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Synthesis, Characterization and DNA Interaction Activities of the Peripherally Tetra Diethyl (phenyl)malonate Substituted Zn(II) and Co(II) Phthalocyanine Complexes

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Summary: The peripherally tetra-substituted zinc (II) and cobalt (II) phthalocyanine complexes containing diethyl 3,4-dicyanophenylmalonate were synthesized and charaterized. These newly synthesized complexes have been described by utilizing FT-IR and UV/Vis procedures. Electronic absorption, fluorescence, melting denaturation, viscosity and electrophoresis procedures were applied to evaluate the interaction mechanism of tetra substituted **4** and **5** complexes with CT-DNA. Electronic spectra and emission experiments confirmed that **4** and **5** interact substantially by CT-DNA. The binding constant values for **4** and **5** were determined as 1.87 x10^6 M^{-1} and 1.64 x10^6 M^{-1}, respectively. Kb data disclosed that the complexes attach to DNA through an intercalative binding mechanism. The results obtained from melting point technique also confirmed that the attachment of **4** and **5** complexes to DNA is an intercalative manner. In addition to above techniques, electrophoresis and viscosity technique were utilized to explain interaction features of **4** and **5** complexes with DNA. The findings obtained from viscosity and electrophoresis procedures demonstrated that the complexes interact with the DNA. All the data verified that **4** and **5** complexes may have a potential anticancer features.

Keywords: Phthalocyanines, DNA interaction, Absorption spectroscopy, Emission Spectroscopy, Zinc (II), Cobalt (II).

Introduction

Phthalocyanines are widely employed as special functional chemical products because of their chemical characteristics [1,2]. Since phthalocyanines and their metal complex derivatives are very important chemical agents, the extensive research on these compounds has been going on for many years. So far, phthalocyanines and their derivative compounds have been applied in various sectors including sensors, liquid crystals of liquid, films [3-6] and they are available for photodynamic treaments of cancer [7,8]. Photodynamic cancer treatment has recently been fulfilled as a procedure impelenmented in the healing of various cancer types like lung, skin and other cancer types [9, 10]. The working mechanism of photodynamic treatment procudure is to eliminate cancer cells through the production of reactive oxygen in environment of oxygen, light and photosensitizers. Phthalocyanines are preferred as photosensitizers in photodynamic treatments for their high singlet oxygen output, powerful absorption, stability and interactivity with biological molecules [11,12]. Such as chemical compounds are also utilized as curing agents in biological application fields like antiviral, antioxidant and antibacterial medications for the elimination of diseases triggered by infections [13-18]. However, the solubility of these substances in water is not as high as in organic solvents, which limits their utilization in biological applications [19].

Research on the reaction of DNA with anticancer molecules has recently emerged as one of the major areas of current enquiry in the fields of chemistry such as medicinal sciences [20-24]. DNA is a very critical target inside the cell to inhibit the unmanaged spread of cancer cells. Because of this, the reaction of cancer treatment agents by DNA has emerged as one of the most prominent objective for cancer treatments [25, 26]. Consequently, phthalocyanines and their derivatives are worthy materials for the preparation of potential new antitumour agents [27].

In this research, peripheral substituted zinc (II) and cobalt (II) phthalocyanine complexes were

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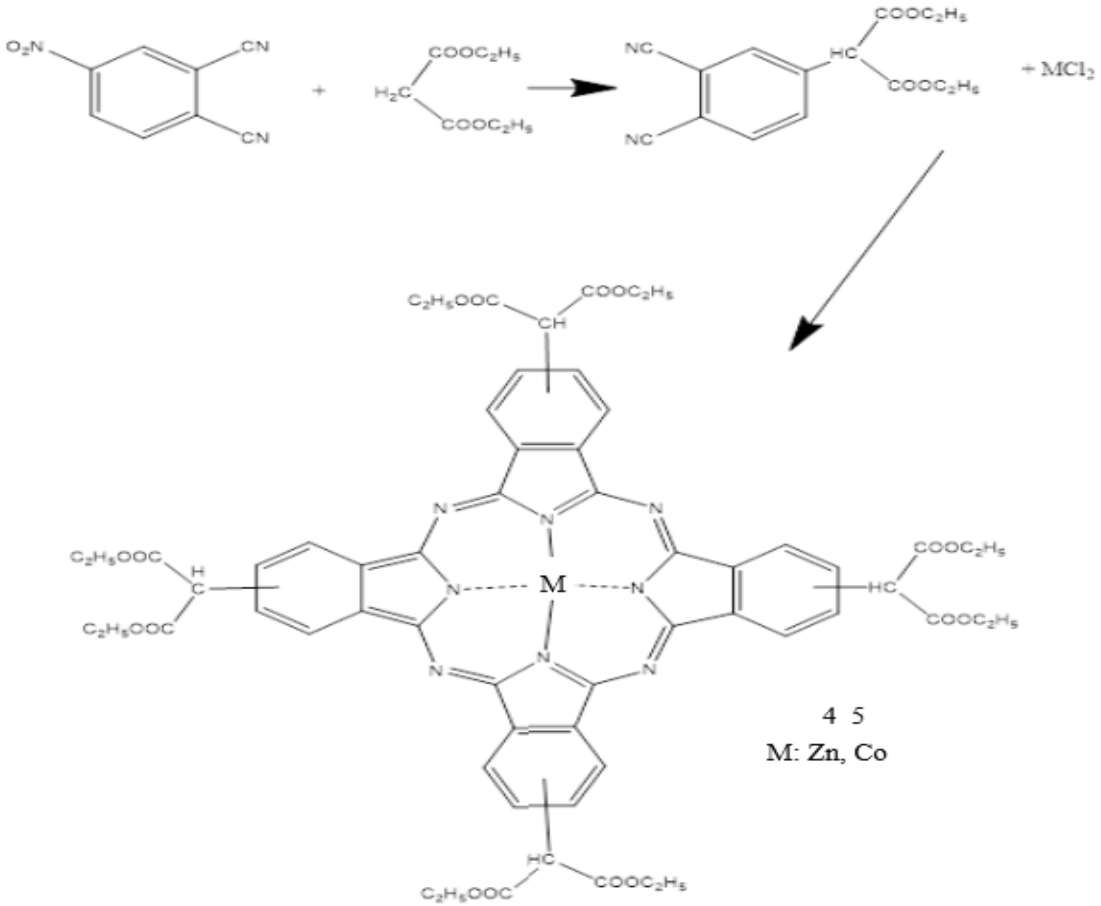
produced utilizing diethyl 3,4-dicyanophenylmalonate as a starting material to investigate their DNA binding abilities of phthalocyanine complexes were investigated by absorption studies, fluorescence studies, viscosity thermal denaturation and electrophoresis in a buffer system at pH 7.34.

Experimental

Materials and instruments

Firstly, zinc tetra (diethoxycarbonylmethyl)phthalocyanine **(4**) and cobalt tetra (diethoxycarbonylmethyl)phthalocyanine **(5**) were synthesized and characterized. The synthesises of these compounds were made by adapting the method of Roze [28]. The structures corresponding to **4** and **5** complexes are shown in Scheme-1. The reagent of Calf Thymus (CT)-DNA and all other chemicals needed were acquired from Sigma Aldrich. DNA reagent was utilized as a stock solution without undergoing purification and then the DNA sample was preserved at 4 ºC. The concentration of the main DNA sample was measured by UV absorption at 260 nm. The degree of purity of CT-DNA was assessed by tracking the absorbance at 260 nm and 280 nm. The finding of measurement revealed that the DNA specimen did not containing any protein [29–31]. All the chemical reactives were high graded and dual distilled water was employed through the study.

Absorption data were collected by Hitachi U-2900 Spectrophotometer, Cary 60 UV/Vis and emission data were acquired by Perkin Elmer LS fluorescence spectroscopies. Thermo Scientific FT-IR spectrophotometer was utilized for functional group vibrations. Gel electrophoresis experiments, another method of DNA interaction with the complexes, were performed with the Thermo Scientific Owl electrophoresis system. Furthermore, viscosity data were obtained using Ubbelohde viscometer to observe the DNA interaction activity of the complexes.



Scheme-1: Synthesis mechanism of **4** and **5** complexes.

Synthesis

Zinc(II) tetra (diethoxycarbonylmethyl)phthalocyanine **(4)**

0.486 g (1.7 mmol) diethyl 3,4-dicyanophenylmalonate and 0.43 mmol, 0.079 g anhydrous zinc (II) acetate were stirred at 170 ºC under nitrogen. Then temperature was increased to 185 ºC and stirred for 12 hours. The colour changed to the characteristic phthalocyanine colour. A small amount of alcohol was taken on the product and transferred immediately. The product was then dissolved in acetone and solid wastes were removed. The green product was chromatographed on a Al_2O_3 with hexane: acetone (1:3) as eluent. After removing the solvent, the product was dried in a vacuum oven at 90 °C. The **4** complex produced dissolves in organic solvents such DMF and DMSO. Yield: 25 mg (21 %), FTIR (ATR), ν/cm^{-1}: 2995, 2910, 2823, 1670, 1510, 1436, 1406, 1388, 1309,1255, 1093, 1043, 952, 929, 896, 696. UV/Vis (THF, 1×10^{-5} M): λ_{max}/nm (logε): 670 (5.19), 345 (4.88). ^{1}H NMR (400MHz, DMSO-d_6), (δ): 9.04, 8.01, 4.43, 3.34, 2.73, 2.52, 1.23.

Cobalt(II) tetra (diethoxycarbonylmethyl)phthalocyanine (5)

0.572 g (1.99 mmol diethyl 3,4-dicyanophenylmalonate and 0.064 g anhydrous $CoCl_2$ were stirred at 180 ºC in an oil bath under nitrogen. In the first one hour, the colour changed to the characteristic phthalocyanine colour. The product was stirred at 180 ºC for 8 hours. The product was then dissolved in acetone and the solid waste was removed. The green product was chromatographed on a Al_2O_3 with hexane: acetone (1:3) as eluent. After removing the solvent, the product was dried in a vacuum oven at 90 °C. This compound dissolves in the organic solvents like DMF. Yield: 33 mg (23 %), FTIR (ATR), ν/cm^{-1}: 2995, 2943, 2910, 2821, 1670, 1498, 1436, 1406, 1388, 1309,1255, 1093, 1043, 952, 929, 896, 696. UV/Vis (THF, 1×10^{-5} M): λ_{max}/nm (logε): 665 (5.06).

Results and Discussion

*Synthesis of **4** and **5** Complexes*

Diethyl 3, 4-dicyanophenylmalonate had been obtained the reaction of anhydrous zinc acetate and $CoCl_2$ metal salts as illustrated in Scheme 1. Purification of both phthalocyanine complexes was done by column chromatography. The compounds were obtained in reasonable yields. In FT-IR values of **4** comlex as illustrated in Fig. 1, it is clearly seen that the vibrations of the ethyl groups are at 2995-2823 cm^{-1}, the vibration of C=O is at 1670 cm^{-1}, and C=C vibration is at 1510 cm^{-1}. In FT-IR spectrum of **5** complex as displayed in Fig. 2, it is clearly seen that the vibrations of the ethyl groups are at 2995-2821 cm^{-1}, the vibration of C=O is at 1670 cm^{-1}, and C=C vibration is at 1498 cm^{-1}.

The characteristic Q and B bands specific to phthalocyanine expected for compound **4** are observed at 670 and 345 nm, respectively as seen in Fig. 3. The fact that the Q band gives a sharp peak without any splitting is a sign that zinc metal has settled in the center of the phthalocyanine complex. The UV/Vis Q absorption band of the **5** compound is also observed at 665 nm as can be seen in Fig. 4.

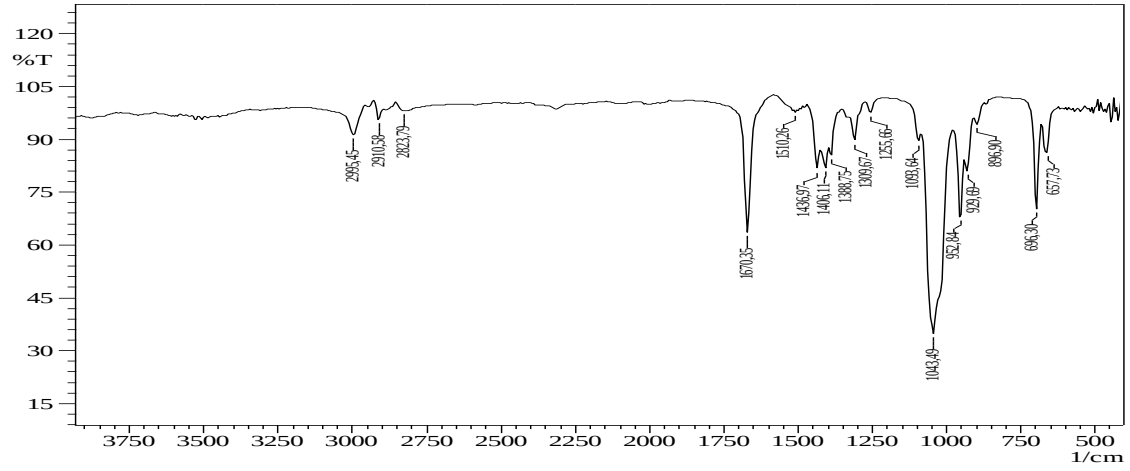


Fig. 1: FT-IR spectrum of compound **4**.

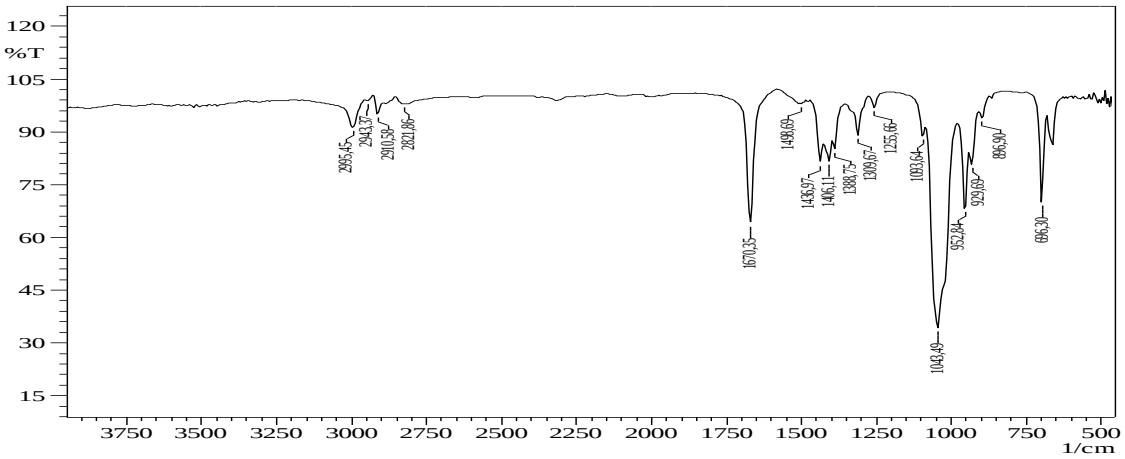


Fig. 2: FT-IR spectrum of compound **5**.

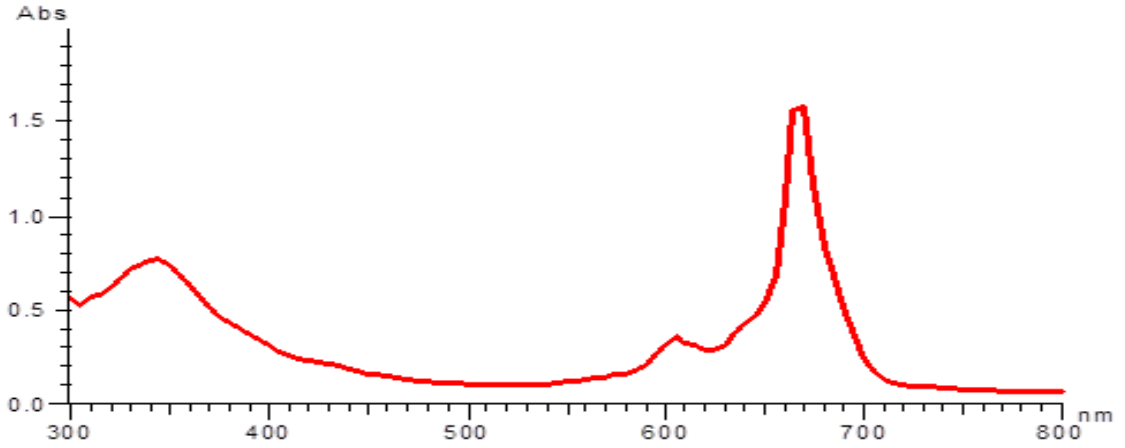


Fig. 3: UV/Vis spectrum of compound **4**.

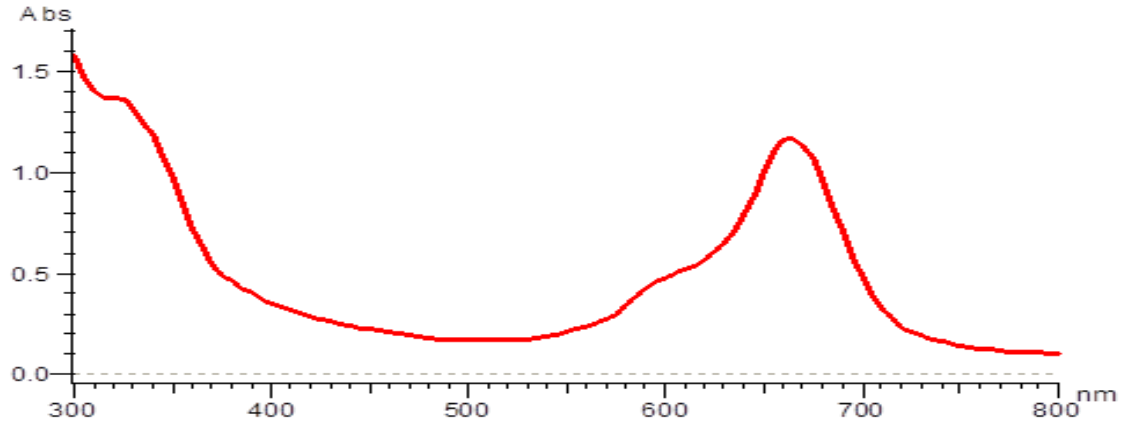


Fig. 4: UV/Vis spectrum of compound **5**.

*Electronic absorption spectrum analysis for **4** and **5** complexes*

In investigation of DNA binding, absorption titration assay is a convenient approach to acquire knowledge about the binding mechanism. In Figs. 5 and 6, the electronic spectra of **4** (15 µM) and **5** (15 µM) complexes at the given concentrations are plotted separately and in the presence of CT-DNA (0- 2.5 µM). As can be seen from Figs. 5 and 6, the solutions of the complexes **4** and **5** had been titrated with consecutive adding of DNA and the hypochromic impact was detected in the absorption spectrum in the 600-720 nm for **4** and 600-750 nm for **5** zone with no spectral shift in electronic spectra values. Pathways of binding of tiny molecules to DNA like groove attachment, electrostatic and intercalative mechanisms are recognized [32]. Owing to the forming of a compound, hyperchromic either hypochromic alterations in absorbance and wavelength shifts can be observed.

The intercalation attachment mechanisms demonstrated that the complexes interact with the DNA and the absorption intensities typically lowered. Literally, decline in the electronic spectra were observed when DNA was put into the reaction medium of **4** and **5** complexes as illustrated in Figs. 6 and 7. By using the results obtained from spectral titrations, the K_b constant values were derived from Eq 1 and the plots of $[DNA]/(\varepsilon_a-\varepsilon_f)$ were arranged using the findings derived from the data produced from the absorbance data against [DNA]. The K_b constants for **4** complex was computed as 1.87 x 10^6 M^{-1} and for **5** complex as 1.64 x 10^6 M^{-1} as indicated in Figs. 5 and 6 [33].

$$[DNA]/\varepsilon_a - \varepsilon_f = [DNA]/\varepsilon_b - \varepsilon_f + 1/K_b\,(\varepsilon_b - \varepsilon_f) \qquad \text{Eq1.}$$

Here [DNA] stands for the concentration of DNA in nucleotides, ε_a refers extinction constant at a known DNA amount, ε_f stands for the extinction coefficient of free compound and ε_b represents the extinction coefficient of compound when totally attached to DNA. The K_b of DNA binding of doxorubicin and idarubicin intercalative anticancer medicines were estimated in the literature [34]. From the K_b constant values obtained, the complexes **4** and **5** displayed a tendency to bind to DNA.

When metal compounds like phthalocyanine complexes react with DNA, these complexes are known to cause to changes in absorbance values. These alterations comprise hyperchromism and a blue or red shift in wavelength [35]. Previously, the presented study in literature, intercalative attachment can be primarily characterized by hypochromism [36]. A relatively weaker attachment to DNA molecule in general does not produce a variation in the absorbance wavelengths [24]. Intercalative attachment of metal complexes to DNA lead to hypochromism owing to rigorous packaging of aromatic compounds with DNA bases [24]. Eventually, in this method, hypochromism was observed for **4** and **5**, the complexes attach to the DNA via an intercalative binding mechanisms. Intercalative binding results in decreases in absorbance spectra. These decreases in absorbance cause hypochromism [24].

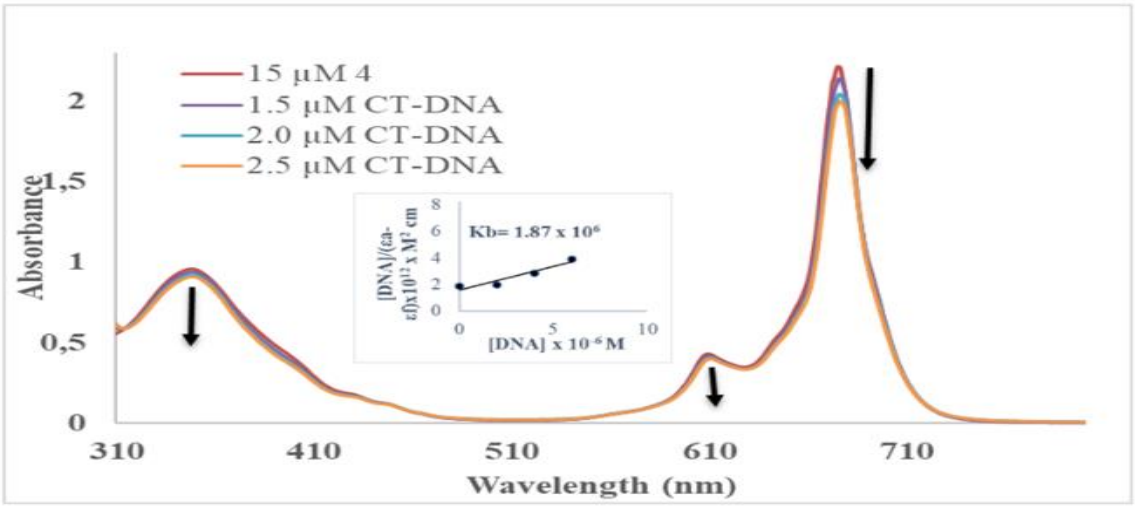


Fig. 5: The spectra of electronic titration of **4**+DNA complex formed via gradual addition of increasing amounts of the DNA (1.5, 2.0, and 2.5 µM) to **4** (15 µM) (red line) in the buffer at a pH of 7.34.

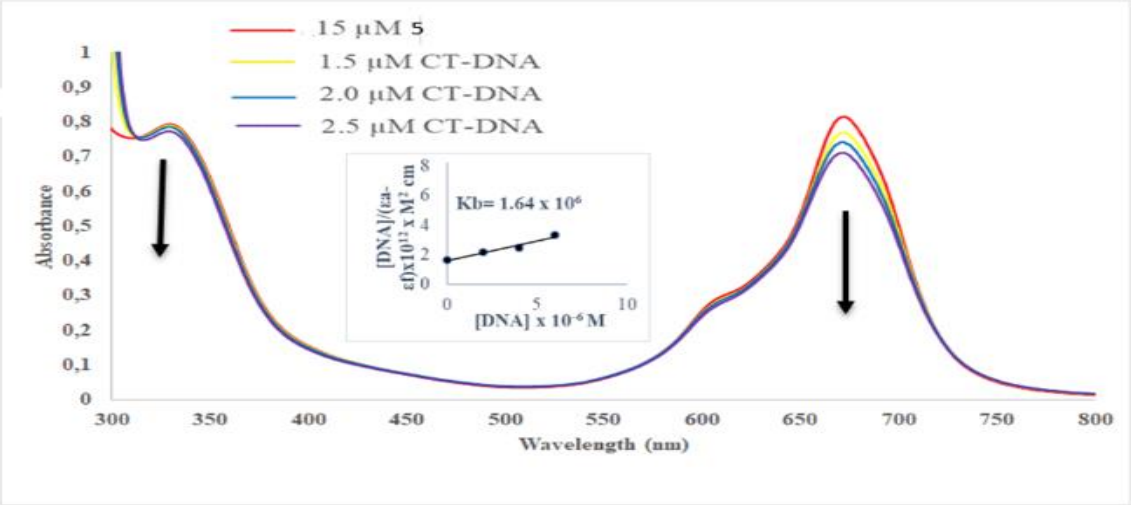


Fig. 6: The spectra of electronic titration of **5**+DNA complex formed via gradual addition of increasing amounts of the DNA (1.5, 2.0, and 2.5 µM) to **5** (15 µM) (red line) at a pH of 7.34.

Fluorescence titration studies

Ethidium bromide (EB) reagent is recognized intercalating chemical compound that is widely utilized to identify DNA interaction mechanism by its fluorescence technique. The presence of any other molecule in the mixture that interacts with DNA in a competitive manner with EB+DNA complex when the amount of the intercalating molecule increases, leading a decline in intensity values of EB by interfering with the EB+DNA complex [24]. The competitious EB exchange tests for complexes **4** and **5** were conducted utilizing fluorescence spectrophotometry. First, EB substitution experiment was conducted the adding of EB (15 µM) to CT-DNA (0-20 µM) sample. EB+DNA complex was titrated with varying concentrations of **4** and **5** from 0 to 15 µM and emission spectra were collected ranging from 450 nm to 750 nm. It was detected that **4** and **5** react with DNA competitively with EB, distort the EB+DNA complex when the amount of **4** and **5** concentrations are increased and lead a diminution in emission intensities of EB+DNA as illustrated in Figs. 7 and 8. Findings obtained from the method demenstrated that **4** and **5** phthalocyanine complexes interact with DNA via an intercalative mechanisms.

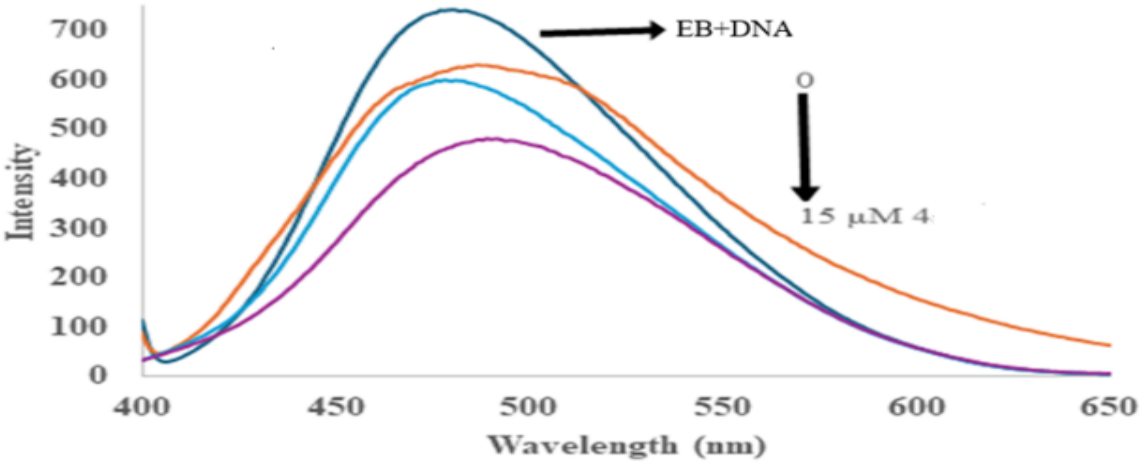


Fig. 7**:** Emission spectra of addition of increasing amounts of **4** complex (0, 5, 10 and 15 µM) to EB+DNA complex (green line).

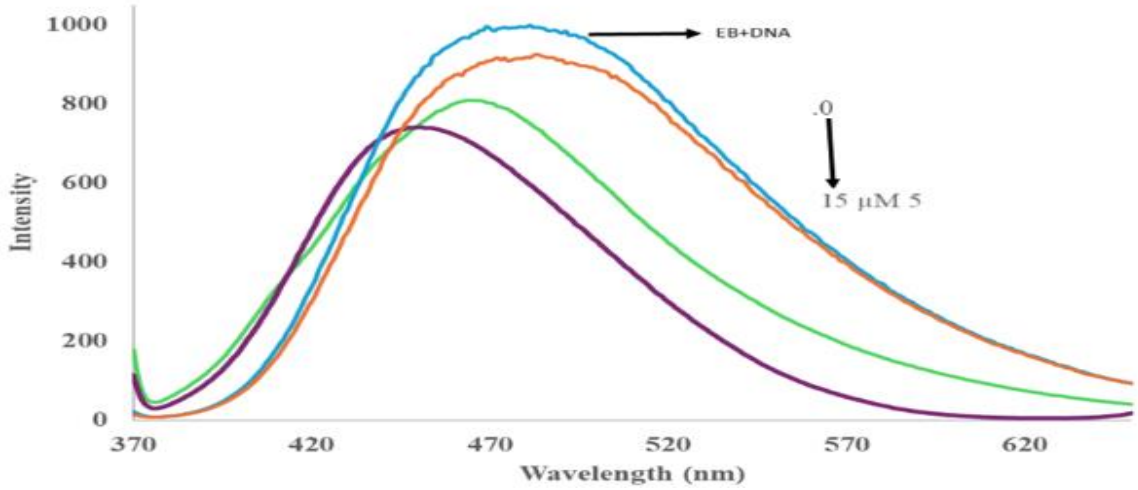


Fig. 8: Emission spectra of addition of increasing amount of **5** complex (0, 5, 10 and 15 µM) to EB+DNA complex (blue line).

Viscosity assay

In the present study, the viscosity tests for the complexes **4** and **5** have been done at room temperature by the system of Ubbelohde viscometer. The objective was to have a more in-depth look at the DNA attachment mechanisms of **4** and **5** complexes by means of viscosity assays. It is reasonable to assume that the viscosity assay will generate valuable data on the DNA binding mechanism, which is sensitive to DNA length variation and is considered a key test for DNA attechment mechanism in the lack of conformation data [37,38]. In a general way, when a small compound is penetrated into DNA, DNA extends as base pairs are split to shelter the attached group, this leads to an increasing DNA viscosity. Nonetheless, metal complexes that react with DNA via the mode of non-classical intercalation may lower efficient size of DNA via kinking strand, leading to a decline in the viscosity of DNA [39]. In adding to this information, the electrostatic and groove attachment mechanisms have a low influence upon the viscosity of the DNA.

As can be seen in Fig. 9, the relative viscosities of DNA rised steadily with the addition of increasing amounts of **4** and **5** to DNA (0-20 µM). Relative viscosity values were charted versus [complex]/[DNA]. Here η_0 and η represent relative contributions of DNA to specific viscosity in the absence and presence of **4 (**0-20 µM) and **5** (0-20 µM) complexes as shown in Fig. 9. The cause of this rise in relative viscosity because of the lengthening of the DNA molecule. The data obtained with this method is an important piece of evidence that **4** and **5** compounds insert themselves efficiently between DNA base pairs. There was a remarkable change in relative viscosity of DNA, suggesting an intercalative binding mechanism. In the light of these data, it was concluded that complexes **4** and **5** attach to DNA via an intercalative mechanism.

*Examination of the interaction of **4** and **5** with DNA by gel electrophoresis*

The impact of varying concentrations of complexes **4** and **5** upon the DNA was tested via electrophoresis to detect the reactivity of **4** and **5** compounds with DNA. The outcome of methodology is presented in Fig. 10. The DNA bands generated for **4** (0- 20 µM) and **5** (0- 20 µM) were found to decrease in their intensity after attachment to CT-DNA (20 µM) by comparison with band produced for control CT-DNA. The distortion of the DNA double helix is responsible for the decline in intensity of the bands identified after binding of **4** and **5** to DNA. Degradation of DNA structure is thought to occur by backbone cleavage due to nucleophilic interactions of basic residues, according to previous studies published in the literature [40]. As well as the total number of molecules, the intensity of the ethidiumbromide bands built into DNA base pairs was also found to be dependent on the length of the DNA [41]. Thus, the reduced intensity of the electrophoretic lanes of CT-DNA when it interacts with complexes **4** and **5** may be attributed to the complex hindering the interaction between the overlaid bases inside the surface binding to active nucleophilic sites in the DNA double helix. The band intensity reduction of complexes **4** and **5** is about 76.8% and 71.3%, respectively.

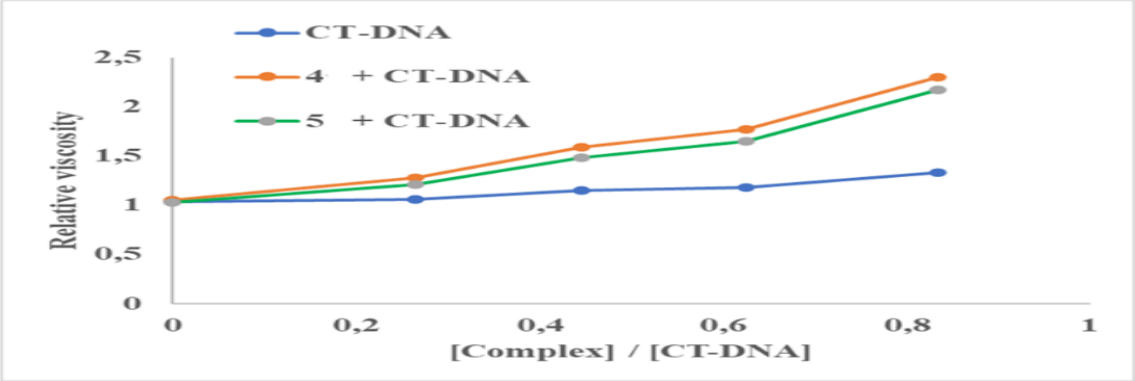


Fig. 9: Influence of the increases in the amount of **4** and **5** on the relative viscosity of CT-DNA (blue line).

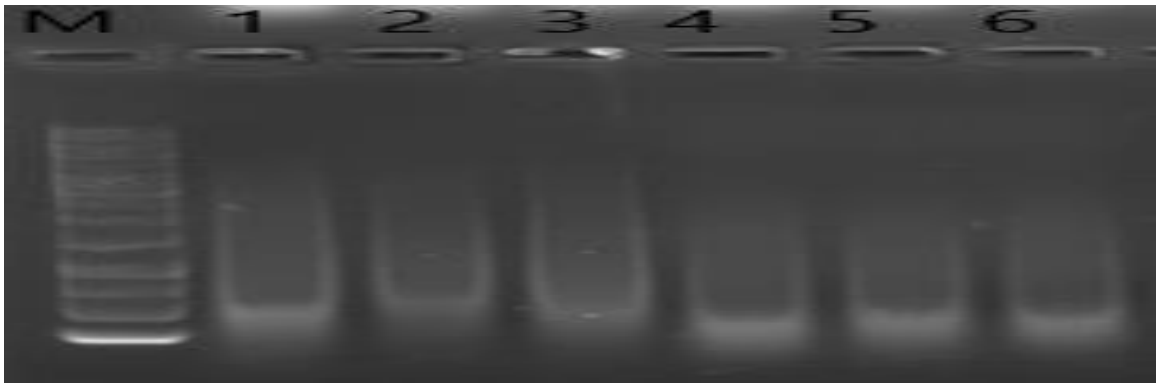


Fig. 10: The electrophoresis revealing the interactivity of the complexes (**4** and **5**) with CT-DNA. Lane M refers to DNA ladder. Lanes 1-3 belong to CT-DNA (20 µM) + **4** complex (10, 15 and 20 µM) and lanes 4-6 represent the CT-DNA (20 µM) + **5** complex (10, 15 and 20 µM), respectively.

Thermal melting point studies

The substantial details about the mechanism of attachment of small moieties to DNA are gained from the melting temperature data. To validate the efficiency of peripherally quaternised tetra-substituted **4** and **5** phthalocyanine complexes with DNA, melting point experiments were employed. The melting point (T_m), the value where half of the total base pairs are no longer aligned, gives an indication of the stability of the DNA double helix [42].

In the present investigation, the T_m value of CT-DNA (0-20 µM) was obtained to be 76.77 ºC in the lack of the complexes. The Tm values of the DNA+**4** (0-20 µM) and DNA+**5** (0-20 µM) were assigned to 82.38 ºC and 81.97 ºC as listed in Table-1, respectively. The data revealed that **4** binds to CT-DNA to a greater extent than **5**. This was in agreement with the data derived from the absorption spectroscopy experiments. Typically, when the ΔT_m value, the melting temperature deviation between the DNA and the DNA+complex, is high, the binding mechanism is said to be intercalative, whereas when it is not, the binding mode is said to be non-intercalative. It can be proposed that the binding of **4** and **5** to DNA is intercalative, according to the results obtained with this technique.

Table-1: T_m data of the DNA in the lack and in the existence of **4** and **5** complexes.

Samples	*T_m values*
CT-DNA	**76.77 ºC**
4+CT-DNA	**82.38 ºC**
5+CT-DNA	**81.97 ºC**

Conclusion

In this study, peripheral tetra substituted zinc (II) and cobalt (II) phthalocyanines were synthesized utilizing diethyl 3,4-dicyanophenylmalonate as a starting material. FT-IR and UV/Vis spectroscopy were applied to characterize the complexes. This is the first work about interaction of **4** and **5** phthalocyanines with DNA. Structural activity relationship is important because identical compounds have the same physical and biological characteristics. There is a link between

molecular structures and biological properties. The interaction mechanism of Zn(II) (**4**) and Co(II) (**5**) phthalocyanines with CT-DNA was analyzed by absorption titration, emission spectra, viscosity, electrophoresis and thermal denaturation methods. From the results obtained from electronic, emission spectra, viscosity and thermal melting point techniques estimated that the **4** and **5** complexes binds to DNA intercalatively. The electrophoresis assay for the complexes also support that the complexes interact with the DNA. From the results it can be said that the phthalocyanine **4** and **5** complexes could have a potential usage in cancer therapy. In order to confirm the data obtained, we recommend further research on this subject.

Acknowledgements

Authors declare no conflict of interest.

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