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DNA Interactions of Polymerized Schiff Base Ligand and Its Complexes Obtained from Naringenin

Naringeninden Elde Edilen Polimer Schiff Bazı Ligandı ve Komplekslerinin DNA Etkileşimleri

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Abstract

(4E)-4-[(2-{[(4E)-5,7-dihydroxy-3-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-ylidene] aminoethyl)imino]-2-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-5,7-diol (L^1) ligand derived from naringenin and ethylenediamine was synthesized according to the literature (Yang and Li 2008). In addition Co(II) and Cu(II) metal complexes were obtained with monomer ligand of L^1. Then it was polymerized by oxidative polycondensation reaction to get the poly-Schiff base ligand (L^2). Cu(II) and Co(II) were characterized by elemental analyses, magnetic susceptibility, molar conductivity, UV-Vis, FT-IR and TGA/DTA. L^2 was characterized UV-Vis., FT-IR, ^{1}H NMR, TGA/DTA and GPC. Our aim was to examine the interaction of these compounds with DNA. For this purpose they were used for direct interaction with DNA and presence of H_2O_2 experiments; serious damage to DNA only the complex of L^1Cu. In the presence of H_2O_2, L^2 and L^1Co compounds were significantly reduced the damage to DNA while L^1Cu increased the damage of the DNA complex.

Keywords: DNA interaction, Oxidative polycondensation, Poly Schiff base

Öz

Naringenin ve etilen diaminden elde edilen (4E)-4-[(2-{[(4E)-5,7-dihidroksi-3-(4-hidroksifenil)-3,4-dihidro-2H-1-benzopiran-4-yliden] aminoetil)imino]-2-(4-hidroksifenil)-3,4-dihidro-2H-1-benzopiran-5,7-diol (L1) ligandı literatüre göre sentezlenmiştir (Yang and Li 2008). Buna ek olarak Co(II) ve Cu(II) kompleksleri de monomer L^1 ligandı ile elde edilmiştir. Daha sonra oksidatif poli-kondensasyon tepkimesi ile polimerleştirme gerçekleştirilerek polimerik -Schiff bazı ligandı (L^2) elde edilmiştir. Cu(II) ve Co(II) kompleksleri elementel analiz, manyetik duyarlık, molar iletkenlik, UV-Vis, FT-IR ve TGA/DTA ile karakterize edilmiştir. Polimer yapılı L^2 ise UV-Vis., FT-IR, $\underline{1}$H NMR, TGA/DTA ve GPC ile yapısal olarak aydınlatılmıştır. Bizim bu çalışmadaki amacımız bu bileşiklerin DNA ile etkileşimlerini incelemektir. Bu kapsamda bileşikler direkt olarak ve H_2O_2 varlığında DNA ile etkileştirilmiştir. Sadece L^1Cu kompleksi DNA'ya ciddi hasar vermiştir. H_2O_2 varlığında L^2 ve L^1Co bileşikleri DNA'ya hasarı belirgin bir şekilde azaltırken, L^1Cu bileşiğinin DNA'ya olan hasarı artmıştır.

Anahtar Kelimeler: DNA etkileşimi, Oksidatif polikondensasyon, Polimerik Schiff bazı

1. Introduction

Double-stranded DNA helix is stabilized mainly two ways: hydrogen bonds between nucleotides and base-stack interactions between aromatic nucleobases (Yakovchuk and Protozanova 2006). The two helix strands form DNA backbone. Two imaginary grooves can be found by following the gaps between these threads. These grooves are adjacent to base pairs and can create a place for to connect to them. Because of these grooves are not opposite each other, sizes are not the same. The major groove of these (major groove) is in 22 Å width, and small (minor) groove is in 12 Å width (Dickerson 1980). Due to the narrowness of the minor groove, to access to the edge of the base is difficult from the major groove. Because of this, the proteins like the transcription factor that binds to DNA's specific sequences contact the sides of the bases from the major groove (Pabo and Sauer 1984).

A lot of biological test show that the intracellular primary goal of cancer drugs that is developed for to use interactions between the small molecules and DNA due to effects that damage to cancer cells and to cause death on cancer cells by dividing them is DNA. So to research of mechanism of

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regressions of DNA of the compounds is important that they also provide resources to other research and benefit for development of less toxic and more effective drugs (Li and Yang 2009). As a result of studies, the interactions between transition metal complexes that include multi-dentate aromatic ligands and DNA have been taken into account more. This is because, potential probes of the DNA construct and potential usability as conformation through novel therapeutic agents and photo-chemical properties of them. Designs of the small sized complexes which bind and interact with particular DNA sequences are becoming important. To understand DNA of the target region as specifically integrated will lead not only for develop new chemotherapies, will lead for also to develop competence in chemists' DNA probe and to develop high-sensitivity diagnostic agents. As well, the transition metal complexes are applied in the forepart for these purposes (Wang and Yang 2006; Li and Yang 2006).

The acid hydrazides (R–CO–NH–NH_2), and as to convenient for it, the aryl hydrazones as one class of Schiff base (R–CO–NH–N=CHR'), and the transition metal ions in living systems with their chelating structures are major focus of attention. It was reported that aryl hydrazones' coordination compounds behave as enzyme inhibitors and are useful for pharmaceutical applications (Xu and Chen 2008). DNA with hydrazones and metal complexes of them with DNA interaction studies are considerable for more understanding of hydrazones' pharmacology (Wang and Yang 2005). Many small molecules interact with DNA. These interactions are important, because they effect the DNA replication and role for getting of the base sequence in the DNA, and for understanding of DNA structure. The interactions between metal complexes and DNA may be summarized like below: 1. Inner Sphere Binding, 2.Outer Sphere Binding, 3.Intercalation, 4. Strand Breakage (Aslanoglu 1997).

The flavonoids are responsible for the pigments that occur on vascular plants generally as natural, and for most colours in nature. These natural compounds are anticancer, antibacterial, antioxidant, antiallergenic and anti-inflammatory agents as pharmacological agents because they can inhibit or adapt the enzyme systems. The naringenin that is lesser-known among flavonoid shows anti-cancer and anti-bacterial properties. Also some hydrazones and metal complexes of them have often biodiversity and drug usage activities (Wang and Yang 2005).

2. Material and Methods

2.1. Materials

Naringenin (Aldrich), N,N-dimethylformamide (Fluka), Ethanol (Fluka), Methanol (Fluka), Acetone (Fluka), Dimethyl sulfoxide (Merck), $Cu(CH_3COO)_2.H_2O$ (Fluka), $Ni(CH_3COO)_2.4H_2O$ (Fluka), $Zn(CH_3COO)_2.2H_2O$ (Merck), 4-aminobenzoic hydrazide (Sigma), Triethylamine (Merck), NaOCl (Merck), KOH (Riedel-de Haën), CH_3COOH (Fluka).

2.2. Instrumentation

The Infrared spectra of the compounds were measured by Perkin Elmer Spectrum 100 Series FTIR-ATR Spectrophotometer between the region 225 and 4000 cm^{-1}. ^1H NMR spectra were obtained at 400 MHz by Bruker AV Spectrometer in DMSO-d_6. UV–Vis measurements were recorded using a Perkin Elmer Lambda 25 Spectrophotometer. GPC measurement of the L^2 was recorded on an Agilent 1100 Series spectrophotometer. The elemental analyses for hydrogen, nitrogen and carbon were carried out on a CHNS-O Costech Combustion System instrument; the obtained values were confirmed according to the calculated ones. Thermal behaviors were investigated on a Shimadzu DTG-60 instrument. Melting points of all compounds were determined on Barnstead Electrothermal 9100. Molar conductivity was measured with a WTW LF 330 by using convenient solutions of the complexes in DMF. Magnetic Susceptibilities were calculated by the data obtained from Sherwood Scientific Magnetic Susceptibility at room temperature (25 °C).

2.3. General Process for Synthesis

2.3.1. Synthesis of Schiff base Ligand (L^1)

Naringenin (20 mmol, 5.44 g) and ethylenediamine (10 mmol, 0.61 g) were dissolved in EtOH (ethyl alcohol) and then the AcOH (acetic acid: 2.0 mL) was added slowly to mixture. It was stirred for 5 minutes to get a homogenous medium and it continued overnight. The yellowish solution was concentrated by decreasing the solvent. A yellow solid precipitated after it was cooled. The yellow precipitate was filtered, washed with plenty of water and recrystallized in ethanol to obtain ligand (Figure 1) (Xu and Chen 2008).

2.3.2. Synthesis of L^1Cu(II)

A solution of $Cu(CH_3COO)_2.H_2O$ (1 mmol) in ethanol (10 mL) was poured into a solution which containing equivalent amount of ligand (**L^1**) in ethanol (20 mL). After

5 min, triethylamine (0.2 mmol) was added rapidly and the mixture was stirred for 10 h at 25 °C. The precipitated compound was filtered and then washed with cold EtOH. Obtained $L^1Cu(II)$ complex was dried in vacuum oven overnight (Figure 2) (Li and Yang 2008). m.p: >250 °C. Anal. Calc.: C 61.10; H 4.15; N 4.46. Found: C 61.29; H 4.45; N 4.75. IR (ν cm^{-1}): **υ(C=N):** 1584, **υ(Ar-C=C):** 1517, υ(Ar-O): 1254, **υ(Cu-N): 486, υ(Cu-O): 600.** UV-Vis (λ_{max} nm): λ_1=256, λ_2=284, λ_3=310, λ_4= 351 (in DMF). Λ_M(DMSO) : 1.25 $\Omega^{-1}.mol^{-1}.cm^2$. μ_{eff}: 1.83 BM

2.3.3. Synthesis of $L^1Co(II)$

To a solution of $Co(CH_3COO)_2.4H_2O$ (1 mmol) in EtOH (10 mL) was added into a solution including equivalent amount of ligand (**L^1**) in EtOH (20 mL). After 5 min., triethylamine (0.2 mmol) was poured quickly and the solution was stirred for ten hours at at 25 °C. The precipitated compound $L^1Co(II)$ was filtered and washed with cold EtOH. Then it was dried in vacuum oven overnight (Figure 3). m.p: >250 °C. Anal. Calc.: C 59.73; H 4.39; N 4.35. Found: C 59.50; H 4.50; N 4.94. IR (ν cm^{-1}): **υ(C=N):** 1585, **υ(Ar-C=C):** 1519, **υ(Ar-O):** 1248, **υ(Co-N): 482, υ(Co-O): 600**, **υ(HOH): 525.** UV-Vis (λ_{max} nm): λ_1=254, λ_2=265, λ_3=332, λ_4=382 (in DMF). Λ_M(DMSO): 5 $\Omega^{-1}.mol^{-1}.cm^2$. μ_{eff}: 1.64 BM

2.3.4. Synthesis of Polymer Schiff Base Ligand (L^2) from (L^1) Precursor

Polymer ligand of (L^1) (0.568 g, 1 mmol) was dissolved in solution of KOH (10%, 0.056 g, 1 mmol) as a first step. The reaction flask was mounted with spiral condenser, thermometer and a dropping funnel including NaOCl.

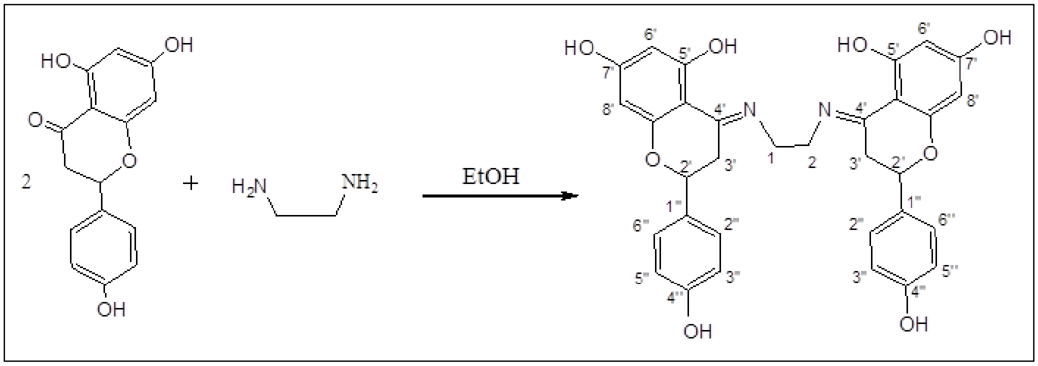


Figure 1. General depiction of ligand synthesis (**L^1**) (Li and Yang 2008).

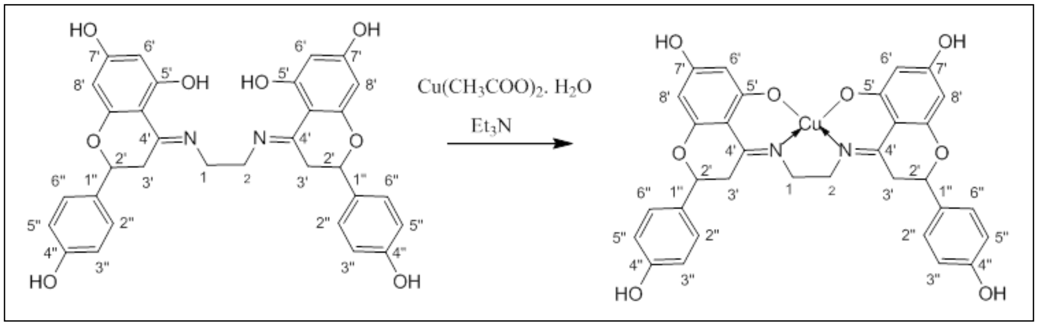


Figure 2. The synthesis of copper complex (**L^1Cu**).

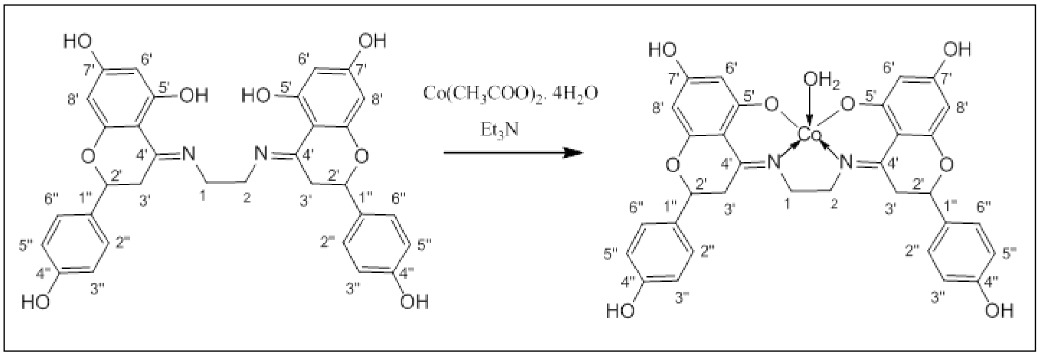


Figure 3. The synthesis of cobalt complex (**L^1Co**).

NaOCl was poured dropwise in the course of 15 min after heating the solution to 60 °C. The reaction was continued for 13 h at 90 °C. To neutralize solution diluted HCl (37 %, 1 mmol) was added at room temperature. After that, the precipitate was filtered and washed with hot water (3×50 mL) to eliminate remained mineral salts. Finally, it was dried overnight in an oven at 110 ºC (Figure 4) (Demetgül and Karakaplan 2008). m.p: >250 °C. IR (ν cm^{-1}): υ(OH): 3171, υ(Ar-C=C) : 1512, υ(C=N): 1576, υ(Ar-O): 1230. ^{1}H NMR(ppm, DMSO-d_6): 7.47 (d, *J*=12 Hz, 2″,6″-H), 9.22 (s, 4″-OH), 9.79 (s, 7´-OH), 12.06 (s, 5´-OH), 2.09-2.5 (1,2,3´ -CH$_2$-). UV-Vis (λ_{max} nm): λ_1=253, λ_2=411 (in DMF). GPC spectra: Mn: 2870, Mw: 4590, Mz: 7075, PDI (Mw / Mn): 1.6, DP: Mw/M$_{monomer}$: 8.05

3. Results and Discussion

Synthesis, characterization and DNA interactions experiments of ligands, Co(II) and Cu(II) complexes are summarized.

3.1. ^{1}H NMR Spectra

The ^{1}H NMR data of the ligand L^{2} support literature data which were acquired previous similar applications (Xu and Chen 2008). The reduction and enlargement of the peaks in NMR spectrum are ascribed to the polymerization. However, peaks in ^{1}H NMR (Figure 5) which have been enlarged as a result of polycondensation process can be explained that repeated monomer are exist (Tuncel and Özbülbül 2008).

3.2. GPC

The numbers of (Mn) average molecular weight and (Mw) weight-average molecular weight of the polymer was identified by Gel Permeation Chromatography (GPC). The z-average molar mass (Mz) can be determined with ultracentrifugation. Mz gives information about the melt elasticity of a polymer (Seymore and Caraher 1992). It is depicted as a graphic in Figure 6. According to obtained chromatogram, the Mn and Mw values of **L^{2}** was found as 2870 g mol^{-1} and 4590 g mol^{-1}, respectively. PDI which is the ratio of Mw/Mn was determined about 1.6 and the DP which is the ratio of Mw/Monomer was found approximately 8 that explain how many of monomers compose the **L^{2}**. As it is clear from the results, the polydispersity index (PDI) show that the **L^{2}** has polydispersity properties.

3.3. IR Spectra

The main vibrations of FT-IR of the polymeric ligand (**L^{2}**), monomeric ligand (**L^{1}**) and its complexes (**L^{1}Cu**), (**L^{1}Co**) were summarized in Table 1. O-H stretching vibration in 3171 cm^{-1} (Ngan and Lo 2011) C=N stretching vibration in 1576 cm^{-1} (Li and Yang 2008). Ar-O vibration in 1230 cm^{-1} (Sallomi and Shaheen 1994) are observed. On analyzing the spectrum of the synthesized polymer, it was seem that it is similar to monomer spectrum and so that the structure was not deformed after oxidative poly-condensation process. Also expanding of the sharp peaks of monomers after poly-condensation reaction (being smoother) and being reduced in number show increased molecular weight, namely polymerization has occurred (Demetgül and Karakaplan 2008). On the other hand, shows the conjugation of the polymer (L^{2}) of the bands decrease (Karakaplan 2008).

The C=N stretching vibrations of L^{1} obtained at 1586 cm^{-1} was shifted to 1585 cm^{-1} when it was compared with L^{1}Co(II) complex. Thus, it illustrate the binding from one of the azomethine nitrogen to cobalt (Măluțan and Pui 2008; Tătaru and Humelnicu 2008; Ngan and Lo 2011; Temel and İlhan 2008; Temel and İlhan 2006; Wang and Yang 2005). The change of Ar-O vibration in L^{1}Co also proves the coordination of Co to aromatic oxygen (Sallomi and Shaheen 1994). The weak bands at 482 cm^{-1} and 600 cm^{-1}

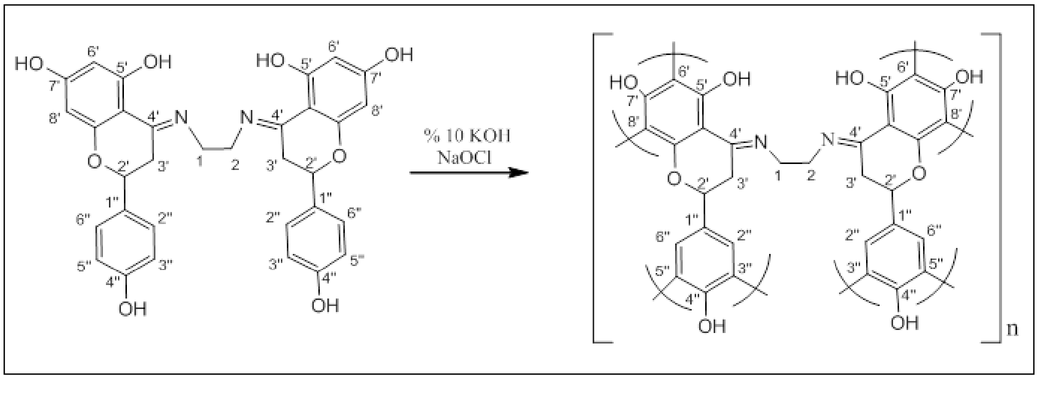


Figure 4. The synthesis of polymeric ligand (**L^{2}**).

indicate Co-N and Co-O coordination bonds, respectively. These spectra confirm that nitrogen of the imine group and aromatic oxygen have bonded to the metal ion. In addition new absorption at 2525 cm^{-1} indicates coordinating H_2O in the complex (Wang and Yang 2006; Li and Yang 2008).

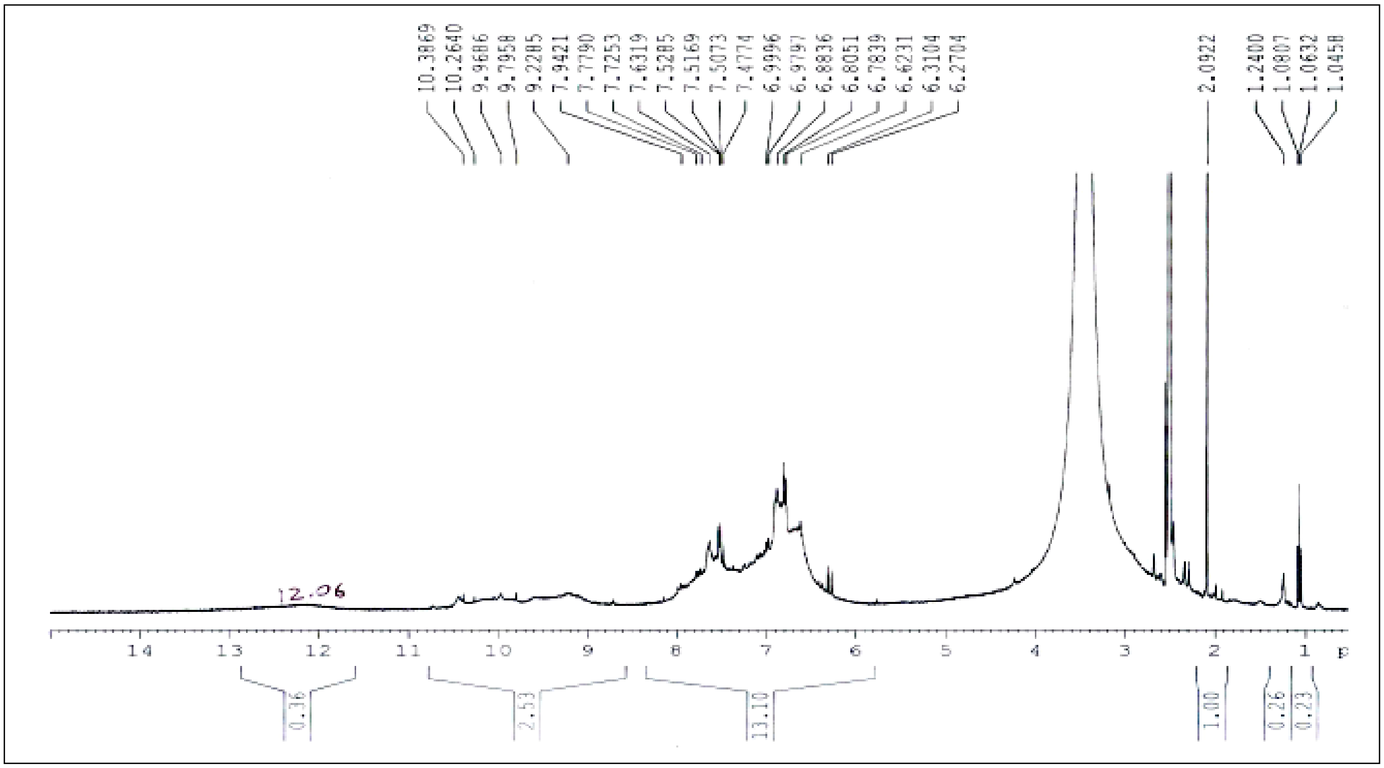
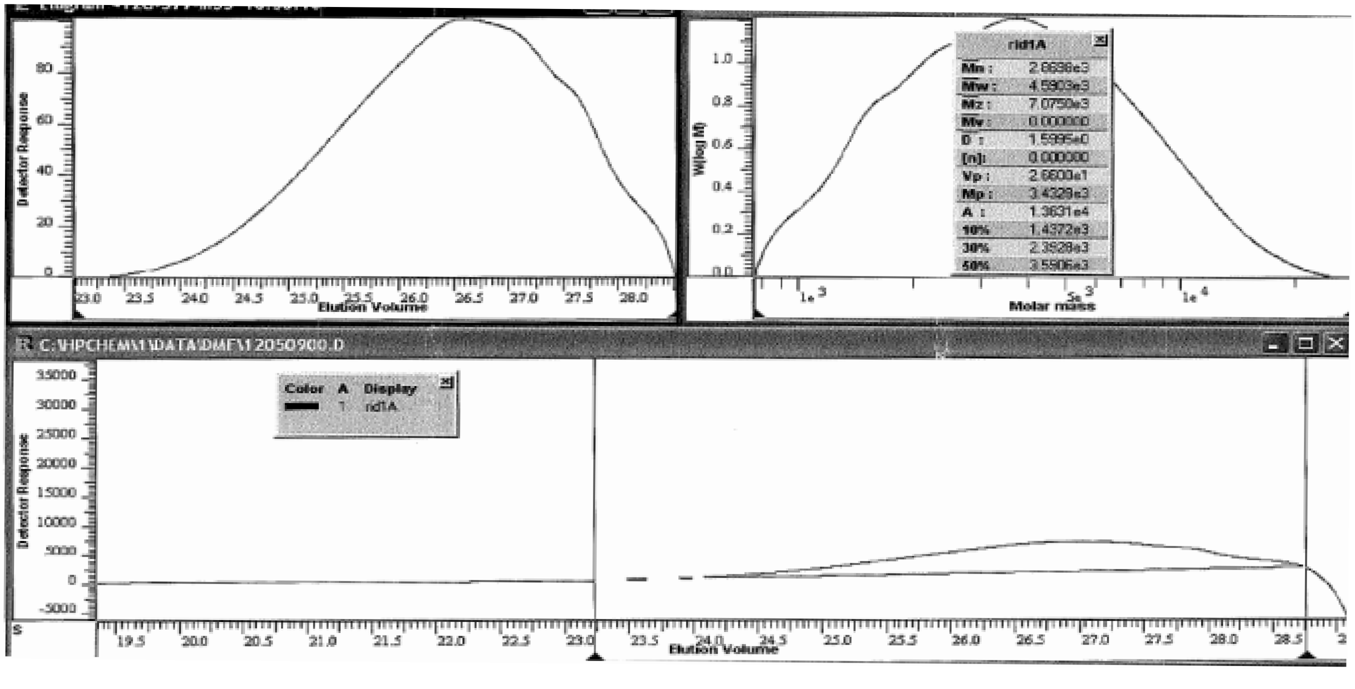


Figure 5. The ^1H NMR data of L^2.



Mn : 2.8698e3
Mw : 4.5903e3
Mz : 7.0750e3
Mv : 0.000000
D : 1.5995e0
[n]: 0.000000
Vp : 2.6600e1
Mp : 3.4329e3
A : 1.3631e4
10% 1.4372e3
30% 2.3928e3
50% 3.5506e3

Figure 6. The GPC result of L^2.

Table 1. The IR vibrations of compounds.

Compound	O-H	C=N	Ar-O	M-O	M-N	H-O-H
L^1	3148,3346	1586	1287	-	-	-
L^1Cu	3183	1584	1254	600	486	-
L^1Co	3197	1585	1248	600	482	525
L^2	3171	1576	1230	-	-	-

3.4. Electronic Spectra

The UV-Vis electronic transitions of compounds which obtained in dimethyl formamide solution displayed various weak and broad bands in spectra. The absorption peaks at 258 nm and 283 nm point out π → π* transition of aromatic structure and the bands at 303 nm and 394 nm can be referred as n → π* transitions for imine groups of **L^1** (Gupta and Kumar 2009; Kazanci 2010). The polymeric ligand **L^2** has quite similar absorption values when it's compared with monomeric form that shows the band at 253 nm for aromatic ring, 411 nm for n → π* transition for imine group (Gupta and Kumar 2009; Kazanci 2010; Tas and Aslanoglu 2004; Temel and Cakir 2004; Temel and Ziyadanogulları 2005; Tuncel and Özbülbül 2008). Shifting of bands on 303 nm and 394 nm in the complex to 310 and 351 nm in UV-Vis spectrum for imine group also proves that copper is coordinated with azomethine group (Wang and Yang 2005; Wang and Yang 2006). On the other hand, weak d-d transition between 500-600 nm intervals is belonging to $^2B_{1g} \rightarrow {}^2A_{1g}$ band (Ünver and Hayvalı 2010). Shifting of bands on 303 nm and 394 nm at ligand for imine group to 332 nm and 382 nm as complex proves that cobalt is coordinated with azomethine group (Wang and Yang 2005; Li and Wang 2007).

3.5 Magnetic Moment Measurement

The magnetic moment was found as 1.64 BM for Cu(II) complex. This value corresponds to unpaired electrons. It is seemed that the complex is occurred according to these data and it is thought that its geometry has the square planar structure as dsp^2 hybridization. On the other hand magnetic moment of Co(II) complex was found as 1.83 BM. Unpaired electron structure corresponding to this value indicates that its geometry has the square pyramid structure as dsp^3 hybridization.

3.6 Molar Conductivity

The molar conductance of all transition metal complexes found approximately between 1.25 $\Omega^{-1}.mol^{-1}.cm^2$ to 5 $\boldsymbol{\Omega}^{-1}.mol^{-1}.cm^2$ in DMF. These values reveal that these complexes have no electrolyte properties (Mohamed and Abd El-Wahab 2003). Hence those all complexes showed that they are non-electrolytes in DMF solvent (İlhan and Temel 2008).

3.7. Thermal Analysis

The thermal analyses were realized by TGA at a heating rate of 20 °C /min under a nitrogen atmosphere. The thermograms are given in Figure 7.

It was determined that the total mass loss of copper and cobalt complexes on TGA curve were respectively as; %51.766 and %64.341. Not being endothermic peak in the copper complex between 150-190 °C supports that water or free ligands are not coordinate to the complex. The endothermic peaks at 196.68 °C in the cobalt complex is due to water that is coordinated to the metal and the loss is 2.724% as to TGA curve, and this value is 1 mol water that is versus 2.79% as theoretically calculated (Karakaplan 2008; Li and Wang 2007).

It was determined that L^1 and L^2 ligands' total mass loss as to TGA curve are respectively; % 62.851 and % 62.653. Also the decomposition has begun at respectively about 310 and 230 as to the curve. This result shows that L^1 is more thermally stable than L^2.

3.8. DNA Interaction Experiments

DNA studies were performed in two stages. In first; interaction of ligands and complexes with DNA directly was examined. For second; also in the presence of H_2O_2, DNA interaction was examined.

In the studies; pcDNA3.1(-) plasmid was used for DNA example. For to see entering into interaction of ligands and complexes with DNA in the first test; the reaction was carried with 1 µg, 1 µl pcDNA3.1(-), 1mM compounds; in ultra-pure water that in an amount to complete to 1 µl PBS and 10 µl; and keeping in PCR instrument for 2 hours at 37 °C. For second test; 0.5 mM H_2O_2 was used.

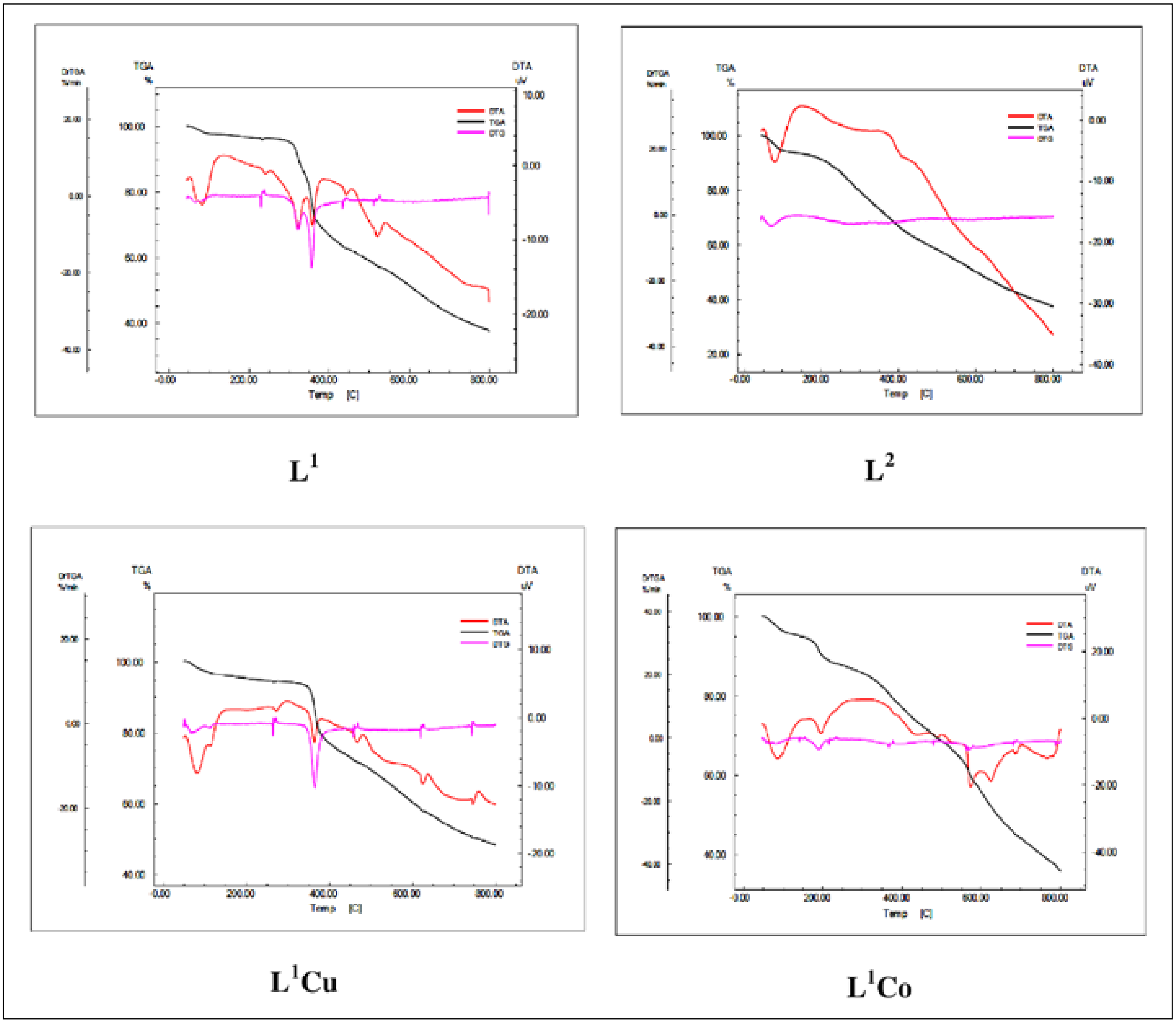
After standing of examples in PCR instrument for 2 hours, the process was continued in 0.8% agarose gel, in TAE buffer, at 100 V for 1 hour. The results were evaluated on the ImageJ Program by taking the image by the camera on the UV trans-illuminator as final.

3.8.1. Direct Interaction with DNA Experiment

The compounds were processed in agarose gel as two lines in PBS (PBS line) and in DMF+PBS (DMF line). Plasmid DNA is being in nicked open circular form like Figure 8. (2.2 % and 18.5 % of them are with red arrow (o.c.)) and super-coiled form (97.8 % and 81.5% of them are with blue arrow (s.c.)). Increasing of o.c. form in the gel shows that the damage occurred in the DNA chain (Hazari and Pandey 2012). Only 2 numbered L^1Cu complex of entire compounds increased plasmid DNA's o.c. form as over 60% and DNA was damaged seriously. **L^1, L^1Co** and **L^2** are referred as number 1, 3 and 4 have no damage onto DNA cleavage.

3.8.2. Experiments with DNA Interaction in the Presence of H_2O_2

In physiological values, H_2O_2 does not damage to DNA but it can increase the activity of compounds that damage to the DNA (Kim and Kang 2006). The plasmid DNA is being form in o.c. (29.6 % and 37% of them are shown with the red arrow) and is being form in s.c. (63% and 70.4% of them are shown with the blue arrow) like Figure 9. for same



L^1

L^2

L^1Cu

L^1Co

Figure 7. The thermograms of compounds.

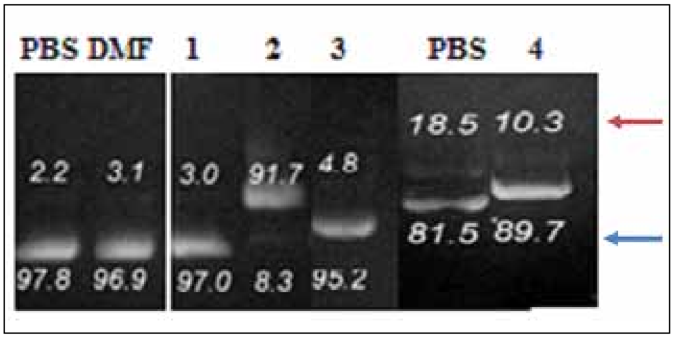


Figure 8. Compounds interact directly with DNA experiments.

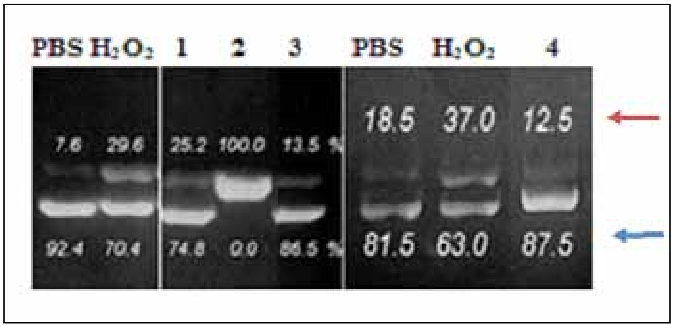


Figure 9. H_2O_2 in the presence of the compounds to interact with DNA experiments.

temperature and time with the compounds in PBS (PBS line) and in H_2O_2+DMF+PBS (H_2O_2 line). The damage of 2 numbered L^1Cu complex in the compounds on DNA chain was increased to 100% as to previous test with being of H_2O_2.

Also the damage of 3 numbered L^1Co complex and 4 numbered L^2 polymer on DNA chain was severely reduced as to previous test with being of H_2O_2. These complexes might be considered as an antioxidant.

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