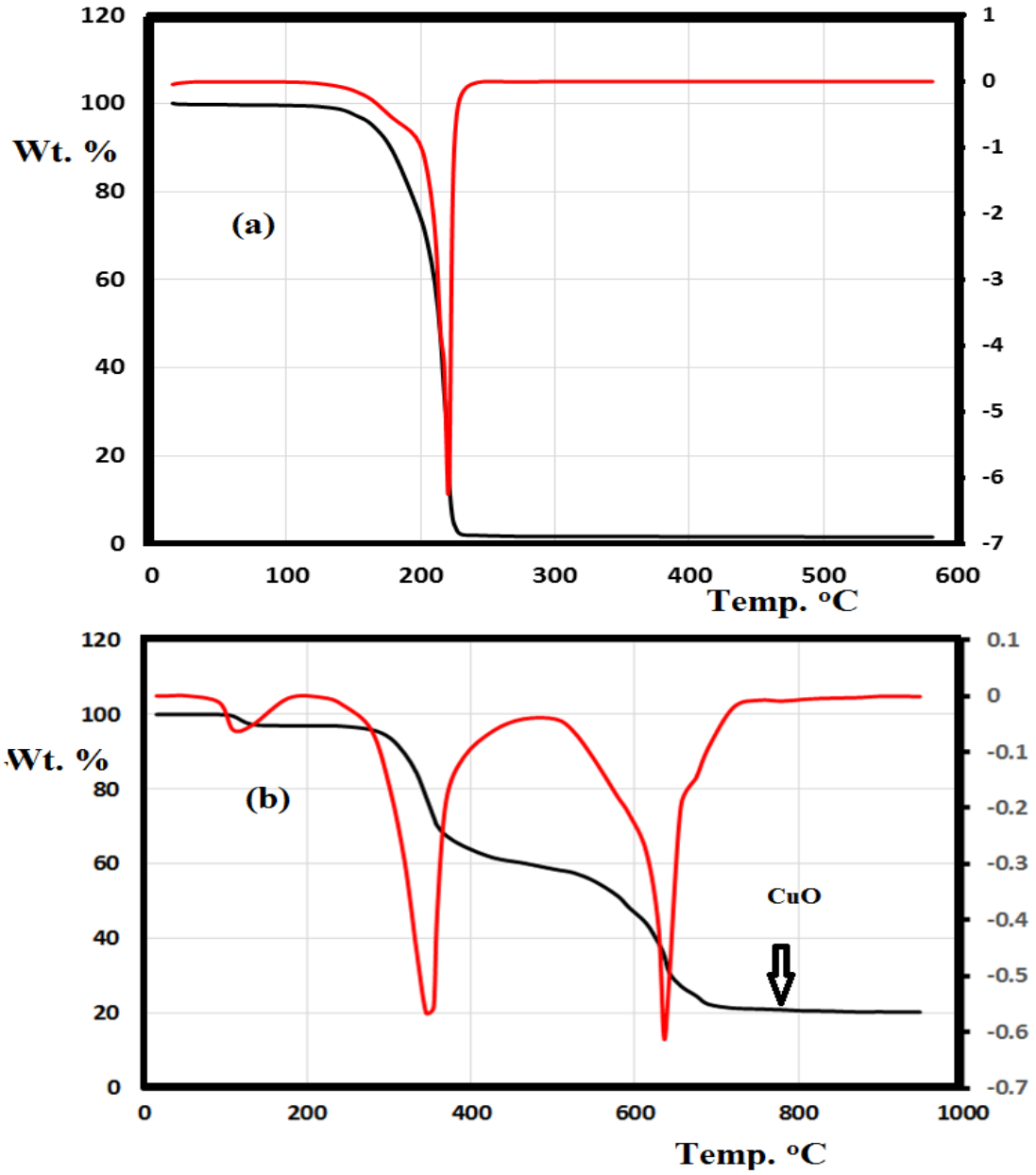


Fig. (3.11): TG/DTG Thermal Curves of: (a) the Ligand and (b) its Complex **2.**

Complexes **1** and **2** revealed similar thermogravimetric behavior, the TG/DTG spectra of complex **2** explained in three main general steps, as shown in Fig.(3.11b).The first minor step (<100°C) was due to loss of uncoordinated water molecules, which agrees with IR results.

The second decomposition step at 280-450ºC, (40% of Wt. lost), where the ligand is de-structured from the backbone of complex **2** to give $CuBr_2$ as final product of the step. The third step started at 460ºC and ended up at 750 ºC. During this step, $CuBr_2$ reacts with O_2 to produce copper oxide (Cu=O) as final product.

Electrochemistry of Complex 2

As a representative example, the electron-transfer conductance of complex **2** in acetonitrile was evaluated by cyclic voltammetry, as shown in Fig. (3.12). The ligand is electro inactive over 0 to -1.5 V studied range, where complex **2** exhibited redox one electron transfer, the electrochemical behavior $E_{1/2}$ = – 0.760 V, *i*pa/*i*pc =0.92 and Δ*E*p =130 mVat a Pt working electrode; plot of *i*pc vs $v^{1/2}$ is linear. All of these parameters suggested the Cu(I)/Cu(II) redox process tends to become quasi-reversible with response at-650 and -780mV *vs.*$Ag/AgNO_3$ reference electrode.

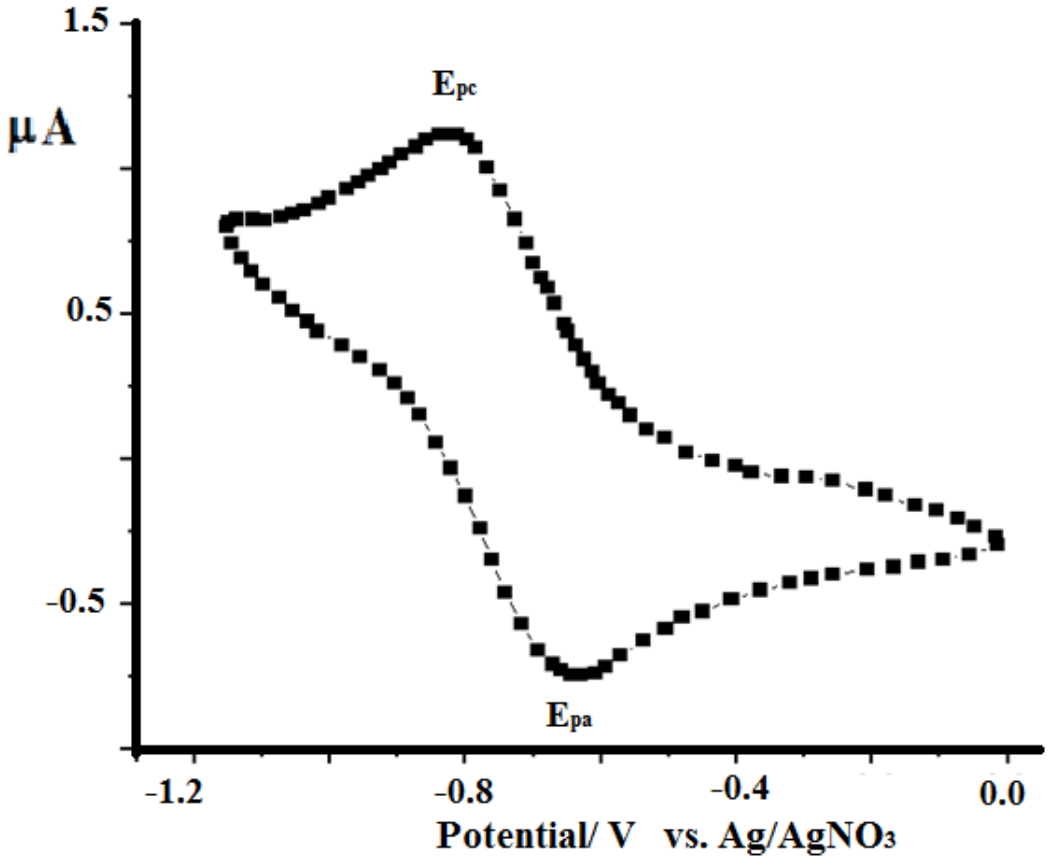


Fig. (3.12): CV-Voltammogram of Complex **1** (1 x 10^{-4} M) Dissolved in Acetonitrile, 0.1 M TBAHF, Scan Rate 0.10 V/s at RT.

SEM and EDS Investigations

The surface morphologies of the free ligand and complex **2** were subjected to SEM and EDS. The SEM micrograph of free ligand Fig. (3.13a) exhibited semi-square single phase with block over block with unequal boundary in various micrometer volumes. The SEM of complex **2** showed different morphology with homogeneous-uniformity rods with smooth and porous different sizesFig. (3. 13b) .

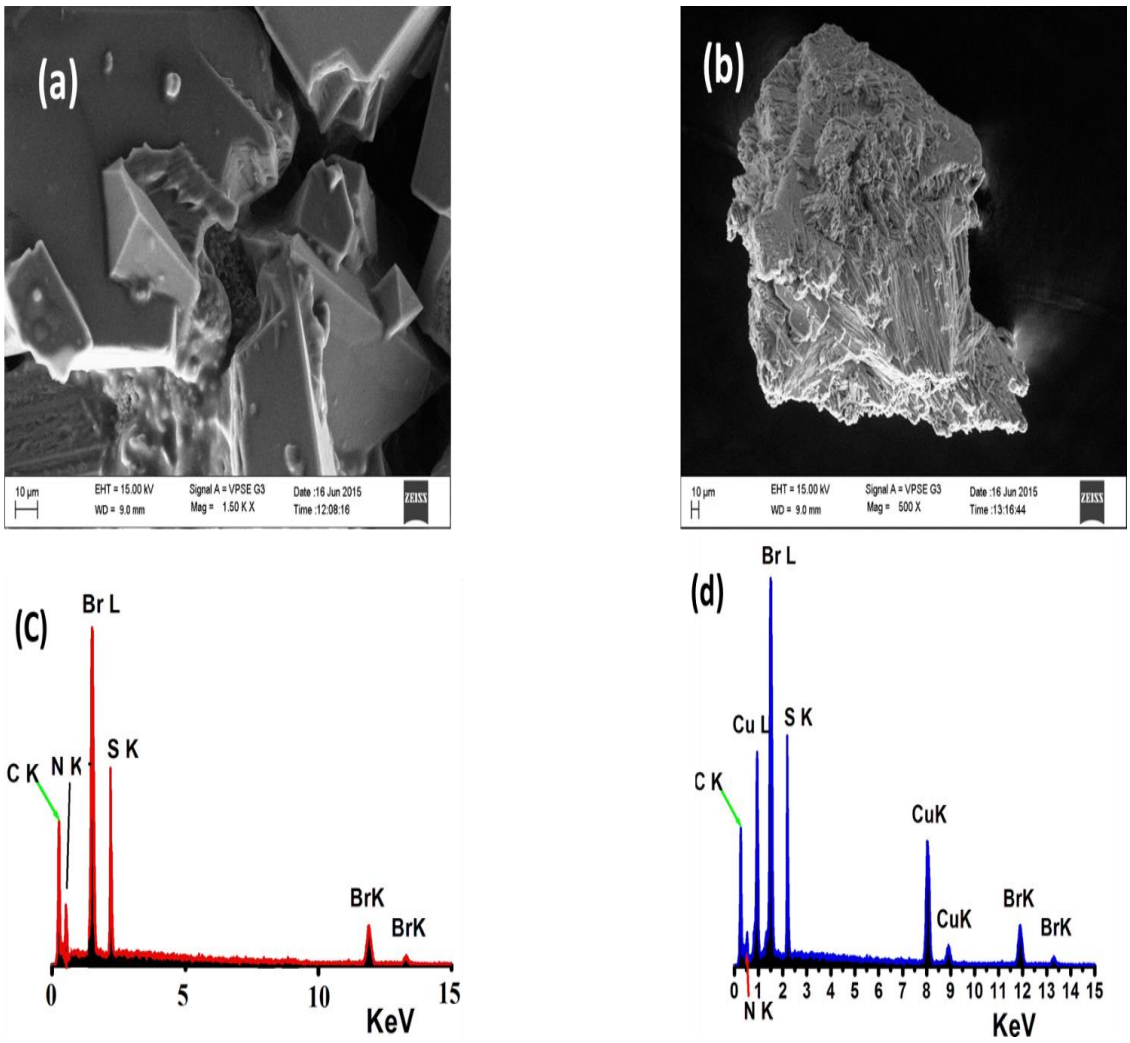


Fig. (3.13): SEM Images of (a) N3S2 Ligand, (b) Complex **2**, and EDS Images of (c) N3S2 Ligand; (d) Complex **2.**

Since SEM surface of the free ligand showed different micrograph compared with its complex, the change in morphology of the ligand before and after coordination process with Cu(II) L→M allow to differentiate between their chemical compositions. Therefore, the compositions of N_3S_2 ligand and its complex were determined by EDS analysis, as shown in Fig. (3.13c) and (3.13d), respectively. By comparing the EDS spectra, of the ligand that contains C, N, S and Br atoms to the complex that contains C, N, S, Br and Cu atoms, confirmed the formation of the desired copper

complexes. The absence of O atoms in the ligand or in the complex confirm the stability of such compounds against atmospheric O_2.

Conclusion:

New Schiff base (E)-N1-((5-bromothiophen-2-yl) methylene)-N2-(2-((E)-((5-bromothiophen-2-yl) methylene) amino) ethyl)-ethane-1,2-diamine of N_3S_2 pentadentate ligand type was synthesized derived from 5-bromothiophene-2-carbaldehyde. N_3S_2 ligand and its complexes were subjected to several physical and DFT-theoretical analysis. The results are consistent with their composition formula. Dicationic with five coordination number around the Cu(II) center $[CuN_3S_2]X_2$ complexes were spectrally suggested. The prepared complexes displayed square pyramidal geometry around Cu(II). TG results showed different thermal behavior between the N_3S_2 ligand and the complexes. Solvatochromism of the desired complexes is remoted by the polarity of solvents. One electron transfers Cu(II)/Cu(I) reversible redox was generated by CV. SEM and EDS result of the free ligand and the complexes. Such result supported the morphology and total composition change upon complexation. The viscosity and absorption results for complex **1** is better CT-DNA binder compared to complex **2**, with K_b values 3.2 x 10^5and2.5 × $10^5 M^{-1}$ respectively.

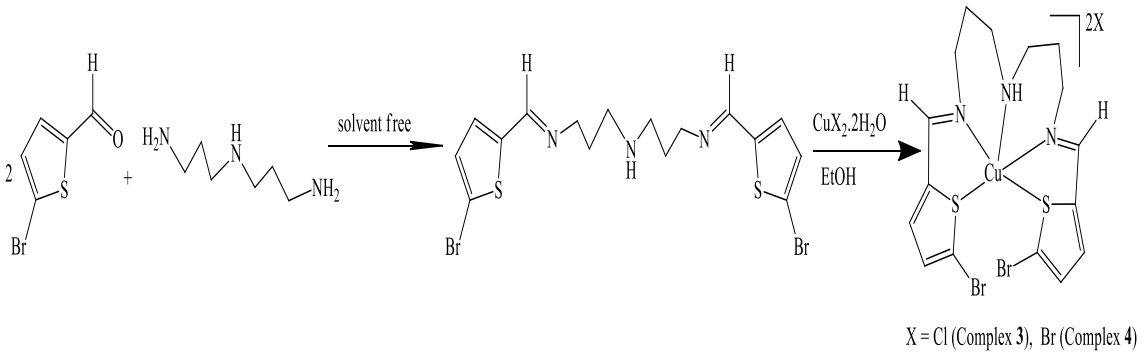
Part II

Physicochemical, syntheses and coordination behavior of pentadentate N_3S_2 ligand derived diproplynetriamine: and its Cu(II) complexes

Results and Discussion

Synthesis

Mixing of 5-bromothiophene-2-carbaldehyde and dipropylene triamine in a 2:1 M ratio, furnished new pentadentate Schiff base(E)-N1-((5-bromothiophen-2-yl)methylene)-N2-(2-((E)-((5-bromothiophen-2-yl)methylene)amino)ethyl)ethane-1,2-diamine N_3S_2 ligand **L2**, as illustrated in Scheme 2.



Scheme 4. Synthesis of the N_3S_2 Ligand **L2** and its Cu(II) Complexes.

The desired complexes 3 and 4 were prepared by direct mixing of L2 with copper (II) salts as mentioned in Part 1

Elemental Analysis and Mass Spectrometry of L2

The elemental analysis of the free ligands is consistent with the proposed molecular formula:

(Calcd. For$C_{16}H_{19}Br_2N_3S_2$: C, 40.42; H, 4.0; N, 8.84. Found: C, 40.25; H, 3.79, N, 8.6%). EI-MS confirmed by the molecular ion peak at [M^+] m/z = 474.0 (theoretical 474.9).

^{1}H and ^{13}C-NMR Spectra of the Ligand

^{1}H NMR for **L2** is shown in Fig. (3.14). which revealed three signals consistent with the aliphatic protons types with δ 1.6 (t), 2.1 (m), and 3.3 (t) ppm due to -CH_2- protons. No signal of NH proton was shown due to the D/H exchange. The two aromatic protons appeared as a multiplet in the region of δ 6.8 and 7.2 ppm, imidazole proton N=CH was detected as singlet at 8.1 ppm as seen in Fig. (3.14).

The theoretical calculation of ligand 2 was illustrated in Fig. (3.15), meanwhile, the comparison between theoretical and exponential ^{1}H NMR was plotted in Fig. (3.16).

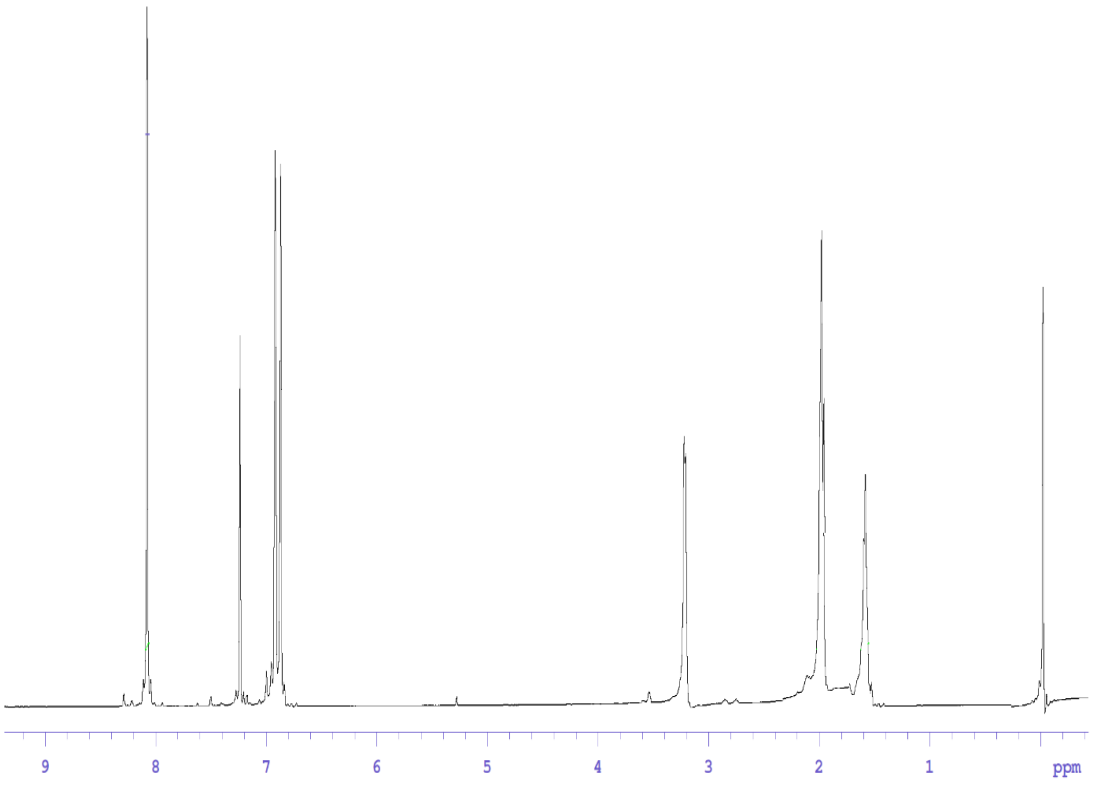


Fig. (3.14): Experimental ^{1}H NMR (ppm) Spectrum of Desired **L2** Ligand Dissolved in $CDCl_3$ at RT.

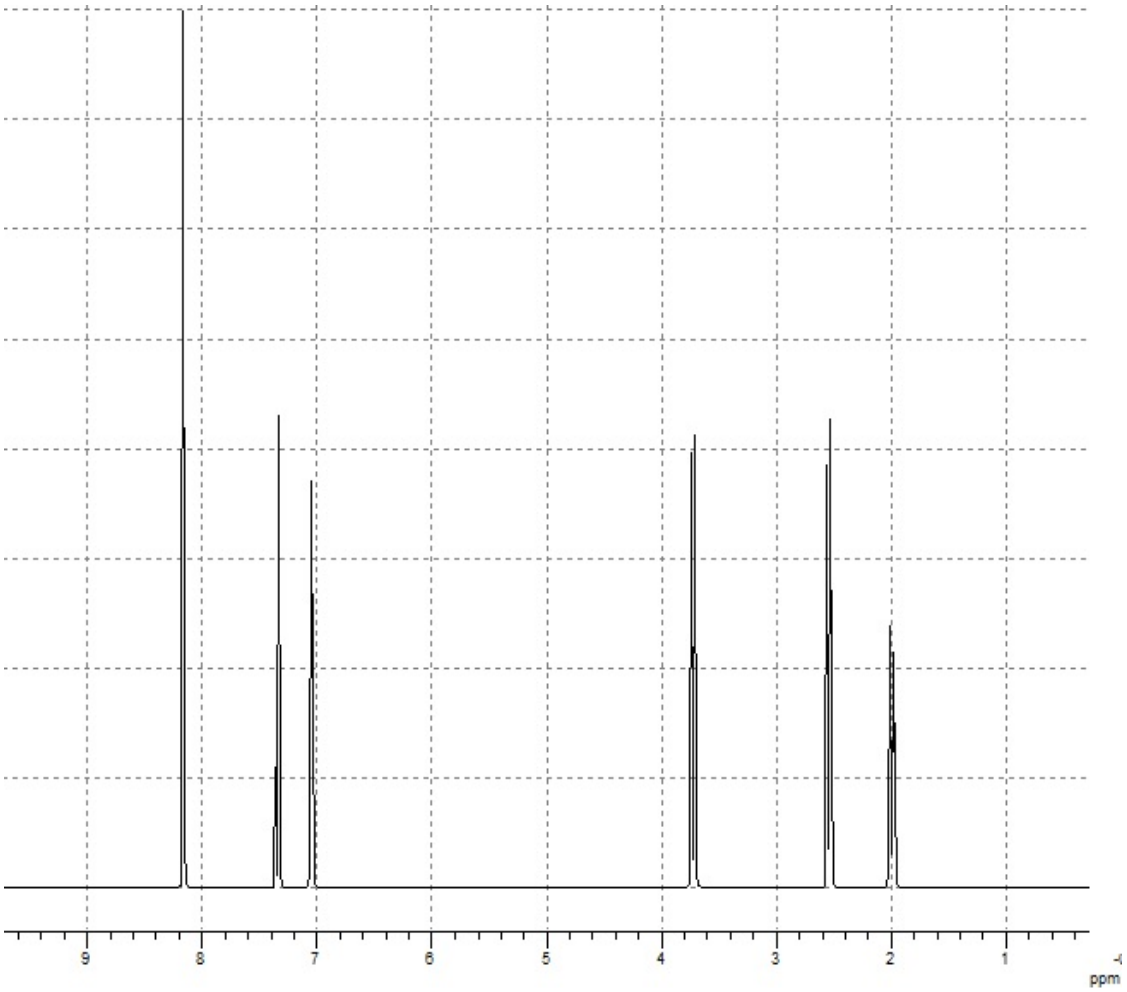


Fig. (3.15): Theoretical ^{1}H NMR (ppm) Spectrum of **L2** Ligand.

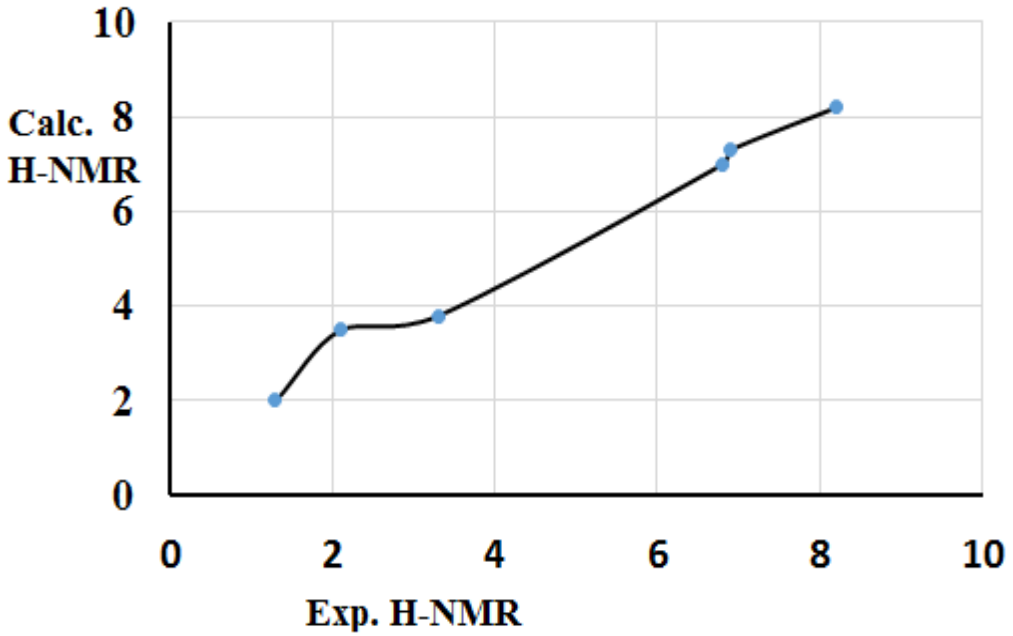


Fig. (3.16): Reflects the Acceptable Degree of Agreement Between Theoretical and Experimental ^{1}H-NMR.

^{13}C NMR for **L2** ligand as shown in Fig. (3.17). There are two signals at δ 24.2 ppm, ($HNCH_2C\underline{H_2}CH_2N$=) and 32.4 ppm ($HNC\underline{H_2}CH_2CH_2N$=), and at 73.2 ppm $HNCH_2CH_2C\underline{H_2}N$=). The four aromatic carbons recorded as signs at δ 110.9, 114.2, 130.1, 144.05 ppm, at 153.3 ppm N=CH was recorded.

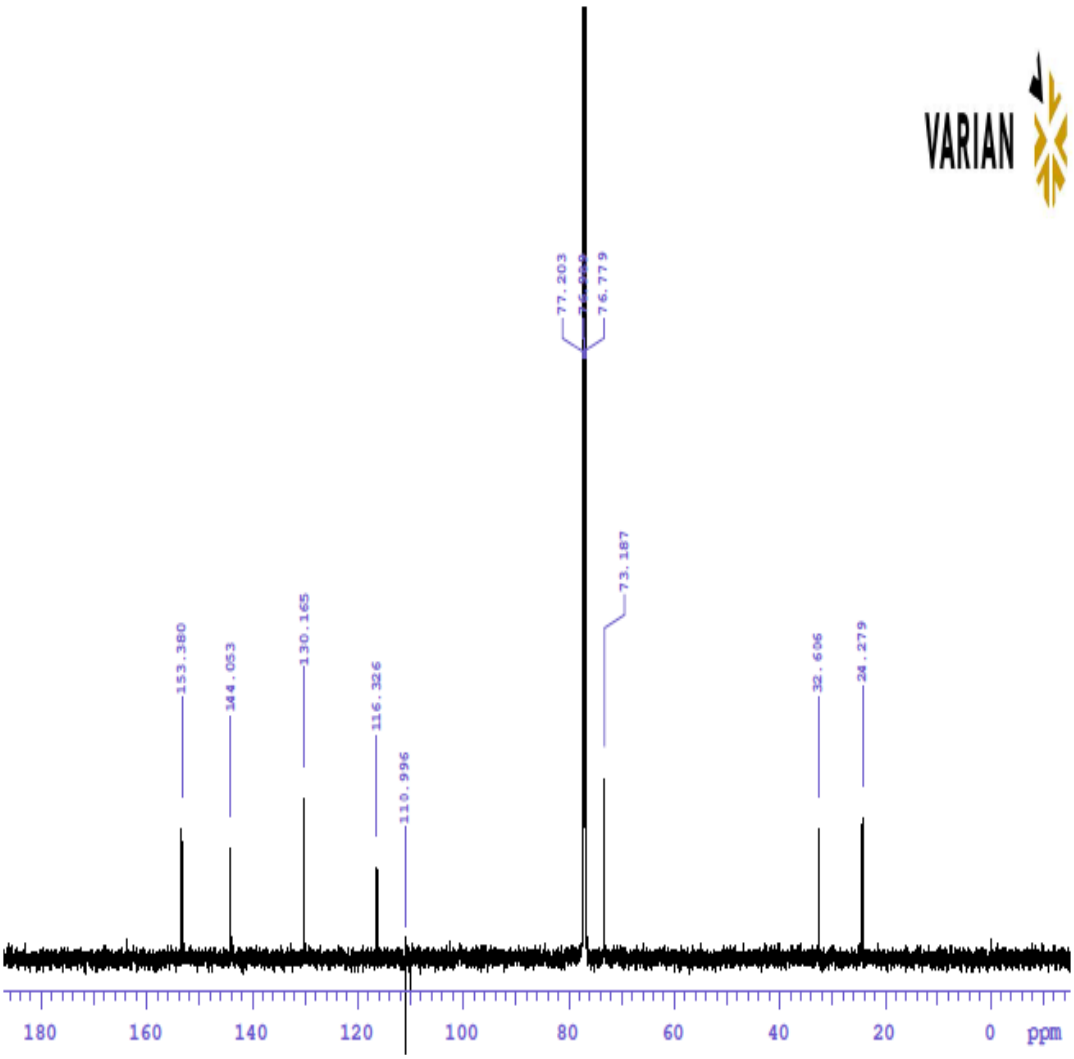


Fig. (3.17): ^{13}C NMR Spectrum of **L2** Ligand Dissolved in $CDCl_3$ at RT.

FT-IR and DFT-IR Spectral Analysis

The IR spectra of the synthesized complexes **3** and **4** showed similar IR-behavior to complex **1** and **2**. Fig. (3.18) illustrates the IR difference between L2 ligand and complex **4**. All the vibrations were cited to their positions as mentioned in part 1.

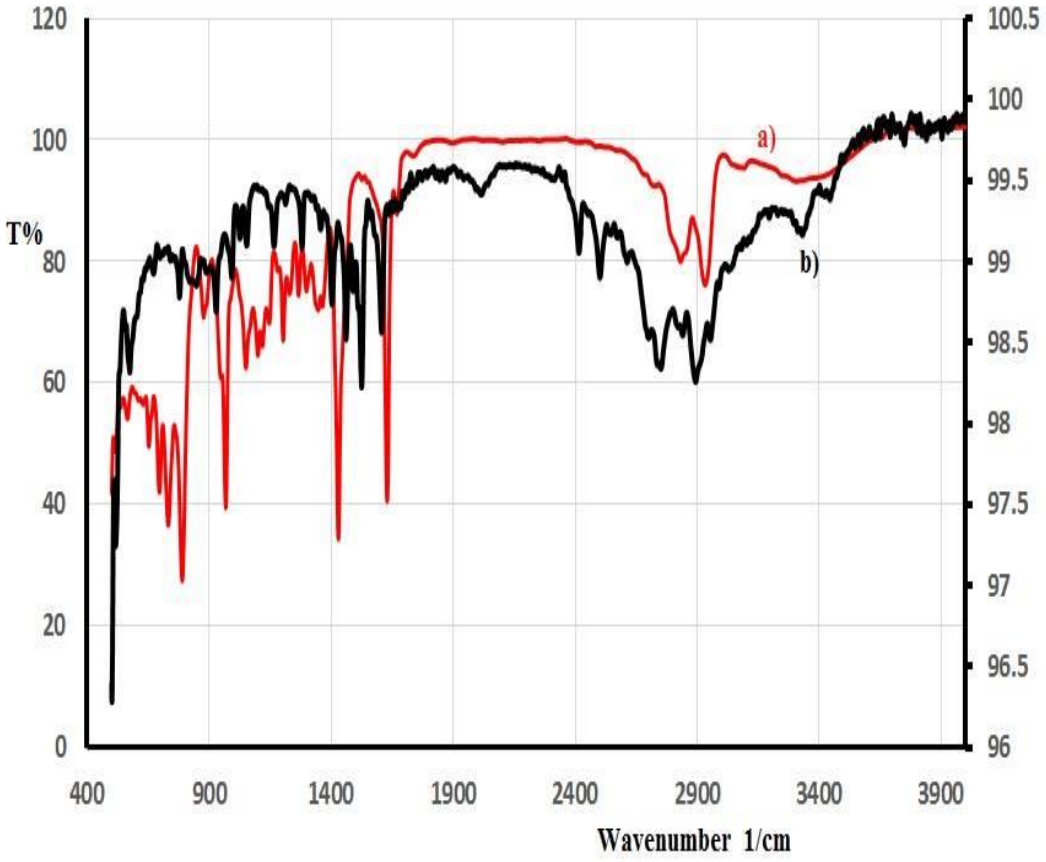


Fig. (3.18): IR-KBr Disk Spectra of a) Free **L2** and b) Complex **4** (with $CuBr_2$).

The electronic Absorption Spectra of L2 and its Complexes

The electronic absorption spectra of **L2** ligand and its Cu(II) complexes revealed similar behavior like **L1** and their complexes. The spectrum of **L2**

ligand show high transitions at λ_{max} = *320 and 260* nm which is due to π-π* electron transition as seen in Fig.(3.19).

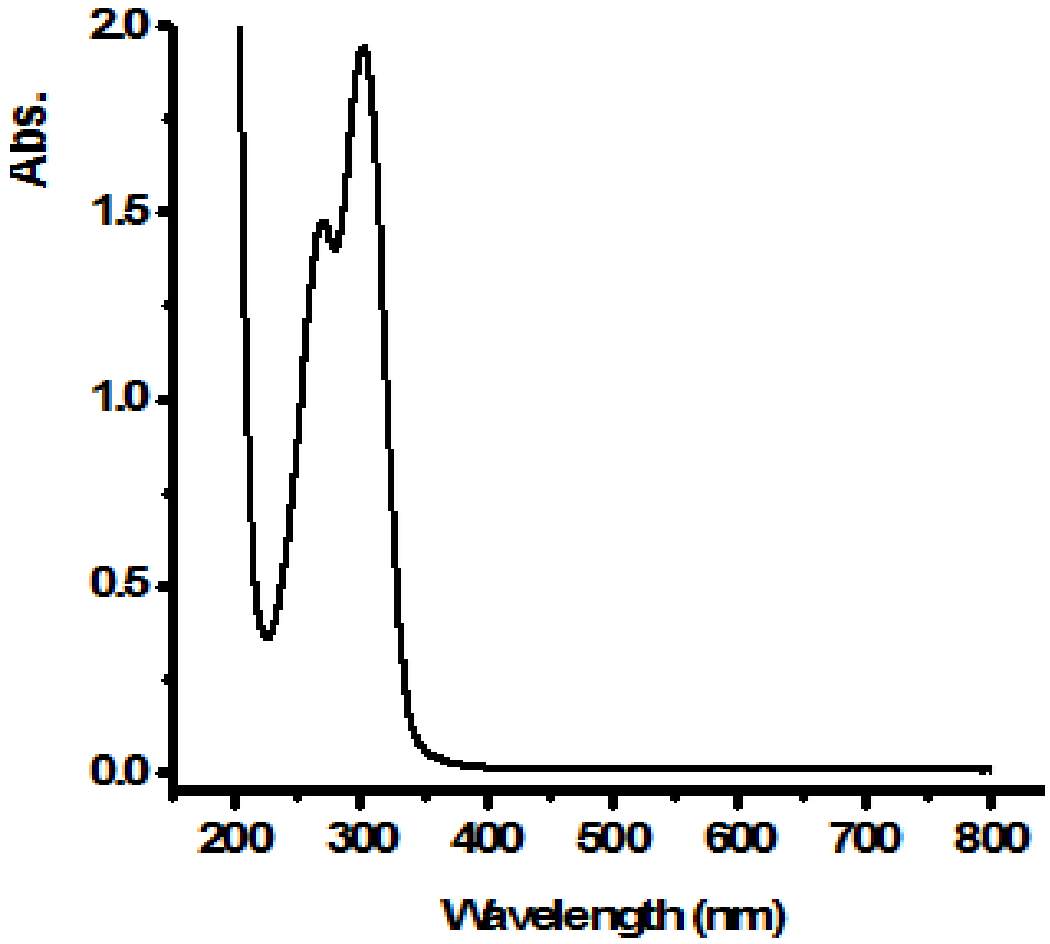


Fig. (3.19): UV-Vis Spectra of Free Ligand in Ethanol at Room Temperature

Actually, the complexes **3** and **4** are having the same UV-Vis behavior: for example, complex **3** Fig. (3.20) revealed signals of π-π* shifted down to ~ 250 nm, d-d electron transition in the visible regions at 610 nm confirmed the ligand Cu(II) coordination.

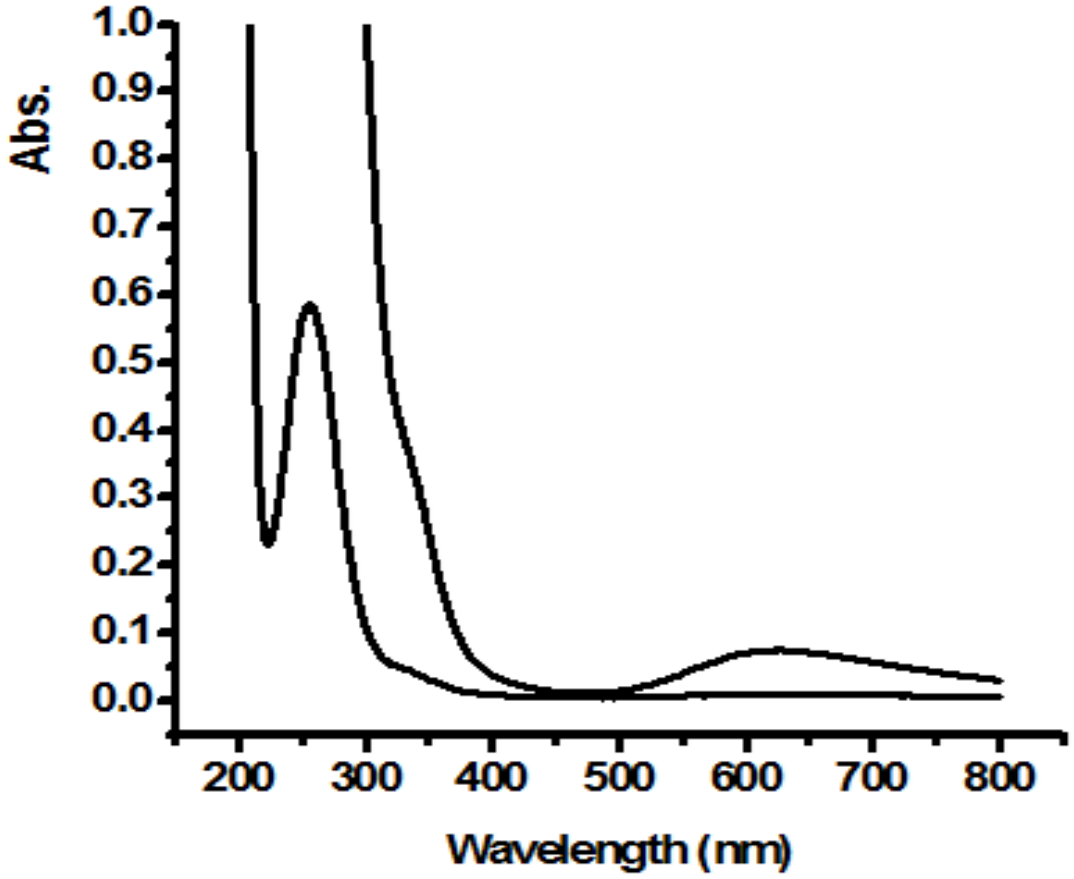


Fig. (3.20): UV–Vis Spectra of Complexes **1** Dissolved in Water at Room Temperture

Chapter Four

Application

CT-DNA Binding Affinity of Complexes 1 and 2

CT-DNA Binding Affinity of Complexes

Absorption Spectral Investigation

Absorption spectroscopy is considered to be one of the most common methods for evaluation of DNA binding affinity [35-38]. The affinity of complex **1** and **2** toward CT-DNA was followed up by UV-visible titrations in Tris–HCl buffer solution. Ordinarily, change expected in UV–Vis. spectra of the desired compound by drug-DNA binding. Commonly, bathochromice shift hypochromism interactions due to strong stacking π to π (aromatic-DNA base pairs) may prove the intercalative binding [38-40]. Figure 4.1 showed the UV-Visible spectra of CT-DNA- **1**- binding. A larger concentration of the complex **1** (5×10^{-5} M) was used in this trial in order to monitor the complex absorption behavior in both UV and Vis. regions during DNA titration. The two characteristic absorption peaks at 250 nm and 625 nm decreased in their intensity upon CT-DNA addition with different concentrations, as seen in Fig. (4.1).

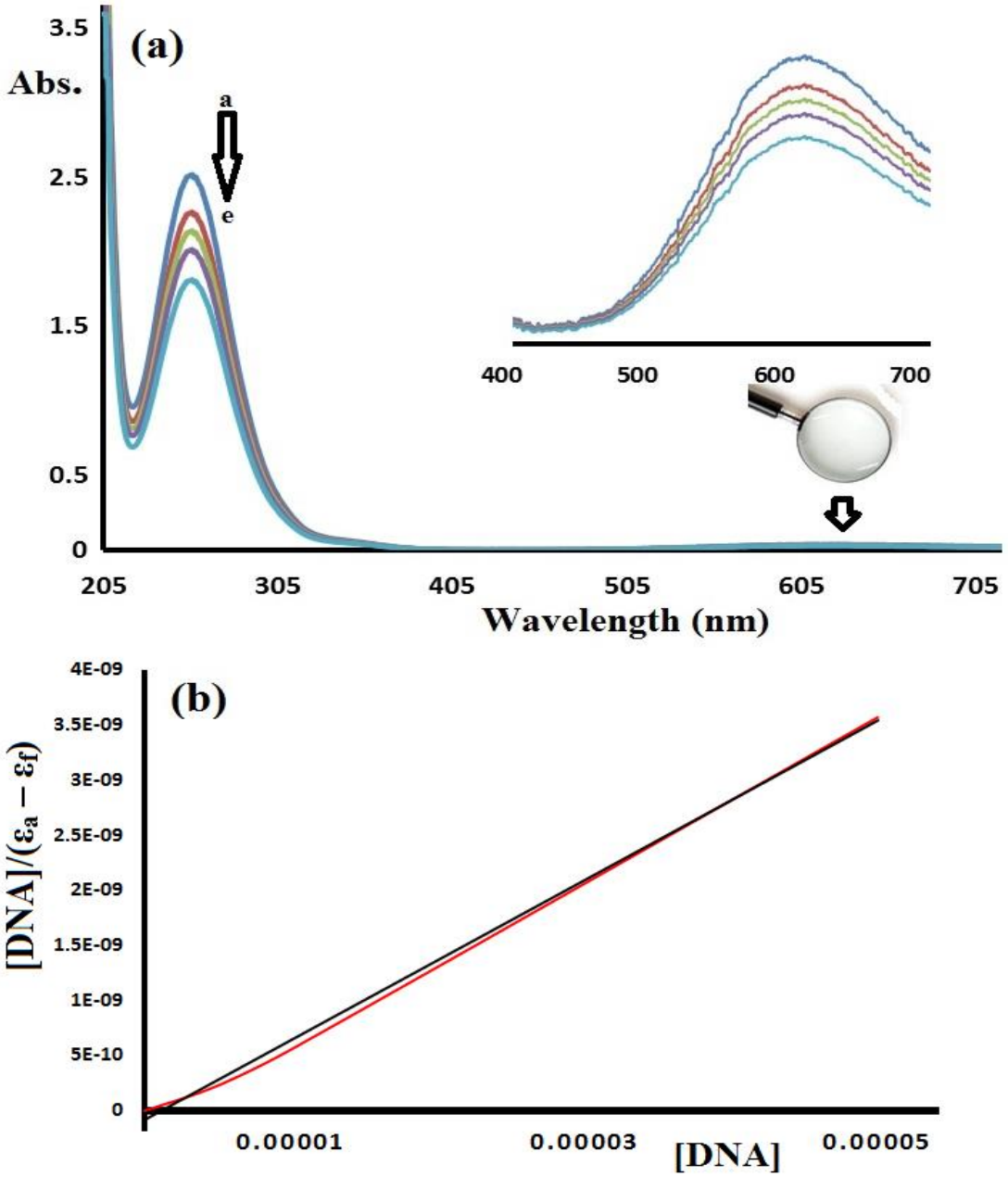


Fig. (4.1): (a) UV/Vis. Spectra of 5.0 $\times 10^{-5}$ M of Complex **1** Interacted With 0, 1.0×10^{-6}, 5.0×10^{-6}, 1.0×10^{-5} and 5.0 $\times 10^{-5}$ M CT-DNA at RT (a⟶e). (b)Plot of [DNA]/($\varepsilon_a - \varepsilon_f$) *vs.*[DNA] at 250 nm to determine K_b**.**

Fig. (4.2) showed the UV spectra of complex**2**-CT-DNA binding titration at 255nm only, since lower concentration (1 x 10^{-5} M) was used.

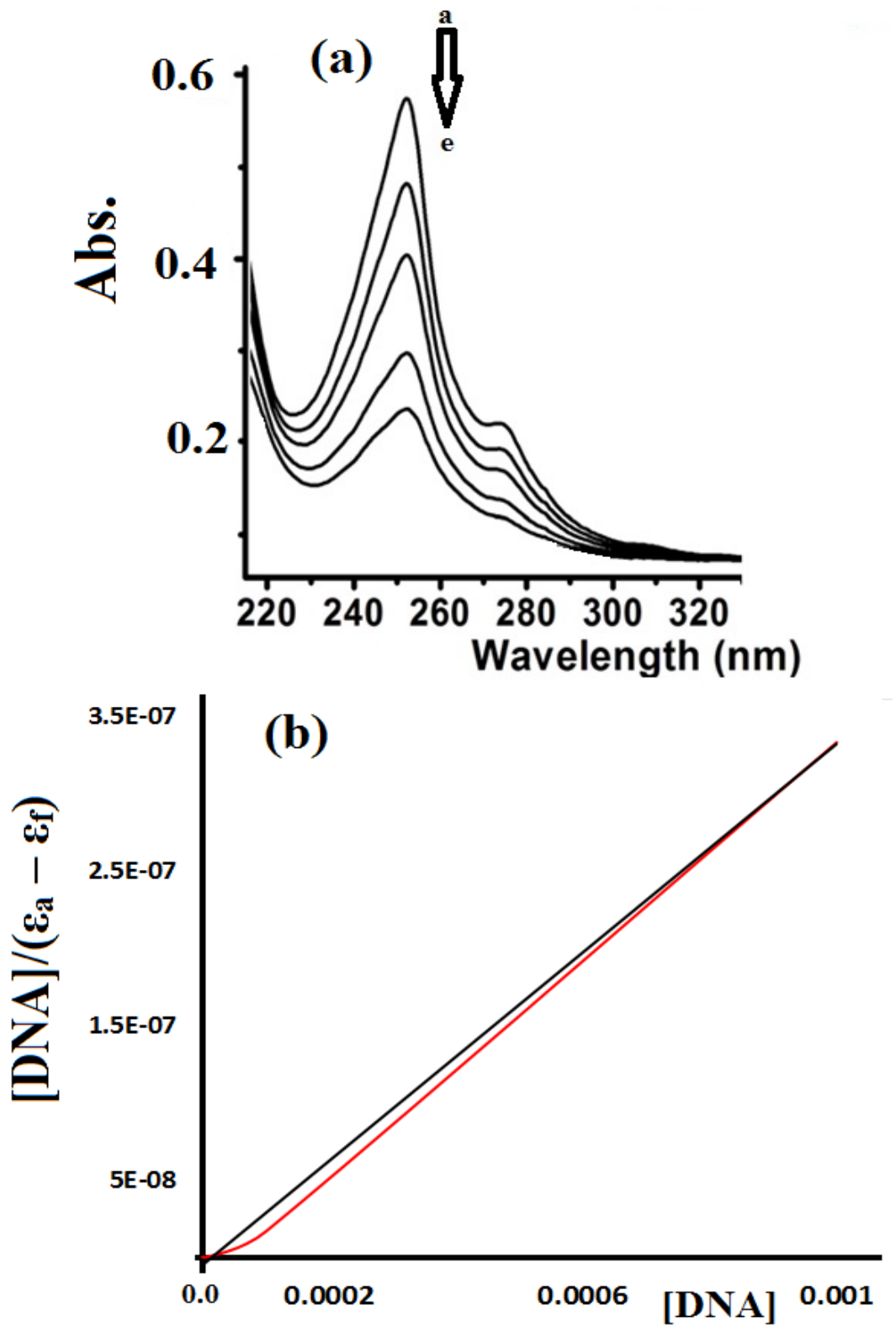


Fig. (4.2): (a) UV Spectra of 1.0 $\times 10^{-5}$ M of Complex **2** Interacted With 0, 1.0×10^{-6}, 1.0×10^{-5}, 1.0×10^{4} and 1.0 $\times 10^{-3}$ M CT-DNA at RT (a⟶e). (b)Plot of [DNA]/($\varepsilon_a - \varepsilon_f$) *vs.*[DNA] at 255 nm to Determine the Intrinsic Binding Constant

To estimate the binding ability of the desired complexes, K_b (intrinsic binding constant) was evaluated by monitoring the changes in Absorbance *vis.* CT-DNA concentrations using the following equation:
[35-38].

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_b - \varepsilon_f) + 1/(K_b\,(\varepsilon_b - \varepsilon_f)$$

[DNA] is the concentrations of DNA in base pairs, ε_f, ε_a, and ε_b are the free-,apparent- and metal-bound-complex extinction coefficients respectively. K_b is the equilibrium binding constant (in M^{-1}) of complex **1** binding to DNA. When plotting [DNA]/(ε_a–ε_f) *vs* [DNA], K_b was obtained by the ratio of the slope to the intercept. The plot of [DNA]/(ε_a – ε_f) *vs.*[DNA] empowered us to calculate and compare K_b for complex **1** = 3.2 × 10^5 M^{-1}(as seen in Figure 4.1) and 2.5 x 10^5 M^{-1} for complex **2** (as seen in Figure 4.2). These features are equivalent to those observed for Cu(II) complexes [38-40].

Viscosity Investigation

To clarify the nature of the desired complexes with CT-DNA interaction and figure out which complexes is better binder, the binding modes were performed by viscosity measurements. The values of relative specific viscosity $(\eta/\eta^o)^{1/3}$ were plotted against [complex]/[DNA] (Fig. 4.3). Viscosity of DNA is relatively increased by the interaction with the complexes concentration since it makes DNA longer [37-40]. In this study,

under identical conditions, it was observed that increasing the complexes concentrations lead to an increase of the DNA viscosity (complex **1**>complex **2)**. Thus complex **1** is a slightly better DNA binder compared to complex **2,** which was consistent with DNA binding result.

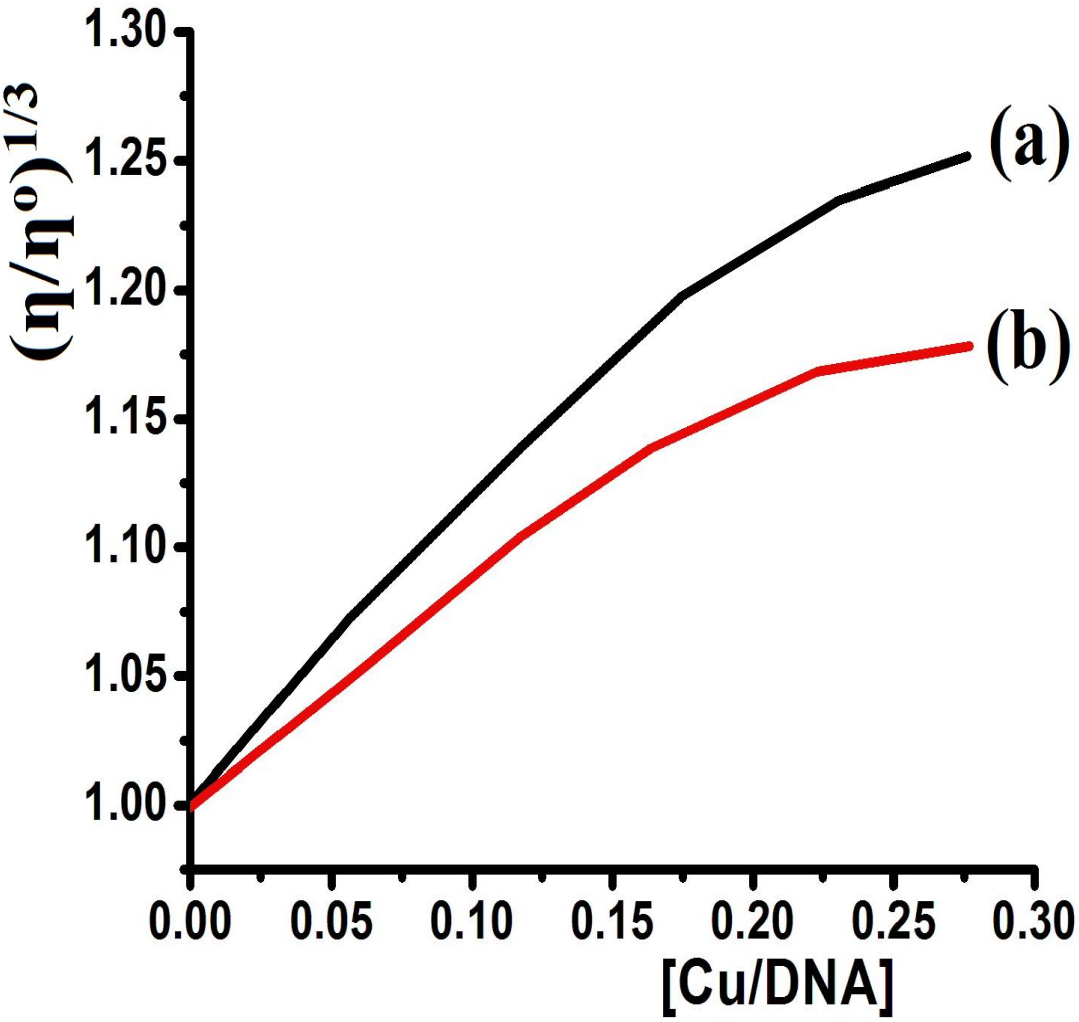


Fig. (4.3): Effect of Complex **1 (**a) and Complex **2 (**b) Concentrations (0, $2.5x10^{-5}$, $6.25x10^{-5}$, $8.75x10^{-4}$, $1.12x10^{-4}$ and $1.37x10^{-4}$) on the Relative Viscosity of 5 x 0^{-4} M CT-DNA at RT and in Tris–HCl Buffer.

Conclusions

New Schiff base, (E)-N1-((5-bromothiophen-2-yl)methylene)-N2-(2-((E)-((5-bromothiophen-2-yl)methylene)amino)ethyl)ethane-1,2-diamine was synthesized by condensation of 5-bromothiophene-2-carbaldehyde with diethylenetriamine and dipropylenetriamine. The ligands were spectrally and theoretically characterized, the condensation reaction during the synthesis was monitored by FT-IR. Because N_3S_2 ligand acted as pentadentate ligand, the water soluble square pyramidal dicationic complexes of general formula $[Cu(N_3S_2)]X_2$ were recorded. TG results showed different thermal behavior for the free ligand and its complexes. The polarity of solvents played a critical role in controlling solvarochromatic behavior of such complexes. SEM and EDS data supported the complexation composition of the N_3S_2 ligands with its complexes. The complexes exhibited one electron redox transfer with negative voltages. Both viscosity and absorption result of complex **1** are better than complex **2** as CT-DNA binder, with K_b values 3.2 x $10^5$and 2.5 $\times 10^5 M^{-1}$respectively.

Suggestions and Future Work.

- A good work for future is getting a crystal from these ligand and characterize their structures through X-ray diffraction.
- Coordinating these ligand with another vital metal for human and studying their properties using several techniques (IR, UV-Visible, T.G/DTA, EA, MS, NMR, SEM, EDS and CV)
- Applying these complexes in medicinal fields and testing their biological activities.

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جامعة النجاح الوطنية
كلية الدراسات العليا

تحضير وقياس أطياف مع تحديد درجة الترابط بـــ DNA لمعقدات مبتكرة من Copper (II) Pentadentate مع قواعد شف SNNNS

إعداد
هديل صادق صالح صبح

إشراف
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قدمت هذه الأطروحة استكمالاً لمتطلبات الحصول على درجة الماجستير في الكيمياء بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس، فلسطين

2016

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الملخص

في هذا البحث يتم التركيز على نوع جديد من قواعد شيف الخماسية N3S2 التي تتلقى اهتماما كبيرا نظرا لدورها كمتصلات عديدة المنح في الكيمياء التناسقية وأيضا ودورها في تكوين وتشكيل مركبات بوجود عنصر النحاس الثنائي

في الجزء الأول تم تشكيل L1 (-(5-bromothiophen-2-yl) methylene)-)-N1-((E)-N2-(2-((E)-((5-bromothiophen-2-yl) methylene) amino) ethyl)-ethane-1,2-diamine)من خلال مفاعله (5-bromothiophene-2-carbaldehyde) مع (diethylenetriamine) ومن ثم دراسة خصائصها من خلال إجراء القياسات الفيزيائية المتعددة (أطياف تحت الحمراء IR-spectrum) وامتصاص الأطياف فوق البنفسجية (UV-Spectrum) ودرجات انصهار والتحليل الحراري الكتلي (DTA/TGA) وجهاز مطياف الكتلة (MS-Mass)

وكذلك دراسة خصائص المركبات الناتجة عن تفاعل L1مع أملاح النحاس في وسط كحولي ومن ثم عزل هذه المعقدات وهي ثنائيه

في الجزء الثاني يتم تحضير قاعدة شيف أخرى L2 -(E)-N1-((5-bromothiophen-2-yl)methylene)-N2-(2-((E)-((5-bromothiophen-2-yl)methylene)amino)ethyl)ethane-1,2-diamine بنفس الطريقة التي تمت فيها تحضير الأولى من خلال الخلط المباشر 5 -bromothiophene-2-carbaldehyde مع

dipropylenetriamine ومن ثم دراسة خصائصها من خلال القياسات الفيزيائية التي أجريت في الجزء الأول

تشكيل مركبات من النحاس بنفس الطريقة من خلال خلط L2مع أملاح النحاس ومن ثم دراسة خصائص هذه المركبات

الدراسة البيولوجية وبالأخص مقدرته على الارتباط ب DNA التي أجريت على المعقدات الأولى والثانية الناتجة من خلط L1 مع بروميد النحاس وكلوريد النحاس والتي تبين مقدره المركب الأول على الارتباط في الحمض النووي بشكل الأفضل من المركب الثاني