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Cobalt (II) and Vanadium (IV, I) Complexes based on Semicarbazide derivatives: Spectroscopic and DNA binding Studies.

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ABSTRACT

Cobalt and Vanadium complexes with a tridentate (O-N-O) based ligand 2- hydroxynaphthaldehyde hydrazinecarboamide (**1**) and 3-ethoxy-2- hydroxybenzaldehyde hydrazinecarboamide (**2**) have been synthesized. The synthesized ligands were structurally characterized by FTIR, ^{1}HNMR and ^{13}CNMR spectroscopy. The complexes were characterized by Energy Dispersive X-ray Spectrometry (EDX). The structures of vanadium complexes were also confirmed by ^{51}V-NMR. Based on the ^{51}V-NMR results, the vanadium revealed two different oxidation states in complexing systems with the ligands **1** and **2**. The activity of ligand and complexes toward the DNA interaction was investigated using UV spectra and viscosity measurement. The results showed the intercalative binding mode of the ligands and complexes with DNA.

Keywords: Semicarbazide, ^{51}V-NMR, EDX, DNA, Viscosity

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INTRODUCTION

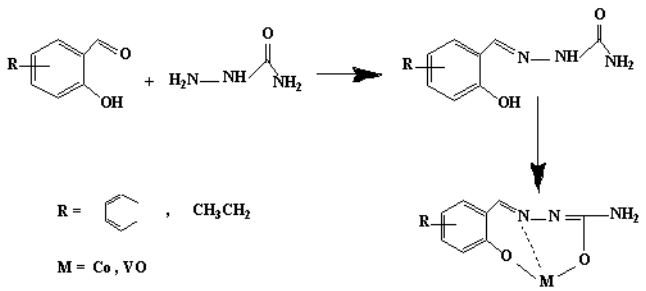
The synthesis and characterization of sulfur and nitrogen donor ligands have received special interest in the last few years as one of the main research fields in coordination chemistry. Semicarbazones and thiosemicarbazones are among the nitrogen/sulfur compounds which are received more attention due to their variable binding modes, structural variety and biological applications [1-3]. The coordination modes of atoms provide flexibility to these ligands which are can be coordinated to the metal ion in a neutral or deprotonated form resulting in mono- or poly-nuclear complexes [4-7]. Metal complexes based on semicarbazone and thiosemicarbazone donor atoms show typical stability that they confer to their complexes by chelation causing to boosting the biological activity, reduced toxicities and become a reliable source for discovering novel biologically active compounds [8, 9].

Cobalt is one of the essential elements distributed in biological systems, so the interaction of the cobalt complex with DNA has attractive attention [10]. Biological role of cobalt is concentrated on its presence in vitamin B12 as a regulator for the synthesis of DNA. Furthermore, the cobalt participates in the vitamin B12 coenzyme that uses as a supplement of the vitamin [11]. Vanadium is another an interest metal element in coordination chemistry. Vanadium complexes are reported as therapeutic agents and promising drugs against diabetes, cancer and parasitic diseases [12, 13]. Moreover, oxovanadium complexes at high-oxidation states are used for versatile organic transformations [14].

DNA plays an important role in the biological processes due to its role in carrying the inheritance information and directed the biological synthesis of proteins and enzymes during the replication and transcription of genetic information in living cells. Metal complexes are used a target for DNA because it provide attractive binding sites [15, 16]. Three noncovalent binding modes are well known for the DNA-complexes interaction; electrostatic, groove and intercalation [17–19]. The interaction of DNA with transition metal complexes has been received an intensive attention to develop new nonradioactive probes of DNA structure [20, 21], new therapeutic agents that cleave DNA and DNA-mediated electron transfer reactions [22-24].

The biological properties of semicarbazones depend on metal ion coordination, especially the lipophilicity that orient the rate of entry into the cell, which modified by coordination [25]. The studies revealed that the metal complexes are exhibit bioactivities more than the free ligand, decrease the side effects and, reduce drug-resistance [26].

In this work, we describe the synthesis, characterization and DNA binding of vanadium and cobalt complexes based on semicarbazone shown in (Scheme 1).



Scheme 1. General synthetic procedure of ligands and complexes

EXPERIMENTAL

Materials

All chemicals were purchased from Sigma Aldrich/Merck, and used without more purification. DNA obtained from human blood. FTIR spectra were recorded on a Shimadzu (FTIR -8400S, Japan) spectrometer using KBr pellets. Energy Dispersive X-ray Spectrometry (EDX) were recorded at room temperature in the rang 0-80 Kev. Electronic spectra were recorded on a UV-Vis double-beam spectrophotometer using cuvettes of 1 cm path length (Spectroscan-80D, England). ^{1}HNMR and ^{13}CNMR spectra were recorded on a BRUKER 500 MHz

spectrometer using DMSO-d_6 as solvent. V^{51}-NMR spectra were recorded on a BRUKER 400 MHz spectrometer using DMSO-d_6 as solvent and the chemical shifts were referenced to neat $VOCl_3$.

Synthesis of ligands

Synthesis of 2- hydroxynaphthaldehyde hydrazinecarboamide (1)

A solution of 2-hydroxynaphthaldehyde (0.774 g, 4.50 mmol) in ethanol (20 ml) was added to a solution of semicarbazide (0.5 g, 4.50 mmol) in ethanol (20ml) .The resulting green solution was refluxed with stirring for 2h and then filtered, and the precipitate was washed with ethanol, then left to dried. M.p:185-187.

Synthesis of 3-ethoxy-2- hydroxybenzaldehyde hydrazinecarboamide (2)

A solution of 3-ethoxy-2-hydroxybenzaldehyde (0.747 g , 4.5 mmol) in ethanol (20 ml) was added to a solution of semicarbazide (0.5 g, 4.5 mmol) in ethanol (20ml) .The resulting faint yellow solution was refluxed with stirring for 2h and then filtered, and the precipitate was washed with ethanol, then left to dried. 193-195.

Synthesis of complexes

An ethanolic equimolar solutions (25 mL) of $VOSO_4\,5H_2O$ or $Co(acac)_2$ and the corresponding ligand were refluxed for 2 h, and filtered and, then the resulting precipitate was collected.

Synthesis of 2- hydroxynaphthaldehyde hydrazinecarboamide VO (1-VO)

A solution of $VOSO_4\,5H_2O$ (0.5 g, 1.97 mmol) in ethanol (25 ml) was added to a solution of 2-hydroxynaphthaldehyde hydrazinecarboamide (0.451 g, 1.97 mmol) in ethanol (25 ml).The resulting yellow solution was refluxed for 2 h, and then filtered, and the precipitate was washed with ethanol, then left to dried. M.p: 239-241.

Synthesis of 3-ethoxy-2- hydroxybenzaldehyde hydrazinecarboamide VO (2-VO)

A solution of $VOSO_4\,5H_2O$ (0.5 g, 1.97 mmol) in ethanol (25 ml) was added to a solution of 3-ethoxy-2-hydroxybenzaldehyde hydrazinecarboamide (0.439 g, 1.97 mmol) in ethanol (25 ml).The resulting red solution was refluxed for 2 h, and then filtered, and the precipitate was washed with ethanol, then left to dried. M.p: 234-236.

Synthesis of 2- hydroxynaphthaldehyde hydrazinecarboamide Co (1-Co)

A solution of $Co(acac)_2$ (0.5 g, 2.00 mmol) in ethanol (25 ml) was added to a solution of 2-hydroxynaphthaldehyde hydrazinecarboamide (0.458 g, 2.00 mmol) in ethanol (25 ml).The resulting brown solution was refluxed for 2 h, and then filtered, and the precipitate was washed with ethanol, then left to dried. M.p:240-242

Synthesis of 3-ethoxy-2- hydroxybenzaldehyde hydrazinecarboamide Co (2-Co)

A solution of $Co(acac)_2$ (0.5 g, 2.00 mmol) in ethanol (25 ml) was added to a solution of 3-ethoxy-2-hydroxybenzaldehyde hydrazinecarboamide (0.446 g, 2 mmol) in ethanol (25 ml).The resulting colorless solution was refluxed for 2 h, and then filtered, and the precipitate was washed with ethanol, then left to dried. M.p: 261-263.

DNA binding assay

The DNA binding was investigated in 6.3 mM Tris-HCl/50 mM NaCl buffer (pH= 7.2) . A stock solution of DNA was prepared by dissolving a suitable amount of DNA in 6.3 mM Tris-HCl/50 mM NaCl buffer (pH= 7.2) at room temperature and stored at in refrigerator for 48 h. A buffered solution of DNA shown a UV absorbance at 260 and 280 nm with ratio of ca.1.9: 1, indicates the DNA was sufficiently free of protein. The DNA concentration

was estimated by the UV absorbance at 260 nm using the known molar absorption coefficient value of 6600 $M^{-1}cm^{-1}$ [27], and scanned from 230 nm to 600 nm in Tris/HCl buffer solution as a reference.

Viscosity measurements were performed using a Cannon Manning Semi-Micro viscometer immersed in a thermostatic water bath at 37 ^{0}C. Flow times were measured manually with a digital stopwatch. The viscosity values were calculated from the observed flow time of DNA-containing solutions (*t*) corrected for that of solvent mixture used (t_0) , $\eta = t - t_0$. Viscosity data were presented as $(\eta / \eta_0)^{1/3}$ versus [complex]/[DNA] where η and η_0 are the viscosity of complex in presence of DNA and the viscosity of DNA alone respectively [28].

RESULTS AND DISCUSSION

VO(II) and Co(II) complexes were synthesized with salicylaldehyde derivatives based on semicarb azones. All the ligands and complexes are air-stable and highly soluble in DMSO and DMF and highly stable in aqueous solutions. ^{1}H NMR and UV spectra were recorded after preparation, 7 days, 30 days, 3 months, while kept at room temperature. All spectra confirmed the stability of the ligand and complexes in aqueous solutions.

The ligands **1** and **2** are displayed FTIR , ^{1}H NMR and ^{13}C NMR spectra. In FTIR, the bands appeared at 1600 cm^{-1} (**1**) and 1585 cm^{-1} (**2**) attributed to (C=N) group are confirm the successful synthesis of ligands. In the ^{1}H NMR spectrum of **1** (Fig. 1), the doublet signals appeared at 7.19 ppm and 8.36 ppm are attributed to aromatic protons 5 and 8. The triplet signals at 7.34 ppm and 7.52 ppm are attributed to the aromatic protons 6 and 7, respectively. The quartet signal appeared at 7.83 ppm is attributed to the aromatic protons 3 and 4. The singlet signals emerged at 8.85 ppm and 10.29 ppm are attributed to the protons of C=N and hydroxyl groups. In the ^{13}C NMR spectrum of **1** (Fig. 2), the signals in the range 110.29 ppm to 140.38 ppm are attributed to the aromatic carbons and the signals at 156.34 and 156.59 ppm are attributed to the carbons of C=N and C=O, respectively.

In the ^{1}H NMR spectrum of **2** (Fig. 3), the signals appeared at 1.34 ppm and 4.04 ppm are attributed to the protons of CH_3 and CH_4 groups, respectively. The doublet signals emerged at 6.90 ppm and 7.32 ppm are attributed to the aromatic protons 4 and 6, respectively. The triplet signal emerged at 6.74 ppm is attributed to the aromatic proton 5. The singlet signal emerged at 8.19 ppm is attributed to the proton of OH group, whereas, the broad signal emerged at 6.37 ppm is attributed to the NH_2 protons. In the ^{13}C NMR spectrum of **2** (Fig. 4), the carbons of the CH_3 and CH_2 groups are appeared at 20.29 and 56.30 ppm, respectively. The signals in the range 112.65 ppm to 145.76 ppm are attributed to the aromatic carbons and the signals at 148.32 and 157.04 ppm are attributed to the carbons of C=N and C=O, respectively.

The complexes were characterized using energy dispersive X-ray spectrometry (EDX) which confirmed that the ligands were successfully complexation with Co and VO (Fig. 5). Moreover, the structure configuration of vanadium complexes were confirmed using V^{51}-NMR. The **2**-VO complex revealed V^{51}-NMR, a rather broad unsymmetrical resonance at a shift value of -532.5 ppm. Actually, the resonance appears two subpeaks with shifts at -531.12 and -535.13 ppm (Fig. 6). The relative amount of vanadium in the two subpeaks are difficult to estimate accurately, but an approximate ratio of 1.0075:1 for the -535.13 ppm versus the -531.12 ppm [29].

Unlike the **2**-VO complex, no V^{51}-NMR was obtained for the **1**-VO complex, indicates the oxidation state of vanadium is +1 in **2**-VO and +2 in **1**-VO, in other word, the complex **2**-VO is diamagnetic and the complex **1**-VO is paramagnetic. Based on these results, the structures of vanadium complexes can be predict as shown in Fig. 7.

To increase stability due to better electron delocalization, in a chelated ring system, the complexes must be have low steric effect for better stereochemistry. Accordingly, the 1-VO and 2-VO have different stereochemistry due to the salicylaldehyde substituent [30].

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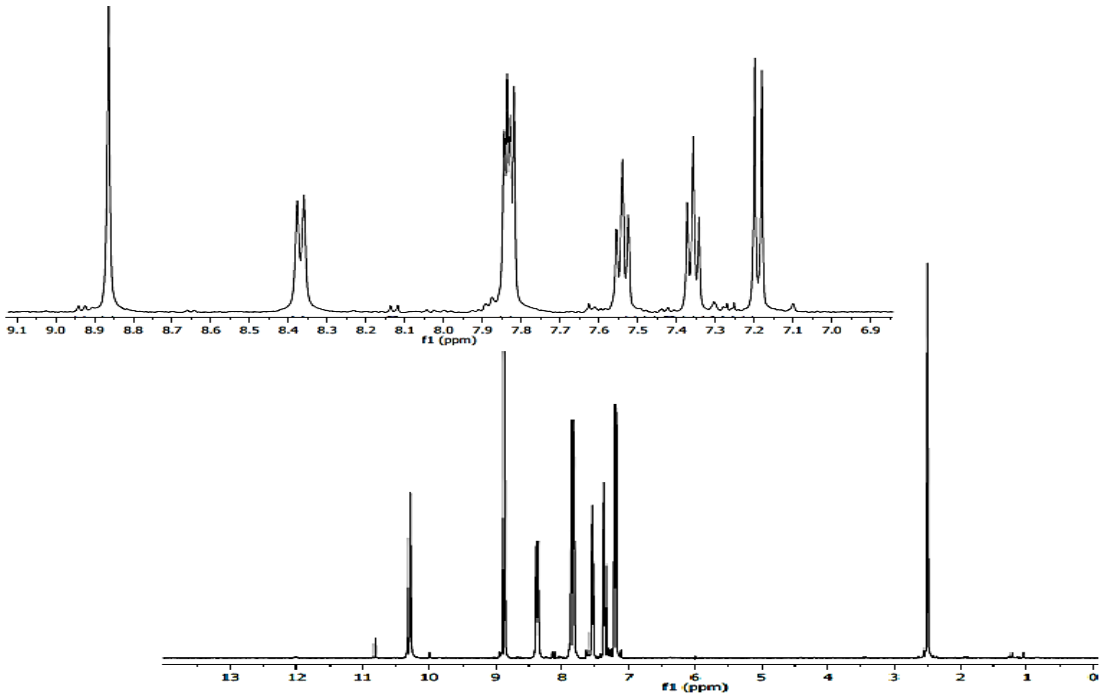

Fig. 1. ^{1}HNMR spectrum of (1)

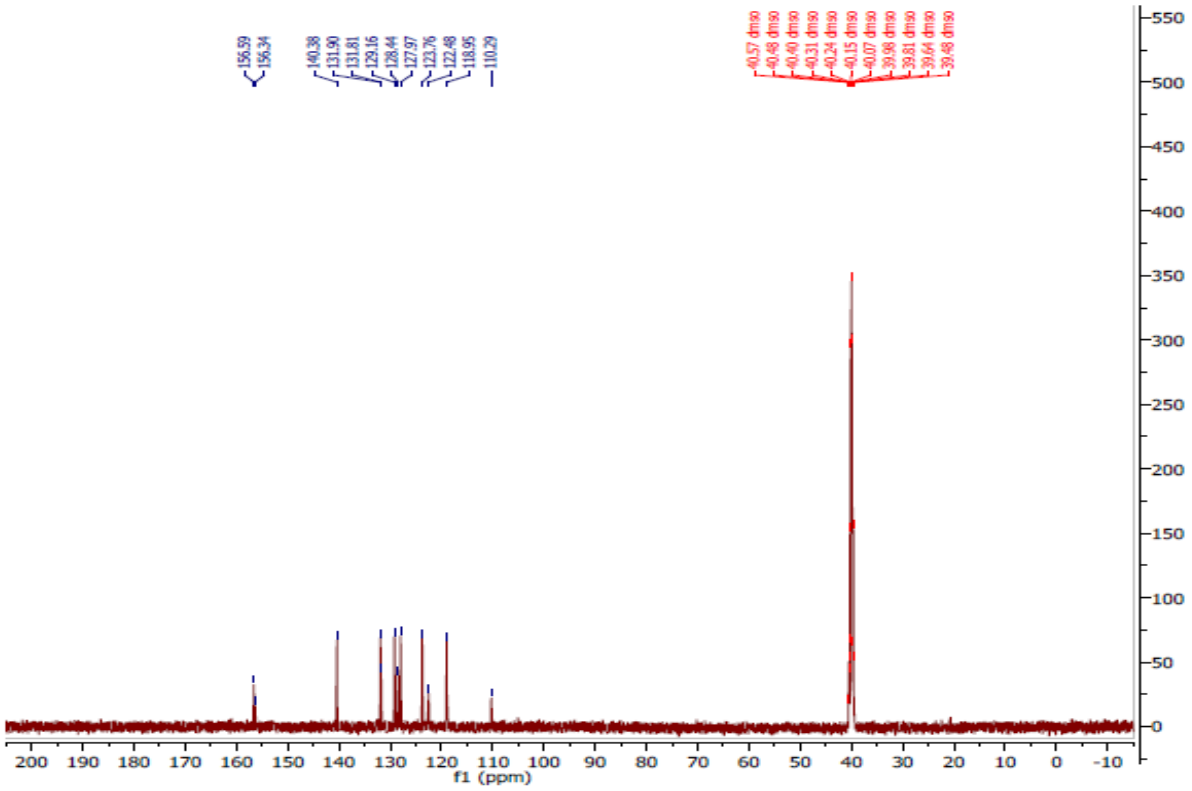

Fig. 2. ^{13}CNMR of ligand (1)

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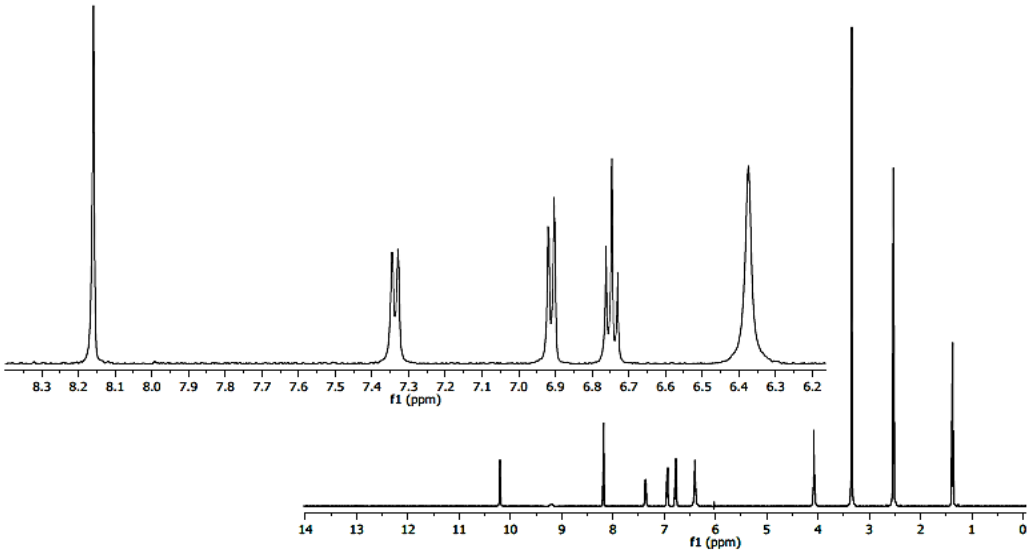

Fig. 3. ^{1}HNMR spectrum of (2)

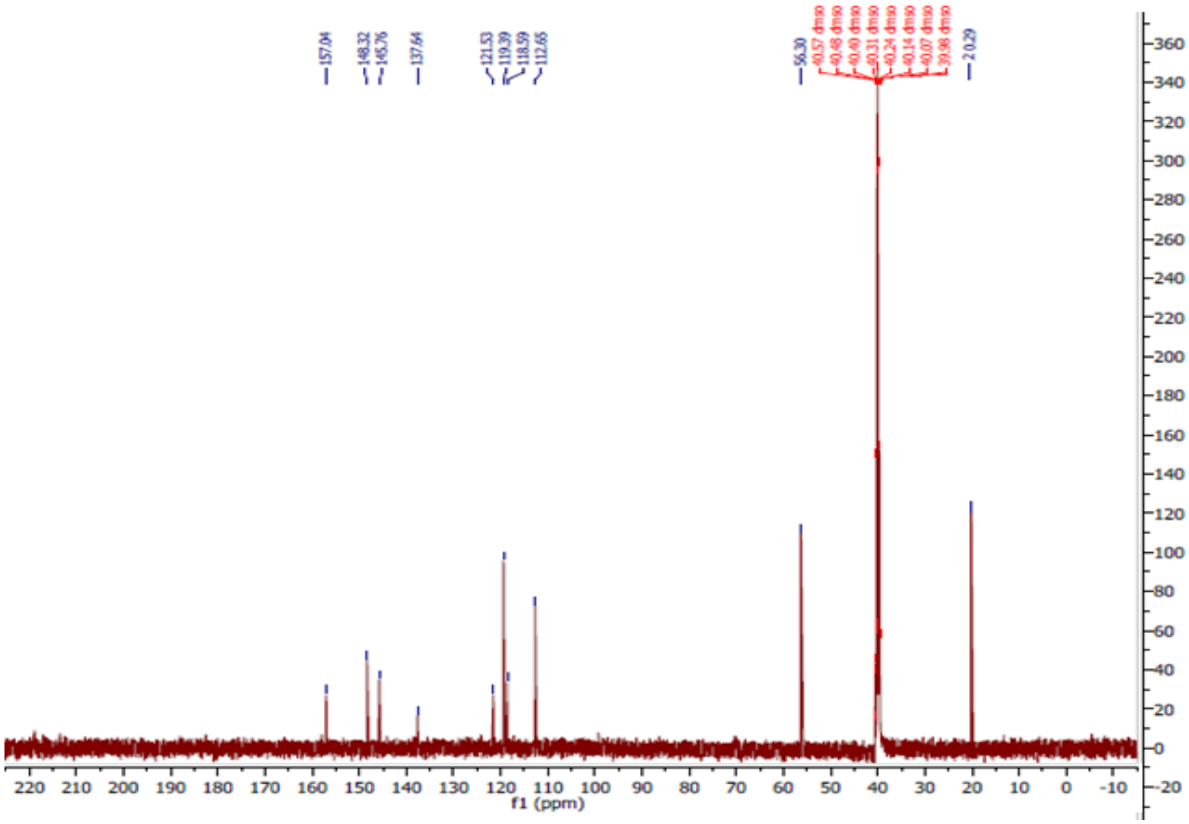

Fig. 4. ^{13}CNMR of ligand (2)

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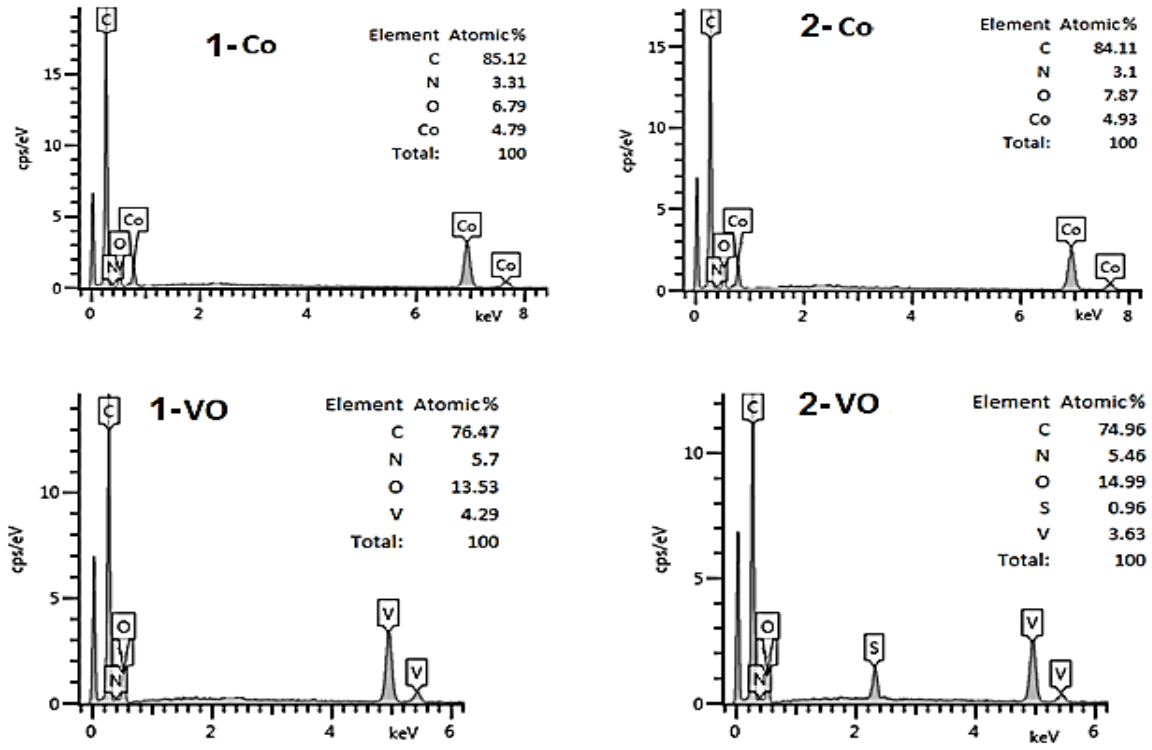

Fig. 5. EDX analysis of complexes

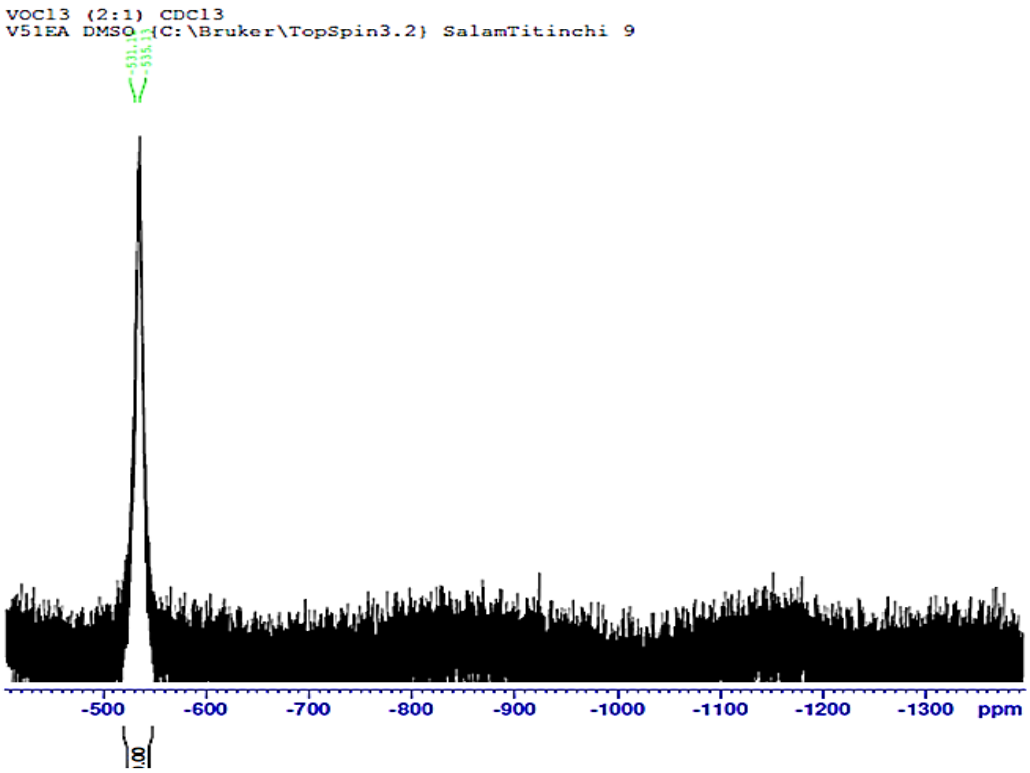

Fig. 6. ^{51}V-NMR of 2-VO

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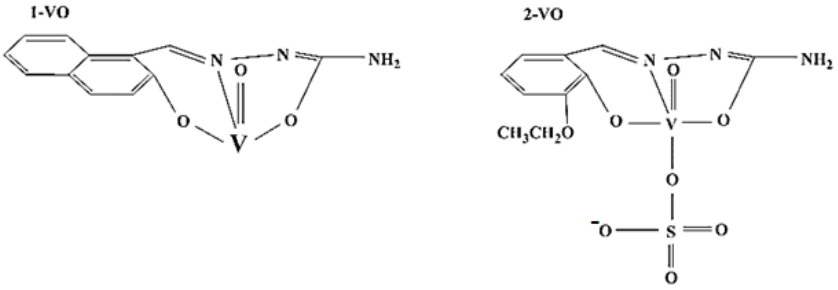

Fig. 7. Suggested structures of 1-VO and 2-VO

Interaction with DNA

Electronic absorption studies

The electronic absorption studies are the most useful methods to follow the DNA binding. Complexes can bind to DNA through covalent bonding via substitution an exchangeable ligand of the complex with a nitrogenous base of DNA [31], or noncovalent interactions of intercalation, electrostatic and groove binding [32]. Absorption spectroscopic studies were performed by titration different amounts of DNA from 10 µM to 50 µM with a known amount of ligand or complex (100 µM) in 6.3 mM Tris-HCl/50 mM NaCl buffer (pH= 7.2). The solution left 10 min. after each addition to reaches equilibrium at 25 ^{0}C, and scanned from 230 nm to 600 nm. The ligands exhibit two absorption bands at 245 nm and 352 nm are attributed to the transitions π-π*and n- π*, respectively. In addition to the band, the complexes exhibited new bands at 403 nm and 670 nm are attributed to d-d transitions for the vanadium and cobalt complexes, respectively. The π-π* absorption bands were chosen to track the interaction of DNA with ligands and complexes. The spectroscopic titrations revealed that the increased amounts of DNA lead to decreasing in the absorption intensity (hypochromism) of the ligands and their complexes (Fig. 8). This spectral behavior suggests intercalative binding to DNA , since lead to hypochromism in the spectral bands [33].

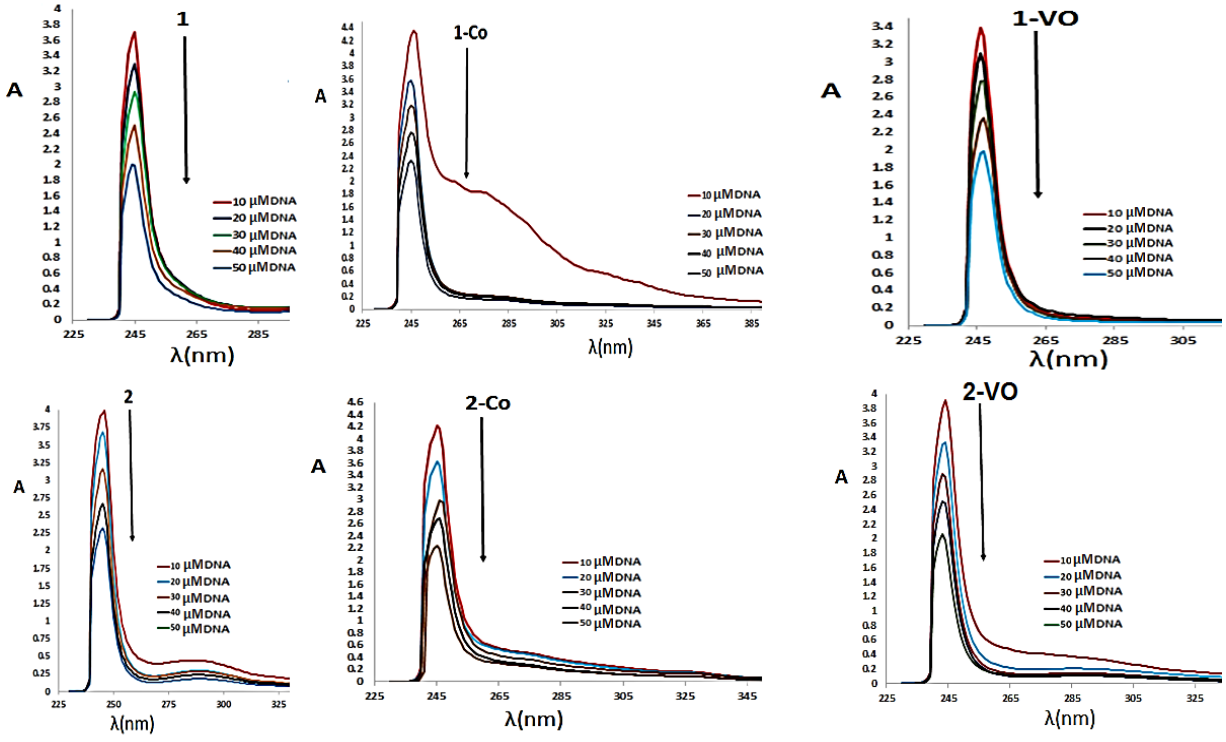

Fig. 8. UV spectra of ligand and complexes.The arrows show the changes in absorbance upon amounts of DNA

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Viscosity studies

Viscosity is one of the most important experiment uses to explain the binding modes of compounds to DNA. The results showed increases the viscosity with increases amounts of ligands or complexes (Fig. 9). These results have confirmed the intercalation of the compounds into DNA because the intercalation leads an extension and stiffing of DNA helix, which consequently leads to increases the viscosity of DNA solutions [34].

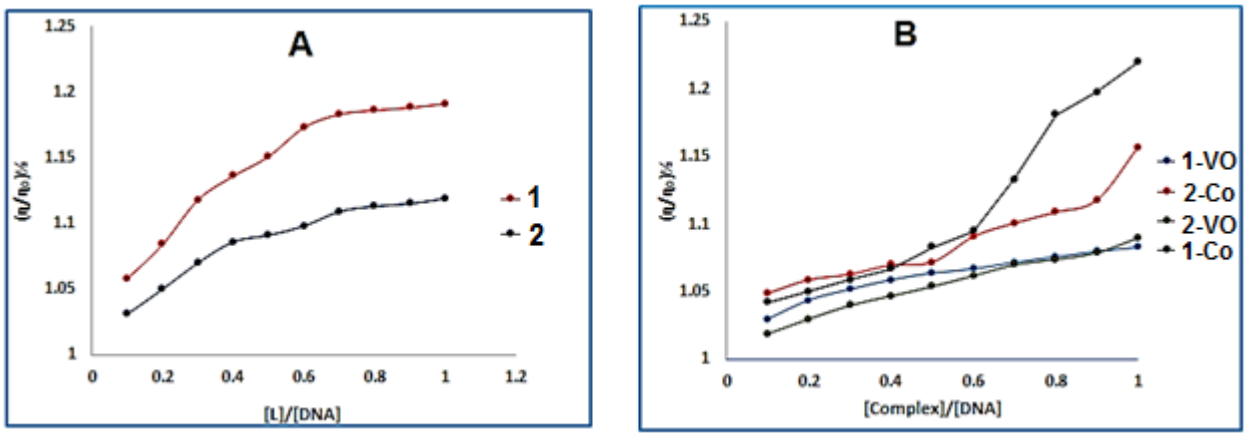

Fig. 9. Viscometric results of ligands (A) and complexes (B) at 37 °C.

CONCLUSION

Four complexes of transition metals of Cobalt and vanadium with tridentate Schiff base ligands have been synthesized. These compounds were characterized by FTIR, 1HNMR, 13CNMR and EDX techniques. The molecular structures of vanadium complexes by 51V-NMR were also discussed. The 51V-NMR presented the 1-VO complex as a paramagnetic, where the vanadium possesses an oxidation state (IV), whereas the 2-VO complex as a diamagnetic, where the vanadium possesses an oxidation state (I). The interaction studies with DNA via UV–Vis spectroscopy and viscosity measurement showed a hypochromic shift and an intercalative mode. The obtained information is presented a therapeutic reagent for some diseases.

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