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DNA Interaction Studies of Newly Synthesized Mixed Ligand Complexes of Cobalt (III)

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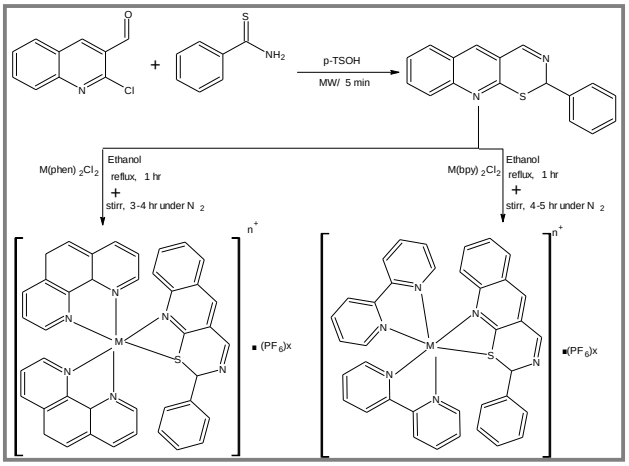
ABSTRACT

DNA binding and Oxidative cleavage characteristics of a series of mixed ligand cobalt (III) complexes of bioactive ligands containing N and S donor atoms viz; $[Co(phen)_2(qtdp)](PF_6)_3$ and $[Co(bpy)_2(qtdp)](PF_6)_3$. 1,10-phenanthroline (phen), 2'2 bipyridene (bpy) have been investigated in detail. Various physico-chemical and biochemical techniques including UV/Visible, viscometric titration, thermal denaturation, and differential pulse voltammeter have been employed to probe the details of DNA binding by these complexes; intrinsic binding constants (Kb) have been estimated under a similar set of experimental conditions. Analysis of the results suggests that intercalative ability of the coordinated ligands varies as phen > bpy in this series of complexes. While the Co(III) complexes investigated in this study effect oxidative cleavage of the supercoiled pUC19 DNA. Results of detailed investigations carried out inquiring into the mechanistic aspects of DNA oxidative cleavage by $[Co(phen)_2(qtdp)]^{3+}$, $[Co(bpy)_2(qtdp)]^{3+}$ have also been reported.

Graphical Abstract



$[M(phen)_2(qtdp)](PF_6)_X$ **$[M(bpy)_2(qtdp)](PF_6)_X$**

M = Co(III), n = 3, x = 3

phen = 1,10-phrnanthroline; bpy = 2'2-bipyridine ; qtdp = quinolino(2,3-b) thiadizepine

Scheme leading to the synthesis of $[Co(phen)_2(qtdp)](PF_6)_3$, and $[[Co(bpy)_2(qtdp)](PF_6)_3]$

Keywords: Oxidative cleavage, Binding constant, 2'2-bipyridine, Voltammeter, Supercoiled.

INTRODUCTION

It has been evident that, from the evolution of life, the metal-based complexes have recorded their existence in several biological systems as well as in medicinal field. Some of those as Haemoglobin (transportation of oxygen in red blood cells), chlorophyll (photosynthesis in green plants) and a few natural metalloenzymes (Vitamin B12) have already established their significance prominently in bio chemistry [**1**]. The bio-activity of the metal complexes obviously depends on the nature of functional groups of the ligand, metal atoms as well as on their oxidation states. After the discovery of cisplatin on various types of malignancy researchers and chemists received much attention and interest in bioinorganic chemistry of metal complexes. Though it is remarkably efficient for treating a variety of malignancy but these platinum complexes exhibited considerable drawbacks in cancer therapy as neurotoxicity, nephrotoxicity and emetogenesis, finally are not orally bioavailable [**2-3**]. These limitations endorsed researchers to improve alternative approaches based on various metals along with substantial biological activity on pointed targets.

In recent years, more and more biochemists and pharmacologists have paid their attention to research on other transition metal complexes such as ruthenium (II), copper (II), zinc (II), nickel (II), cobalt (II) complexes compared with traditional platinum compounds in treatment of human cancer due to their potential applications as chemical and stereoselective probes of nucleic acid structures as well as diverse biological activities [**4-8**]. Among these Cobalt complexes has attracted much attention, because of their applications in the biological systems such as, presence of active centre of Vitamin B12. Since the Firsts reported studies into the biological activity of cobalt complexes [**9**], diverse structurally characterized cobalt complexes showing antitumor antiproliferative [**10, 11**], antimicrobial [**12, 13**], antifungal [**14, 15**], antiviral [**16, 17**], and antioxidant [**18**] activities have been reported.

Deoxyribonucleic acid (DNA) plays a significant role in the life process because it carries the inheritance information and leads the biological synthesis of proteins and enzymes through the replication and transcription of genetic information in living cells. DNA is especially a good target for metal complexes as it gives a wide variety of potential metal binding sites [**19-21**]. For example, the rich DNA electron bases and phosphate groups are suitable for direct covalent coordination at the metal centre. There are noncovalent binding behaviors such as hydrogen bonding and electrostatic binding in the grooved regions of the DNA, along with the intercalation of planar aromatic ligands in the stacked base pairs [**22–29**]. The interaction of DNA with transition metal complexes has gotten intensive attention in the last few years in order to develop new novel nonradioactive probes of DNA structure [**30,31**], new therapeutic agents that cleave DNA [**32-34**] and DNA-mediated electron transfer reactions [**35**].

Recently, binding of metal complexes with dppz or modified dppz moieties to DNA has attracted much attention [**36-38**]. Synthesis of new cobalt (II) complexes enabled chemists to extensively study the ability of these complexes to act as probes in investigating the structure of DNA, when these metal complexes are incorporated with either dppz or a modified dppz moiety as one of the ligands. Among such metal complexes of intercalatable ligands, those incorporating new polypyridyl ligands (1, 10-phen/2'2-bpy) are known to possess unique characteristics [**39**].

Taking into consideration the biological role and activity of cobalt and its complexes containing intercalating ligands, we have initiated the investigation of the interaction of cobalt (II) with two phenanthroline and one of our synthesized ligands. In this context, we report the synthesis, characterization, and DNA-binding studies of a new cobalt(II) complex containing two 1.10

phenanthroline (phen) / 2'2 bipyridine (bpy) and one quinolino[2, 3-*b*]thia-diazepine (qtdp) as ligands to find the effect of different kinds of ligands on the mode of DNA binding.

MATERIALS AND METHODS

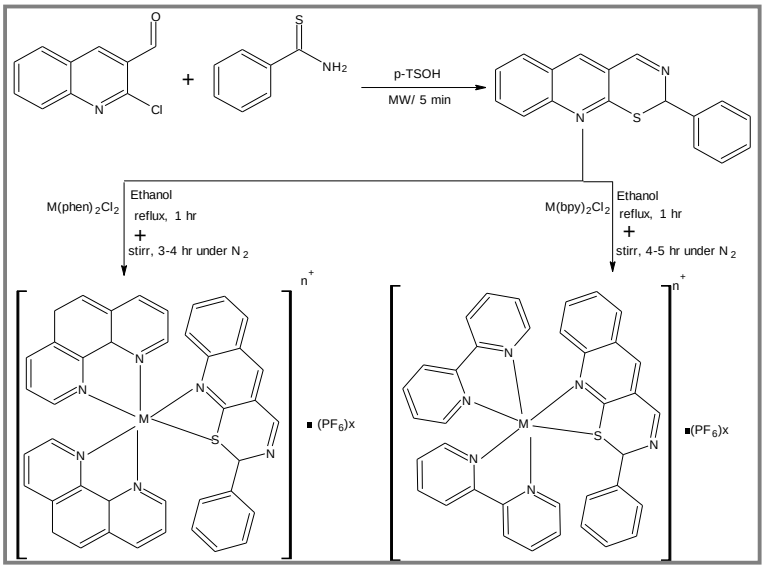
Formyl quinoline, $[Co(phen)_2Cl_2]Cl.3H_2O$, $Co(bpy)_2Cl_2]Cl.3H_2O$ were prepared by the reported procedures [40]. Synthesis of quinolino [2, 3-*b*] thia-diazepine (qtdp) and its corresponding complexes of Co (III) with 1.10 phenanthroline and 2.2′-bipyridine are described below.

Synthesis of $[Co(phen)_2(qtdp)](PF_6)_3$ (1): To a 50 mL ethanolic solution of $[Co(phen)_2Cl_2]Cl.3H_2O$ (0.57 g, 1 mM) was added to a ethanolic solution of quinolino[2,3-b] thia-diazepine (qtdp) (0.162 g, 1 mM). The mixture was refluxed for 4 hr with constant stirring under nitrogen. It was then filtered and the complex was precipitated upon addition of a saturated ethanolic solution of ammonium hexafluorophosphate. The complex was filtered and dried under vacuum before being recrystallized (acetone-ether).

Synthesis of $[Co(bpy)_2(qtdp)](PF_6)_3$ (2): To a 50 mL ethanolic solution of $[Co(bpy)_2Cl_2]Cl.3H_2O$ (0.53 g, 1 mM) was added to a ethanolic solution of qtdp (quinolino[2,3-b] thia-diazepine) (0.162 g, 1 mM). The mixture was refluxed for 4 h with constant stirring under nitrogen. It was then filtered, and the complex was precipitated upon addition of a saturated ethanolic solution of ammonium hexafluorophosphate. The complex was filtered and dried under vacuum before being recrystallized (acetone-ether).

RESULT AND DISCUSSION

The ligand quinolino[2,3-*b*] thia-diazepine (qtdp) was prepared by the reaction of 2-chloro-3-quinoline carbaldehyde with thiobenzamide in presence of *p*-toluene suphonic acid in a microwave oven. The corresponding metal complexes were synthesized by reacting the appropriate precursors, viz: $[Co(phen)_2Cl_2]Cl.3H_2O$ and $[Co(bpy)_2Cl_2]Cl.3H_2O$ with quinolino[2,3-b] thia-diazepine (qtdp) ligand in 1:1 ratio. Synthesis of qtdp and the corresponding mixed ligand complexes of cobalt (III) with phen/bpy are illustrated in figure 1.



$[M(phen)_2(qtdp)](PF_6)_X$ **$[M(bpy)_2(qtdp)](PF_6)_X$**

M = Co(III), n = 3, x = 3

phen = 1,10-phrnanthroline; bpy = 2'2-bipyridine ; qtdp = quinolino(2,3-b) thiadizepine

Figure 1. Scheme leading to the synthesis of $[Co(phen)_2(qtdp)](PF_6)_3$, and $[[Co(bpy)_2(qtdp)](PF_6)_3]$.

Characterization of complexes: The newly synthesized complexes were air stable and soluble in polar solvents such as acetone, ether, DMF, and DMSO. The elemental analysis UV-visible, IR, ^{1}H NMR and magnetic susceptibility data of the new complexes are summarized in Table 1. The elemental analysis data are agreed with the theoretical values within the limit of experimental error and confirm the molecular formula of the complexes.

In the IR spectra of ligand the strong bands appearing at 1611 cm^{-1} and 1355 cm^{-1} were assigned to γ(C=N) of azomethine group and γ(C-S-C) of thiophene moiety. They have been shifted to lower frequency in all the complexes by 21-30 cm^{-1} revealing the participation of azomethine nitrogen and thiophene sulfur in coordination to the metal. In the ^{1}H NMR spectra of Co (III) complexes, the peaks due to various protons of 1,10-phenanthroline/2'2 bipyridine and qtdp are seen to be shifted in complexation with corresponding free ligands suggesting complexation.

Table 1. Analytical and physical properties of the Ligand and mixed ligand Co(III) complexes.

Compound	Yield (%)	Colour	Mol.wt	Found (Cal.)%				
				C	H	N	S	M
qtdp	76	Yellow	276.35	78.81 (78.88)	4.16 (4.38)	10.25 (10.14)	11.57 (11.60)	
$[Co(phen)_2(qtdp)](PF_6)_3$	78	Pink	1188.01	40.36 (40.43)	2.97 (3.03)	5.16 (5.24)	6.23 (6.04)	(4.96)
$[Co(bpy)_2(qtdp)](PF_6)_3$	74	Pink	1139.97	37.18 (37.93)	3.26 (3.15)	6.69 (6.59)	7.20 (7.12)	(5.16)

UV-visible spectrum of qtdp is characterized by prominent low energy, structured absorption bands in the 210-260 nm regions. The ligand also shows high intensity bands in the UV region, Fig.2. Considerable shifts in the wavelengths of absorption maxima (λ_{max}) and molar extinction coefficients (ε) were noticed for these low energy (and also the high energy) bands of qtdp in comparison with those obtained for either the physical mixture or the summation spectra involving the corresponding starting materials. This is not surprising if one considers that phen and the pyrenyl chromophores are directly fused to each other in this ligand.

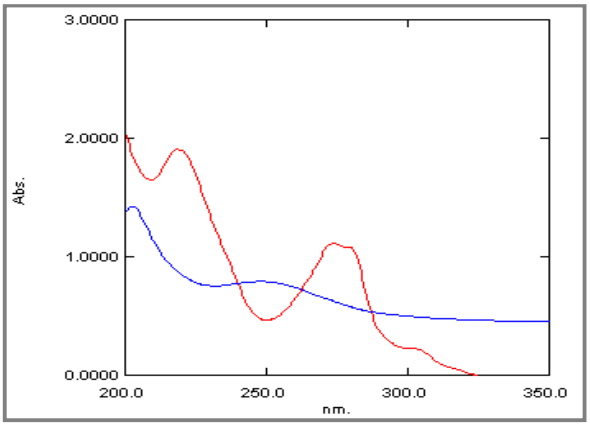


Figure 2. UV-Visible spectra of qbdp(blue) and $[Co(phen)_2(qtdp)]^{3+}$ (red) DMF.

DNA binding studies: The interaction of two new complexes viz; $[Co(phen)_2(qtdp)]^{3+}$ and $[Co(bpy)_2(qtdp)]^{3+}$ with calf thymus DNA was investigated by electronic absorption spectra, thermal denaturation, viscosity measurements and cyclic voltammetric studies.

Absorption Titration: The electronic absorption spectra of complexes in buffer (50 mM Tris-HCl, 50 mM NaCl, pH 7.2) were performed using a fixed complex concentration to which increasing amounts of calf thymus DNA solution were added. A solution of calf thymus DNA (CT-DNA) in the buffer gave a ratio of UV absorbance at 260 and 280 nm of ca. 1.8-1.9:1 indicating that the DNA was sufficiently free from protein. The concentration of CT-DNA was determined spectrophotometrically using the molar absorptivity 6000 mol^{-1} cm^{-1} at 260 nm. Stock solutions were stored at 4°C and used in no more than four days. The complex and DNA solutions were allowed to incubate for 10 min before the absorption spectra were recorded.

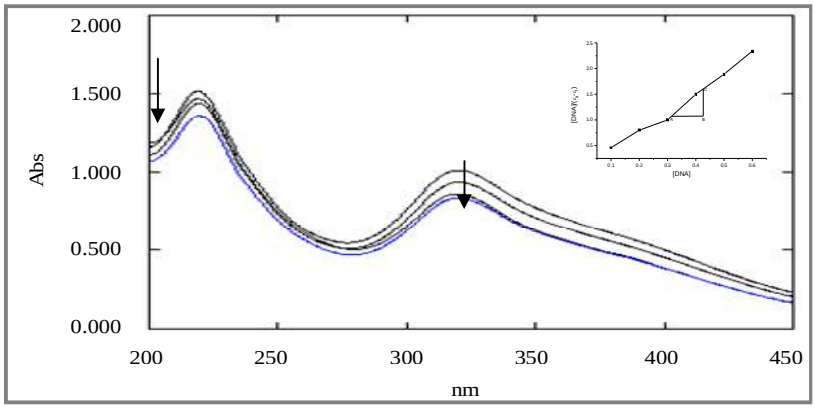


Figure 3. Absorption spectra of complex $[Co(phen)_2(qtdp)]^{3+}$ in Tris-HCl buffer upon addition of DNA. [Co] = 0.5 μM, [DNA] = 0.1μM. Arrow shows the absorbance changing upon the increase of DNA concentration.

The inner plot of [DNA]/ (ε_a-ε_f) vs [DNA] for the titration of DNA with Co (III) complex

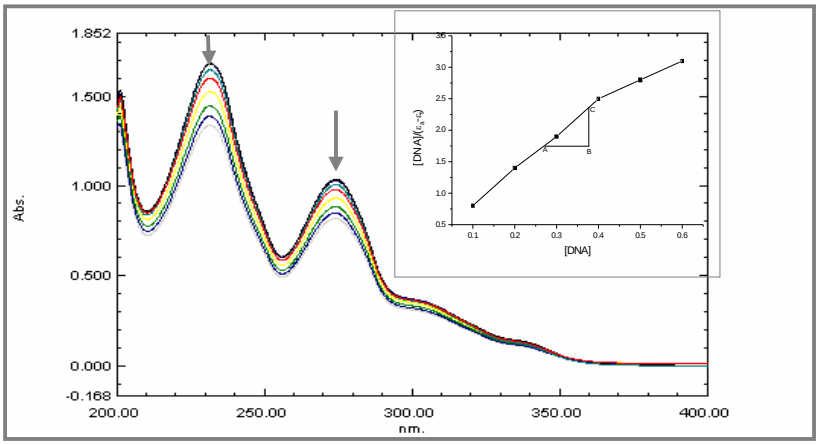


Figure 4. Absorption spectra of complex $[Co(bpy)_2(qtdp)]^{3+}$ in Tris-HCL buffer upon addition of CT DNA. [Co]=0.5 μM, [DNA]=0.1μM. Arrow shows the absorbance changing upon the increase of DNA concentration.

The inner plot of [DNA]/ (ε_a-ε_f) vs [DNA] for the titration of DNA with Co(III) complex

The addition of increasing amounts of CT-DNA to all the complexes shows a decreases of molar absorbtivity (hypochromism, Δε, 16-28%,) (Table 2) (Fig. 3 and Fig. 4) of the π-π* absorption bands as well as a red-shift of a few nm (4-6) indicating the binding of the complexes to DNA in different modes and to different extents. The binding of an intercalative molecule to DNA has been well characterized by large hypochromism and significant red-shift due to interaction between the aromatic chromophores of the qtdp and DNA base pairs. The extent of hypochromism and red-shift

commonly consistent with the strength of intercalative interaction. The magnitude of hypochromism and red-shift observed for both the cobalt (III) complexes are comparable to those observed for typical classical intercalators and partially intercalating metal complexes bound to CT-DNA [41].

To enable quantitative comparison of the DNA binding affinities the intrinsic binding constant, K_b of the complexes for binding with CT-DNA were obtained by using the equation,

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

where [DNA] is the concentration of DNA in base pairs, ε_a corresponds to the apparent absorption coefficient $A_{abs}/[M]$, ε_f corresponds to the extinction coefficient for the free metal [M] complex and ε_b corresponds to the extinction coefficient for the metal [M] complex in the fully bound form. Each set of data, when fitted to the above equation, gave a straight line with a slope of $1/(\varepsilon_a-\varepsilon_f)$ and y-intercept of $1/ K_b(\varepsilon_b-\varepsilon_f)$ and K_b was determined from the ratio of the slope to the intercept (Fig. 3 and 4). The intrinsic binding constants K_b obtained for the complexes follow the order $[Co(phen)_2(qtdp)]^{3+}$ > $[Co(bpy)_2(qtdp)]^{3+}$ suggesting that the qtdp of the complexes were involved in DNA binding and that the coordinated phen and bpy is engaged in partial insertion in between the base pairs of DNA. The observed K_b values are summarized (Table 2), and are comparable to those observed for typical classical intercalators [EthBr, K_b, $1.8x10^6$ M^{-1} in 25 mM Tris-HCl/40 mM NaCl buffer, pH 7.9) and partial intercalating metal complexes $[Ru(phen)_2(dppz)]^{2+}$, dppz = dipyrido-[3,2-d: 2′,3′-f]-phenazine, $K_b>10^6$ M^{-1}] bound to CT-DNA. So, it is obvious that the synthesized complexes are involved in weaker intercalative interaction obviously due to steric clash between the qtdp ligand and DNA double helix. However, the strongest binding affinity exhibited by the phen containing complexes is expected on the basis of additional aromatic ring of 'phen', which enhances the extent of stacking with the DNA base pairs.

Table 2. Absorption spectral properties of Co(III) complexes bound to CT-DNA.

Compound	Ligand –based				
	λ_{max} (nm)	Change in Abs.	Δε (%)	Red-shift (nm)	K_b x 10^5 (M^{-1})
$[Co(phen)_2(qtdp)](PF_6)_3$	214	Hypochromism	27	4	3.4
$[Co(bpy)_2(qtdp)](PF_6)_3$	223	Hypochromism	18	4	1.6

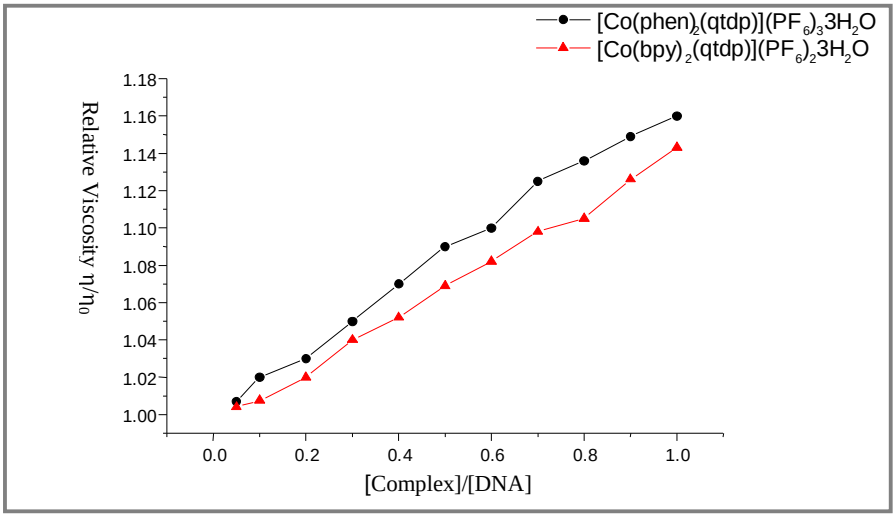


Figure 5. Effect of increasing amounts of the complex $[Co(Phen)_2(qbdp)](PF_6)_3$ [----●---] and $[Co(bpy)_2(qbdp)](PF_6)_2$ [----∇----] on the relative viscosities of CT-DNA at 25 (±0.1)^{0}C.

Viscosity measurements: To understand the nature of DNA binding of the mixed ligand cobalt (III) complexes, viscosity measurements were carried out on CT-DNA by varying the concentration of the added complexes. The values of relative specific viscosity (η/η_o), where η and η_o are specific viscosities of DNA in the presence and absence of the complex respectively, are plotted against 1/R (=[Complex]/[DNA]) = 0-1 (Fig.5). The ability of the complexes to increase the viscosity of DNA depends upon the qtdp ligand. The obtained results are parallel to the hypochromism and K_b values observed for the complexes in absorption studies.

The effect of both complexes on the viscosity of DNA is shown in (Fig.5). The viscosity of DNA is increased with the increasing the addition of each complexes, and it is similar to the behaviour of well known DNA-intercalator ($[Ru(bpy)_2(dppz)]^{2+}$)[**42**]. These results supported that all the complexes intercalated between two adjacent base pairs of DNA through intercalation mode.

Thermal Denaturation Studies: The absorbance at 260 nm was continuously monitored for solutions of CT-DNA (0.1μM) in the absence and presence of the complexes (0.5 μM) through the variation of temperature. The temperature of the solution was increased by 1^0C min^{-1}.

Thermal denaturation experiments carried out on CT-DNA in the absence of any added complex revealed that the T_m and σ_T values for the duplex are 60±2 and 24±1^0C, respectively, under the same experimental conditions. Addition of complex (1) and (2) increased the T_m by 5±1 and 4±1^0C, respectively. By contrast, addition of complex to DNA increased the T_m value by < 6°C. The σ_T values are 26±1 and 25 ±1^0C for complex (1) and (2) respectively (Fig. 6).

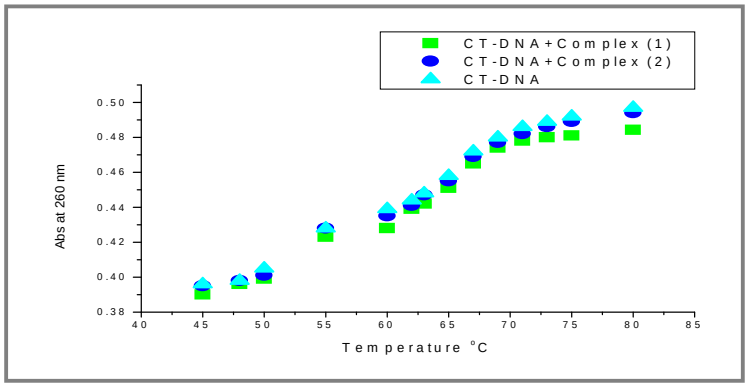


Figure 6. Melting curves of CT-DNA in the absence and presence of complexes $[Co(phen)_2(qtdp)]^{3+}$ and $[Co(bpy)_2(qtdp)]^{3+}$.

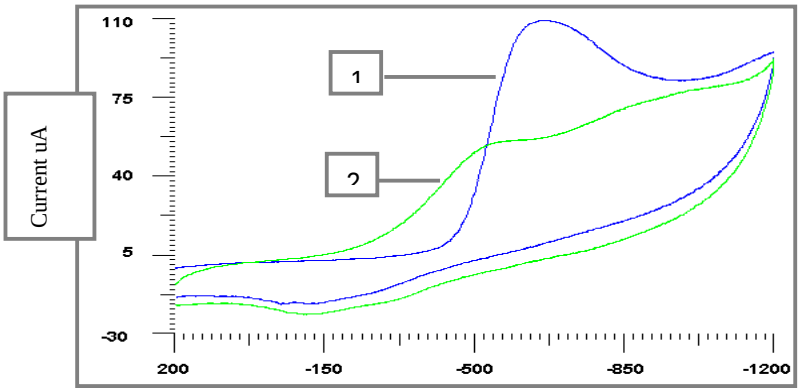


Figure 7. Cyclic voltammograms of complex in Tris –HCl buffer in absence **(1)** and presence of DNA **(2).**

Cyclic voltammetric Studies: The application of cyclic voltammetry to study of the interaction between complexes and DNA provides a useful compliment to the previously utilized methods of investigation such as UV-Vis and viscosity experiments. The typical cyclic voltammogram of 0.02 mM solution of complexes without and with DNA at carbon paste electrode in Tris-HCl buffer were carried out (Fig. 7).

The results of oxidative DNA cleavage experiments carried out with the complexes of Co (III) (at the concentration of 20 μM and 40 μM) as mentioned by the agarose gel electrophoresis method. Control experiments suggested that untreated DNA does not show any cleavage (lane 1; Fig. 8). It is show that the complexes (1) and (2) at higher concentration (40 μM) shown more cleavage activity in which super coiled (Form-I) DNA cleaved and supercoiled would relaxed and produced a slower moving nicked circular form (Form-II) (lane 3 and 5; Fig. 8) compared to lower concentration (20 μM) (lane 2 and 4; Fig. 8). In conclusion at higher concentration of 40 μM both complexes show more cleavage activity. From these results we infer that the cobalt (III) complexes at higher concentrations act as a potent nuclease agents.

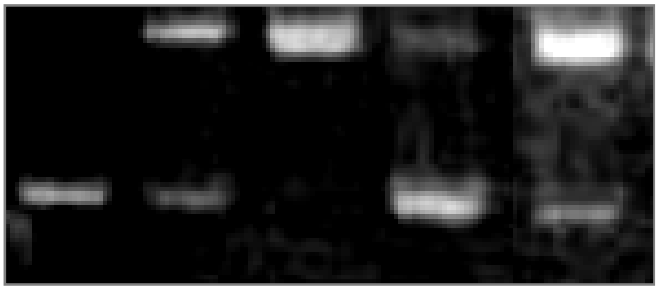


Figure 8. Cleavage of supercoiled pUC19 DNA (0.5 μg) by the cobalt (III) complexes with phen/bpy and qtdp ligands in a buffer containing 50 mM Tris-HCl and 50 mM NaCl at 37 °C. Lane 1 DNA alone; Lane 2, DNA+20 μM of complex (1); Lane 3, DNA+40 μM of complex (1); Lane 4, DNA+20 μM of complex (2); Lane 5, DNA+40 μM of complex (2). Forms I-II are supercoiled and nicked circular DNA, respectively

CONCLUSIONS

New ligand quinolino[2,3-*b*] thia-diazepine (qtdp) containing N and S atom with 1,10,-phenanothroline/2'2 bipridine mixed-ligand complexes of cobalt(III) have been synthesized and characterized by spectroscopic methods. Absorption, viscometric, cyclic voltammetric as well as thermal denaturation studies have revealed that each of these octahedral complexes are bound to DNA. However, the strongest binding affinity exhibited by the phen containing complexes is expected on the basis of additional aromatic ring of 'phen', which enhances the extent of stacking with the DNA base pairs, while both the investigated cobalt(III) complexes affected the oxidative cleavage of DNA at higher concentrations (supercoiled pUC19).

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