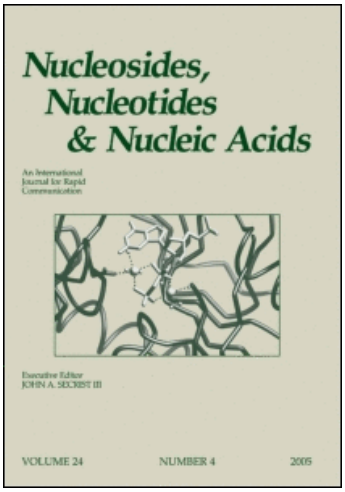

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Binding and Oxidative Cleavage Studies of DNA by Mixed Ligand Co(III) and Ni(II) Complexes of Quinolo [3,2-*b*]Benzodiazapine and 1,10-Phenanthroline

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BINDING AND OXIDATIVE CLEAVAGE STUDIES OF DNA BY MIXED LIGAND CO(III) AND NI(II) COMPLEXES OF QUINOLO [3,2-*b*]BENZODIAZAPINE AND 1,10-PHENANTHROLINE

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□ *Two mixed ligand complexes of the type* $[M(phen)_2(qbdp)](PF_6)n.xH_2O$ *where* $M = Co(III)$ *and Ni(II), qbdp = quinolo[3,2-b] benzodiazepine and phen = 1,10-phenanthroline,* $n = 3$ *or 2,* $x = 2$ *or 3 have been synthesized and characterized by employing analytical and spectral methods. The DNA binding property of the complexes with calf thymus-DNA has been investigated by using absorption spectra, viscosity measurements as well as thermal denaturation studies. The absorption spectral results indicate that the Co(III) and Ni(II) complexes intercalate between the base pairs of the DNA tightly with intrinsic DNA binding constant of* 6.4×10^4 *and* 4.8×10^4 M^{-1} *in Tris HCl buffer containing 50 mM NaCl, respectively. The large enhancement in the relative viscosity of DNA on binding to the quinolo [3,2-b] benzodiazepine supports the proposed DNA binding modes. The complexes on reaction with super coiled (SC) DNA shows nuclease activity.*

Keywords Mixed ligand complexes; Co(III) and Ni(II); phenanthroline benzodiazepine; DNA binding; DNA cleavage

INTRODUCTION

Studies of mixed ligand transition metal complexes, which bind at specific sites along a DNA strand as reactive models for protein-nucleic acid interaction, provide routes toward rational drug design as well as means to develop sensitive chemical probes for DNA. Thus, a number of metal chelates are of current interest for important applications in nucleic acid chemistry as probes of DNA structure in solution, reagents for mediation

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of strand scission of duplex DNA under physiological conditions, and chemotherapeutic agents and in genomic research.[1–4]

Several cobalt(III) complexes have been reported which bind DNA through intercalation and are effective nucleases. Ji and co-workers have shown that these complexes are avid intercalators of DNA. They also have investigated the effect of ligand containing N-N donor atom and hydrogen bonding ability on the DNA binding by cobalt(II) complexes.[5–7] These complexes were shown to effectively cleave DNA and involve $^1O_2$ or OH as the reactive species. The overall DNA-binding and cleavage results obtained for these cobalt(III) complexes were in parallel with those obtained for their parent ruthenium(II) complexes.[8,9]

Large number of nickel(II)-salen (salen = ethylenediamine-N,N′-bis(salicylaldimine)) type complexes are found to be well suited for covalent modification of DNA, since the $Ni^{III/II}$ couple often lies near the redox potential of the ligand. In such cases, the coordinated metal ion serves to trigger redox chemistry that is ligand based, generating a reactive intermediate which couples with nucleobases to form a new covalent bond.[10] Very little attention has been paid to the DNA interactions of nickel(II) octahedral complexes. Except for $[Ni(phen)_2(qdppz)]^{2+}$, most other investigated nickel(II) octahedral complexes are found to be quite ineffective DNA cleaving agents.[11,12] The ability of $[Ni(phen)_2(qddpz)]^{2+}$ to photocleave DNA underscores the importance of the quinone functionality in the qdppz structure in the photochemical cleavage process.[13]

Over the past decade, there has been substantial increase in interest in the design and study of DNA binding properties of potential redox and spectroscopically active Co(III), Ni(II), Cu(II), and Ru(II) complexes[14–17] as new chemical nucleases[18] as they appear to be less readily repaired by DNA repair mechanism.[19] However, it is noted that a vast majority of such studies mainly have focused on those complexes containing the fully planar ligand, and DNA-binding investigations of such complexes containing substituted ligands have been relatively few. In fact, some of these mixed ligand complexes also exhibit interesting properties upon binding to DNA.[20–24] Varying the nature or location on the substituents in the intercalative ligand can create some interesting differences in the space configuration and electron density distribution of Co(III) and Ni(II) complexes resulting in difference in spectral properties, DNA-binding behaviors, and even cleavage properties. Studies of such differences will be helpful to understand more clearly the binding mechanism of Co(III) and Ni(II) complexes to DNA. Therefore, further studies using different structural ligands to evaluate and understand the factors that determine the DNA-binding mode and affinity are necessary.[25] On the other hand, there has been considerable interest in the DNA cleavage activity of the transition metal complexes under physiological conditions for varied applications of such complexes in nucleic

acid chemistry.[26–30] The oxidative cleavage of DNA involves nucleobase oxidation and/or degradation of sugar by abstraction of deoxyribose hydrogen atoms. Such cleavage can occur by chemical or photochemical means. In this article, we report the results of the DNA binding and oxidative cleavage properties of the new cobalt(III) and nickel(II) complexes, viz. $[Co(phen)_2(qbdp)](PF_6)_3.3H_2O$ $[Ni(phen)_2(qbdp)](PF_6)_2.2H_2O$, which efficiently cleave DNA in the presence of ascorbic acid.

EXPERIMENTAL

Materials

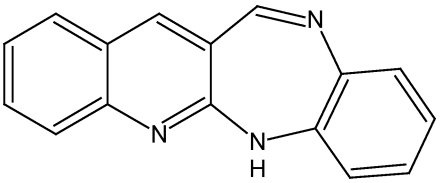
All reagents and solvents were of AR grade, purchased commercially. All the solvents were purified and used. $CoCl_2.6H_2O$, $NiCl_2.6H_2O$, and 1,10-phenanthroline monohydrate and ammonium hexaflurophosphate (NH_4PF_6) were purchased from Qualigens (India). Tris-HCl buffer (5 mM Tris-HCl, 50 mM NaCl, pH-7.2, Tris = Tris(hydroxymethyl) amino methane) solution was prepared using deionized double distilled water. Calf thymus DNA (CT-DNA) was purchased from Bangalore Gene, Bangalore, India.

Synthesis of Ligand

Synthesis of Quinolino[3,2-b]benzodiazepine(qbdp)

2-Chloro-3-quinolinecarbaldehyde (0.958 g, 5 m mo1) dissolved in small amount of acetic acid was taken in a 100 ml borosil beaker. *o*-Phenylenediammine (0.541 g, 5 m mol) and a pinch of potassium iodide were then added. The whole mixture was made into slurry and was irradiated by placing the beaker in a microwave oven for about 10 minutes. The completion of the reaction was monitored by TLC. The product obtained was poured into ice-cold water, the solid separated was filtered, dried, recrystallized, and its physical constants were measured.

Analysis: Calc. for $C_{16}H_{11}N_3$; C, 78.38; H, 4.48; N, 17.13%; Found: C, 78.12; H, 4.26; N, 17.35%; IR (KBr, cm^{-1}): 3330 (N–H); 1576 (C=C); 1658 (C=N); 2924 (C–H, aromatic); ^1H NMR (DMSO-d_6): δ 10.65 (s, 1H, NH); 8.4 (s, 1H, H–C=N); 7.2–7.8 (m, 9H, Ar-H). .



Quinolino[3,2-*b*]benzodiazepine(qbdp)

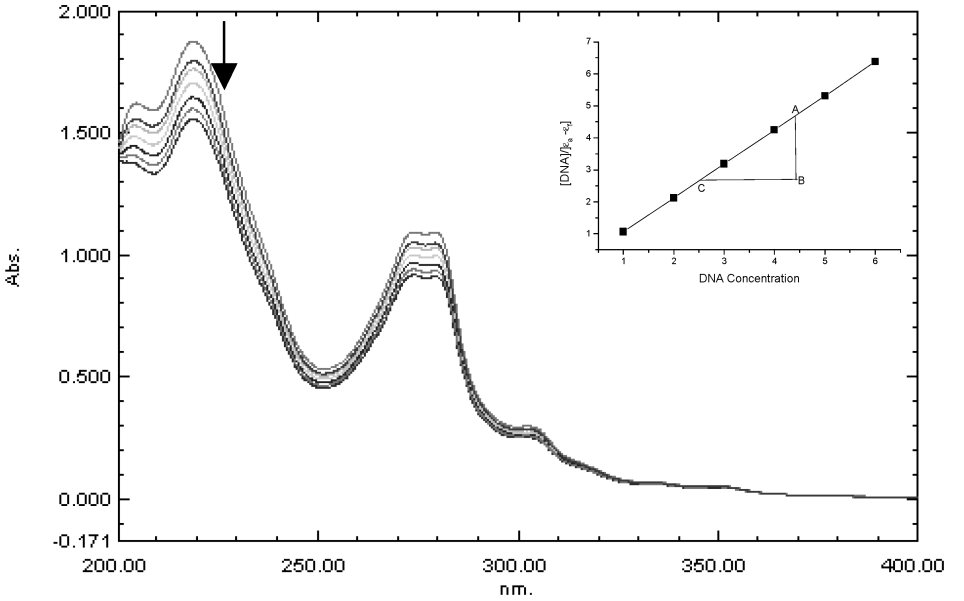


FIGURE 1 Absorption spectra of complex (**1**) in Tris-HCl buffer upon addition of DNA. [Co] = 0.5 μM, [DNA] = 0.1 μM. Arrow shows the absorbance changing upon the increase of DNA concentration. The inner plot of [DNA]/($\varepsilon_a - \varepsilon_f$) versus [DNA] for the titration of DNA with Co(III) complex.

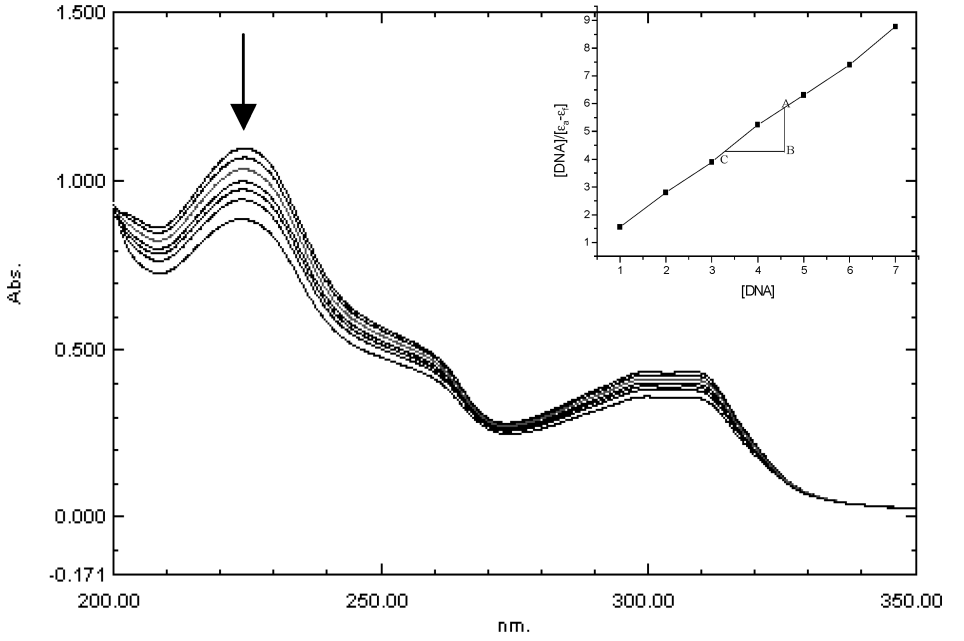


FIGURE 2 Absorption spectra of complex (**2**) in Tris-HCL buffer upon addition of CT DNA. [Ni] = 0.5 μM, [DNA] = 0.1 μM. Arrow shows the absorbance changing upon the increase of DNA concentration. The inner plot of [DNA]/($\varepsilon_a - \varepsilon_f$) vs [DNA] for the titration of DNA with Ni(II) complex.

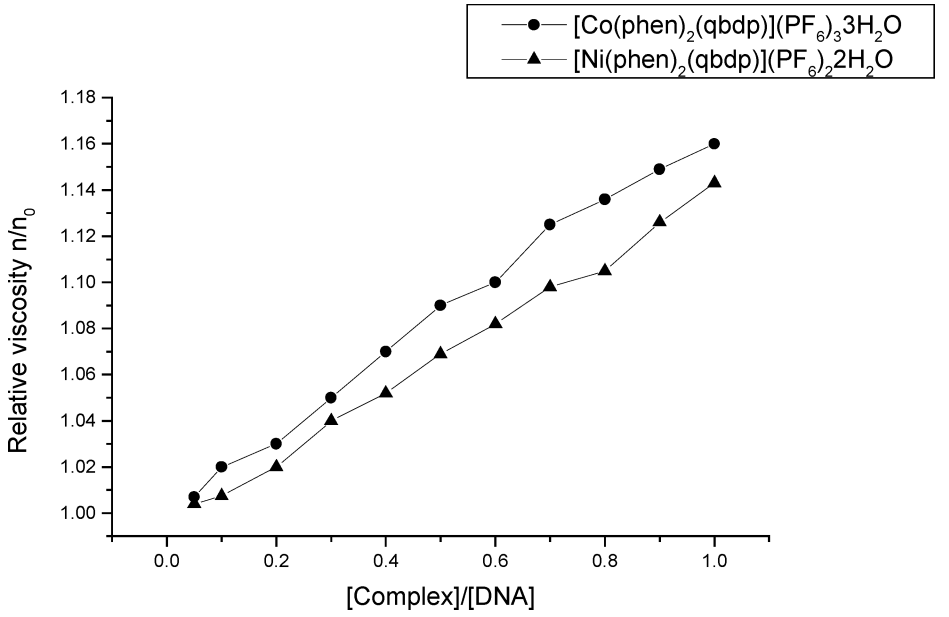


FIGURE 3 Effect of increasing amounts of the complex Co(III) [— ● —] and Ni(II) [— ▲ —] on the relative viscosities of CT-DNA at 25 (±0.1)°C.

Synthesis of Metal Complexes

Synthesis of Co(III) and Ni(II) Complexes

The complexes [Co(phen)$_2$Cl$_2$]Cl.3H$_2$O and [Ni(phen)$_2$Cl$_2$] were prepared as reported previously.[31,32]

Synthesis of [Co(phen)$_2$(qbdp)](PF$_6$)$_3$.3H$_2$O (1). To a 50 ml ethanolic solution of [Co(phen)$_2$Cl$_2$]Cl.3H$_2$O (0.57 g, 1 m mol) was added to an ethanolic solution of quinolino[3,2-b]benzodiazepine (0.245 g, 1 m mol). The mixture was refluxed for 1 hour with constant stirring and further stirred for 4–5 hours under nitrogen. It was then filtered, and the complex was precipitated upon addition of a saturated ethanolic solution of ammonium hexafluorophosphate to the filtrate. The complex was filtered and dried under vacuum before being recrystallized (acetone-ether). Yield 74%, Anal. Calc. for $C_{40}H_{27}N_7P_3F_{18}Co$: C, 43.71; H, 2.45; N, 8.91; Co, 5.36: Found: C, 43.28; H, 2.16; N, 8.34, $[M\text{-}PF_6]^+$,1099. IR, KBr pellets (cm^{-1}): 839, 1321,1431, 1581, 1600. ^{1}H NMR, δppm (DMSO.d$_6$, 200 MHz), ppm (TMS): 9.92 (d, 2H), 9.18 (m, 4H), 8.92 (d, 2H), 8.60 (d, 6H m), 8.29 (d, 2H), 8.00 (m, 8H), 7.70 (d, 4H).

Synthesis of [Ni(phen)$_2$(qbdp)](PF$_6$)$_2$.2H$_2$O (2). A solution containing [Ni(phen)$_2$Cl$_2$] (0.49 g, 1 m mol) and quinolino [3,2-*b*][1,5]benzodiazepine (0.245 g, 1 m mol) in ethanol was refluxed for 1 hour with stirring and further stirred for 4–5 hours under nitrogen, then it was filtered and the crude complex was precipitated upon addition

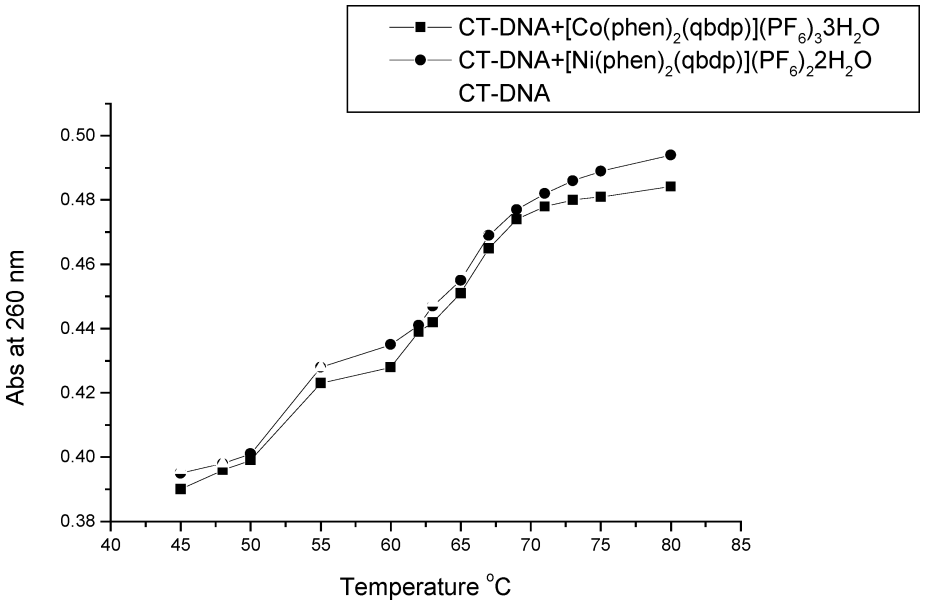
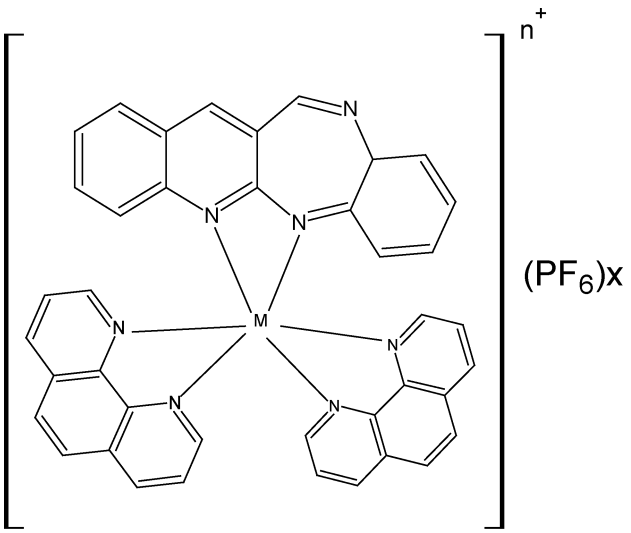


FIGURE 4 Melting curves of CT-DNA in the absence and presence of complexes.

of saturated ethanolic solution of ammonium hexaflurophosphate to the filtrate. The complex was filtered and recrystallized (acetone-ether). Yield 70%, Anal. Calc. for $C_{40}H_{27}N_7P_2F_{12}Ni$: C, 50.36; H, 2.83; N, 10.27; Ni, 6.15: Found: C, 50.32; H, 2.64; N, 10.43; Ni, 6.16. $[M\text{-}PF_6]^+$, 953. IR, KBr pellets (cm^{-1}): 839, 1333, 1420, 1587, 1605. $\mu_{eff} = 2.76 \pm 0.02$ B.M.



Where, M = Co (III) or Ni(II)

n = 2 or 3

Proposed Structure of the Complex

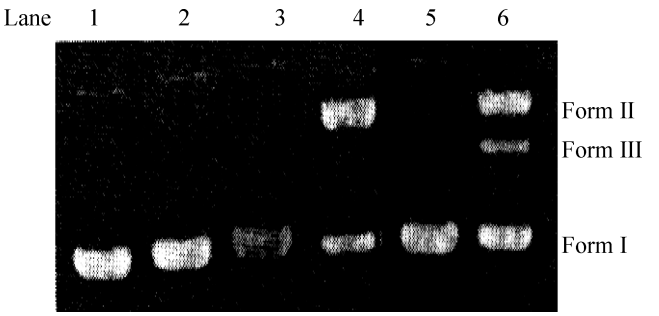


FIGURE 5 Cleavage of supercoiled pUC19 DNA (0.5 μg) by the cobalt(III) complex in the presence of hydrogen peroxide (H_2O_2, 100 μM) in a buffer containing 50 mM Tris-HCl and 50 mM NaCl at 37°C. Lane 1 DNA alone; Lane 2 DNA+control; Lane 3, DNA+30 μM of complex (**2**); Lane 4, DNA+40 μM of complex (**2**); Lane 5, DNA+30 μM of complex (**1**); Lane 6, DNA+40 μM of complex (**1**). Forms I-III are supercoiled, nicked circular, and linear DNA, respectively.

Physical Measurements

Melting points were determined in open capillaries and are uncorrected. Micro analyses (C, H, and N) were performed in Carlo-Erba 1106-model 240 Perkin-Elmer analyzer. IR spectra were recorded with Shimadzu model FT-IR spectrophotometer by using KBr pellets. ^{1}H-NMR spectra were recorded on a Bruker AC-P500 spectrometer (300 MHz) at 25°C in $CDCl_3$ with TMS as the internal reference.

UV visible absorption spectra were recorded using Shimadzu 1650 PC model UV spectrophotometer (Japan) at room temperature. Viscosity measurements were carried out on Brookfield viscometer at room temperature. Thermal denaturation studies were carried out with a Perkin-Elmer Lambda 35 spectrophotometer equipped with a Peltier teyrr controlling programmer.

DNA-Binding Experiments

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 DNA stock 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 4 days.

The complex and DNA solutions were allowed to incubate for 10 minutes before the absorption spectra were recorded. To enable quantitative comparison of the DNA binding affinities the intrensic binding constant, K_b

of the complexes for binding with CT-DNA were obtained by using following equation.

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

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. In plots of $[DNA]/(\varepsilon_a\text{-}\varepsilon_f)$ Vs [DNA], K_b is given by the ratio of slope to the intercept.

Viscosity measurements were carried out using a semimicro dilution capillary viscometer at room temperature. Each experiment was performed three times and an average flow time was calculated. Data were presented as (η/η_o) Vs binding ratio, where η is the viscosity of DNA in the presence of complex and η_o is the viscosity of DNA alone.

Thermal denaturation studies were carried out with a Perkin-Elmer Lambda 35 spectrophotometer equipped with a Peltier temperature controlling programmer ($\pm 0.1^\circ$C). The absorbance at 260 nm was continuously monitored for solutions of CT-DNA (0.1 μM) in the absence and presence of the complexes (0.5 μM). The temperature of the solution was increased by 1°C min^{-1}.

The cleavage of DNA was monitored using agarose gel electrophoresis. Supercoiled pUC19 DNA (6 μl, $\sim$500 μg) in Tris-HCl buffer (50 mM) with 50 mM NaCl (pH 7.2) was treated with the metal complex solution (20, 30 and 40 μM) and ascorbic acid (2 μl, 100 μM) followed by dilution with the Tris-HCl buffer to a total volume 20 μl. The samples were incubated for 1 hour at 37°C. A loading buffer containing 25% bromophenol blue, 0.25% xylene cyanol, 30% glycerol (3 μl) was added, and electrophoresis was performed at 50 V for 3 hours in TBE buffer using 0.8% agarose gel containing 1.0 μg/ml ethidium bromide. Bands were visualized by UV light and photographed. The cleavage efficiency was measured by determining the ability of the complex to convert the supercoiled DNA (SC) (Form-I) to nicked circular form (NC) (Form-II) and linear form (LC) (Form-II). After electrophoresis, the proportion of DNA in each fraction was estimated quantitatively from the intensities of the bands using Gel Documentation System. The fraction of the original supercoiled DNA converted to the NC (nicked circular) and LC (linear form) at the end of the reaction was calculated after correcting for the low level of NC present in the original sample and the low affinity of ethidium bromide binding to SC compared to NC and linear forms of DNA.

RESULTS AND DISCUSSION

Characterization of Metal Complexes

The elemental analysis data, IR, ^{1}H NMR, and magnetic moment data of the new complexes are summarized in the experimental section. The IR spectrum of the PF_6 salt of each complex showed a strong band in the region 837–839 cm^{-1} ascribable to the counter anion and this band was absent for the corresponding chloride salts.[33] In the ^{1}H NMR spectra of the Co(III) complexes, the peaks due to various protons of phen and qbdp ligands are seen to be shifted in complexation with corresponding free ligands, suggesting complexation. Unlike the cobalt(III) complexes, which are diamagnetic, nickel(II) complex was found to be paramagnetic with μ_{eff} value of 2.77 ± 0.02 B.M. as expected for typical d^8 systems.

DNA Binding and Cleavage Studies

It should be noted here that the two new complexes were isolated in their racemic forms and that the DNA-binding behaviors described below are a composite of those of enantiomers. Initially, the interaction of these new complexes with DNA was monitored by the absorption spectrophotometric method, the absorption spectra of which in aqueous buffered solutions were found to be nearly identical to the corresponding spectra of the PF_6 salts. As shown in Figures 1 and 2 in the presence of increasing amounts of CT-DNA, both complexes **(1)** and **(2)** showed a strong decrease in intensity (hypochromicity: 26% for Co(III) and 31% for Ni(II) complexes) and bathochromic shifts (maximum: 4 ± 1 nm for cobalt(III) and 2 ± 1 nm for nickel(II) complexes) for their most red-shift absorption peak maxima. The change in the absorbance values (at 220 nm and 284 nm for complex (**1**) and at 224 nm and 272 nm for complex (**2**)) with increasing amounts of CT-DNA were used to evaluate the intrinsic binding constants (K_b) for the complexes. The values of K_b evaluated for (**1**) and (**2**), using Equation (i) are 6.4×10^4 M^{-1} and 4.8×10^4 M^{-1} respectively. The observed K_b values are comparable to those observed for typical classical intercalators [EthBr, K_b, 1.8×10^6 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.[34]

The DNA binding modes of complexes were further investigated by viscosity measurement, which is sensitive to the increase in length of DNA and is regarded as the least ambiguous and the most critical tests of binding mode in solution in the absence of crystallographic structural data.[35] To understand the nature of DNA binding of mixed ligand Co(III) and Ni(II) complexes, viscosity measurements were carried out on CT-DNA by varying the concentration of the added complex. Representative plots of

η/η_o Vs. [Complex]/DNA are shown in Figure 3. As can be seen, there is positive change in viscosity with increasing addition of the concentration of the complexes to DNA. These results suggested that, both the complexes intercalated between two adjacent base pairs of DNA through a classical intercalation mode.

Thermal behaviors of DNA in the presence of complexes can give insight into their conformational changes when temperature is raised, and offer information about the interaction strength of complexes with DNA. It is well known that when the temperature in the solution increases, the double-stranded DNA gradually dissociates to single strands, and generates a hypochromic effect on the absorption spectra of DNA bases (λ_{max} = 260 nm). In order to identify this transition process, the melting temperature T_m, which is defined as the temperature where half of the total basepairs is bounded, is usually introduced. According to the literature, the intercalation of natural or synthesized organic and metallointercalators generally results in a considerable increase in melting temperature(T_m). As shown in Figure 4, the T_m DNA was found to be 60 ± 1°C under experimental conditions. Under the same set of conditions, addition of complex (**1**) and (**2**) increased T_m (±1°C) by 6°C and 4°C, respectively, which indicates that these compounds stabilize the double helix of DNA. The increase in T_m of the latter is comparable to that of classical intercalators.[36] So from the above data it is concluded that the new Co(III) and Ni(II) mixed ligand complexes act as a new class of DNA intercalators.

In order to determine the ability of $[Co(phen)_2(qbdp)](PF_6)_3.5H_2O$ (**1**) and $[Ni(phen)_2(qbdp)](PF_6)_2.2H_2O$ (**2**) for DNA scission, the complexes were incubated at different concentrations with Supercoiled pUC19 DNA for 1 hour in 50 mM Tris-HCl/50 mM NaCl buffer (pH 7.2) using hydrogen peroxide (H_2O_2) activation. Control experiments using H_2O_2 do not show any apparent cleavage of DNA (Fig. 5., lane 2). At the concentration of 40 μM, the complex (**1**) is able to convert 60% of the initial SC (Form I) to NC (Form II) and linear (Form III) (lane 6) whereas the complex (**2**) is able to convert only 35% of the initial SC (Form I) to NC (Form II) (lane 4). While at lower concentration of 30 μM the complex **(1)** exhibit 24% conversion, (lanes 5). In the same concentration the complex **(2)** exhibit only 15% conversion (lane 3).

Several possible reaction pathways can account for the cleavage dependent on the presence of ascorbate and hydrogen peroxide. The first step is the interaction of Co(III) complex with DNA through the outer sphere while the second step consists of the reduction of Co(III) complex to Co(II) complex through reaction with the reducing agent. Once Co(II) is formed, a metal catalyzed Haber-Weis reaction, which makes used of the Fenton chemistry may be considered to be the major mechanism by which the highly reactive hydroxyl radical generated in the biological systems.[37]

$$\mathrm{Co(III)L + e^- \longrightarrow Co(II)L}$$
$$\mathrm{Co(II)L + O_2 \longrightarrow Co(II)L + O_2^-}$$
$$\longrightarrow$$
$$\longrightarrow$$
$$\longrightarrow$$
$$\mathrm{2O_2^- + 2H^+ \quad H_2O_2 + O_2}$$
$$\mathrm{CoII(L) + H_2O_2 \quad CoII(L) + OH^- + OH^{\cdot}}$$
$$\mathrm{O_2^- + H_2O_2 \quad O_2 + OH^- + OH.}$$

The same mechanism is involved in the case of Ni(II) complex also.

Hydrogen peroxide can react with Co(III)/Ni(II) to produce hydroxyl radical species which could be metal bound. This species, which may be considered analogous to a metal-oxo system, is responsible for initiating DNA strand scission chemistry.[38]

In conclusion, at higher concentration of 40 μM, the Cobalt(III) complex (**1**) shows more cleavage activity compare to the Ni(II) complex (**2**). From these results we infer that the Cobalt(III) complex (**1**) act as a potent nuclease agent. However, the nature of reactive intermediates involved in the DNA-cleavage by the complexes has not been clear yet. Further studies on the mechanism are currently underway.

CONCLUSSION

The above observations indicate that both $[Co(phen)_2(qbdp)]^{3+}$ and $[Ni(phen)_2(qbdp)]^{2+}$ bind to DNA by intercalation with the planar qbdp ligand stacked between the base pairs of the DNA. Binding constants indicate that complex $[Co(phen)_2(qbdp)]^{3+}$ binds more strongly with DNA than $[Ni(phen)_2(qbdp)]^{2+}$. Both the complexes exhibit the oxidative cleavage activity. In the cleavage activity also the Co(III) complex strong cleavage activity than Ni(II) complex.

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