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New Insights into the DNA Interactions of Novel Ru(II) Complexes of Chromeno[2,3-b]Quinoline and Fused Aromatic NN- Incorporated Ligands

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ABSTRACT

Three new Ru(II) complexes, namely[Ru(cq)$_3$](PF$_6$)$_2$, [Ru(bpy)$_2$(cq)](PF$_6$)$_2$ [Ru(phen)$_2$(cq)](PF$_6$)$_2$ (where cq=chromeno[2,3-b]quinoline, phen=1,10-phenanthroline and bpy=2.2′-bipyridine) were synthesized and structurally characterized. The Spectroscopic data designated an octahedral geometry for all the complexes. The binding studies of these complexes with double-stranded (ds) DNA were investigated by absorption spectra, viscosity measurements and thermal denaturation studies. These results suggested that the metal complexes intercalates into the DNA base stack as intercalator. The oxidative nuclease activities of the complexes were studied with supercoiled pUC19 DNA using gel electrophoresis technique and the results shows that the complexes have potent nuclease activity.

Keywords: Ru(II) complexes, binding studies, intercalator, gel electrophoresis.

INTRODUCTION

Metal complexes having planar aromatic heterocyclic functionality that can insert and stack between the base pairs of double helical DNA have contributed to the understanding of fundamental nucleic acid recognition. These metal complexes have been efficient in the development of DNA cleavage reagents; have assisted in the development of low molecular weight drugs, and as stand-alone metal complexes, besides being agents to understand fundamental complex interactions with DNA [1-3]. Transitional metal complexes of 1,10-phenanthroline and their modified variants are broadly employed in studies of DNA in view of their relevance in several research fields, including bioinorganic and biomedicinal chemistries [4-6]. Recently, efforts have been directed towards the design of various mixed ligand-metal complexes containing planar, aromatic, fused heterocyclic compounds (phen/bpy) which have proved to be very useful as structural and functional probes for nucleic acids due to the extensively π-conjugated and planar structure. Prominent among the various mixed ligand metal complexes employed so far in studies with DNA are those metallointercalators which incorporate either 2.2′-bipyridine(bpy)/1,10 phenanthroline or modified bipyridine/phenanthroline moiety or aromatic heterocyclic ring as auxiliary ligand. A singular advantage through these metallointercalators intended for such studies is that the ligands or the metal ion in them can be changed in an easily controlled manner to facilitate individual applications [7-8].

The great success of using Ru–polypyridyl complexes for probing DNA binding is acknowledged in a vast literature [9-11]. Ruthenium complexes are considered as promising alternatives to platinum complexes and numerous ruthenium complexes have now been proposed as potential anticancer substances, demonstrating remarkable anticancer activity and screening lower general toxicity than platinum compounds [1,12]. The significant structural differences between ruthenium and most platinum-based antitumor drugs give a promise that ruthenium-based drugs could be suitable alternatives to cisplatin and carboplatin. Anticancer therapy with ruthenium coordination compounds is depends on the capability of the metal to coordinatively bind to DNA [13].

In view of this, we describe the synthesis and characterization of a new ruthenium(II) complexes $[Ru(cq)_3](PF_6)_2$, $[Ru(phen)_2(cq)](PF_6)_2$, $[Ru(bpy)_2(cq)](PF_6)_2$ having mixed ligand system and examine their and its binding and cleavage efficiency in the presence of DNA.

MATERIALS AND METHODS

All chemicals and solvents required were of AR grade and procured from HiMedia Laboratories Pvt. Ltd. All the solvents were purified by distillation and used. The $RuCl_3 \cdot 3H_2O$, 1,10-Phenanthroline, 2.2′-bipyridine and *Tris*-HCl were purchased from Merck (India). The calf thymus (ds)DNA and Super coiled (SC) pUC19 DNA were purchased from Bangalore Genie (India), Agarose (molecular biology grade) ethidium bromide were purchased from Himedia (India).

Elemental analyses were done on Perkin-Elmer Model 240-C CHN analyzer. Conductivity measurements were determined in DMF (10^{-3} M) using an Equip-Tronic Digital conductivity meter model No. EQ-660A. The electronic spectra of the complexes were measured using Shimadzu spectrometer model UV-1650 PC double beam spectrophotometer. IR spectra were recorded in 4000-250 cm^{-1} region using KBr pellets on Shimadzu (Kyoto, Japan) FTIR-8400S spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker FT NMR spectrometer (300 MHz) at 25 ^oC in DMSO with TMS as the internal reference. Viscosity measurements were carried out on semimicro dilution capillary viscometer. Thermal denaturation studies were carried out with a Perkin–Elmer model 554 with a Shimazdu UV-Vis recording spectrophotometer coupled to a temperature controller (Model TCC-240A) using quartz cuvettes of 10 mm light-path.

Synthesis of Ligands

Chromeno[2,3-b]quinoline (Cq)

The starting compound 2-chloro-3-formyl quinoline was synthesized according to the method reported earlier [14]. Chromeno[2,3-*b*]quinoline was prepared by condensation of 2-chloro-3-formylquinoline (10 mM) and cyclohexanone (10 mM) in the presence of NaOH (10 mM) under microwave irradiation.
Anal. calc. for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.95; Found: C, 81.41; H, 5.27; N, 6.00; IR: (KBr, cm^{-1}): 1640, 1357, 3025. ^{1}H NMR (DMSO-d6 [8.7(s, 2H, CH), 8.17(s, 1H, CH), 7.69-8.14(m, 4H, Ar-H), 3.0(t, 2H, CH_2), 2.6(m, 2H, CH_2), 1.8(m, 2H, CH_2) [M+] = 235.

Synthesis of complexes

Methanolic solution of chromeno(2,3-*b*)quinoline (0.705 g, 3 mmol) was added to the methanolic solution of $RuCl_3 \cdot 3H_2O$ (0.21 g, 1 mmol) in 3:1 molar ratio and the mixture was refluxed for 3-4 hours. The solution was filtered. The complex was precipitated by the addition of 1M methanolic solution of ammonium hexafluorophosphate. The complex was filtered, dried under vacuum and recrystalized.

$[Ru(cq)_3](PF_6)_2$ 1 Anal. calc.% for $C_{48}H_{39}RuN_3O_3$: Yield (66%); C, 71.45; H, 4.87; N, 5.21 Found: C, 71.52; H, 4.90; N,5.38; UV-Visible. λ_{max} (nm): 297,336,451; IR: (KBr, cm^{-1}):1542 ν(C=N), 1310 ν(COC), 428 ν(M-N), 468ν(M-O), ^{1}H NMR (DMSO-d6): 8.2(s, 6H, CH), 8.1(s, 3H, CH),7.57-8.16(m, 12H, Ar-H), 3.2(t, 6H, CH_2,), 2.6(m, 6H, CH_2), 1.7(m, 6H, CH_2) ; Ω_M = 196 mhos cm^2mol^{-1}. M.P. 421 ^oC.

$[Ru(bpy)_2(cq)](PF_6)_2$ 2 and $[Ru(phen)_2(cq)](PF_6)_2$ 3

The complex $[Ru(phen)_2Cl_2]$ and $[Ru(bpy)_2 Cl_2]$ was prepared by a literature method.[15,16] The complex was prepared by mixing a methanolic solution of both $[Ru(Phen)_2Cl_2]$/ $[Ru(bpy)_2Cl_2]$ (1 mmol) and ligand chromeno(2,3-*b*)quinoline (1 mmol) in a1:1 molar ratio and the mixture was refluxed for 4 h. Then, the solution was filtered and the compound was precipitated by the addition of 1 M ammonium hexafluorophosphate and then filtered, dried, and recrystallized

$Ru(bpy)_2(cq)](PF_6)_2$ **3** Anal. calc. for $C_{36}H_{29}RuN_5O$: Yield (56%); C, 66.65; H, 4.51; N, 10.80; Found: 66.60; H, 4.60; N, 10.74; UV-Visible. λ_{max} (nm): 292,386,420,497 IR: (KBr, cm^{-1}):1518 ν(C=N), 1316 ν(COC), 418 ν(M-N), 486ν(M-O); ^{1}H NMR (DMSO-d_6): 8.2(s, 2H, CH), 7.1 -8.1(m, 21H, Ar-H), 2.7(t, 2H, CH_2), 2.6(m, 2H, CH_2,), 1.7(m, 2H, CH_2);.Ω_M = 189 mhos cm^2mol^{-1}. M.P. 415 ^oC.

$[Ru(phen)_2(cq)](PF_6)_2$ **2** Anal. calc. for $C_{40}H_{29}RuN_5O$: Yield (52%); C, 68.95; H, 4.20; N, 10.05; Found: 69.05; H, 4.12; N, 10.11; UV-Visible. λ_{max} (nm): 298, 410, 482 IR: (KBr, cm^{-1}):1521 ν(C=N), 1325 ν(COC), 422 ν(M-N), 473ν(M-O); ^{1}H NMR (DMSO-d_6): 8.1(s, 2H, CH), 7.15 -8.09(m, 21H, Ar-H), 2.7(t, 2H, CH_2), 2.6(m, 2H, CH_2,), 1.7(m, 2H, CH_2); . Ω_M = 212 mhos cm^2mol^{-1}. M.P. 483 ^oC.

DNA binding experiments

The DNA binding experiments were carried out in *Tris*-HCl buffer (5 mM tris (hydroxymethyl) amino methane, pH 7.2, 50 mM NaCl) and viscosity measurements and for thermal denaturation experiments phosphate buffer (1 mM Phosphate, pH 7.2 mM NaCl) was employed. The calf thymus DNA in the buffer medium gave a ratio of UV absorbance at 260 and 280 nm of ca. 1.9:1, suggesting the DNA are apparently free from protein. The concentration of CT-DNA per nucleotide [C(p)] was measured using its known extinction coefficient at 260 nm (6600 M^{-1} cm^{-1}) [17].

Absorption titration experiments were carried out by altering the DNA concentration (0–100 μM) and by keeping metal-complex concentration constant (0.5 μM). Absorption spectra were recorded after each consecutive addition of DNA and equilibration 10 minutes. The absorption data were analyzed for an evaluation of the intrinsic binding constant K_b using reported procedure [18].

Viscosity measurements were determined by using semi-micro dilution capillary viscometer at room temperature. Each experiment was performed three times and an average flow time was calculated. The data was presented as $(\eta|\eta_o)$ vs. binding ratio, where η is the viscosity of DNA in the presence of complex and η_o is the viscosity of DNA alone [19].

Melting studies were carried out by monitoring the absorption of CT DNA (50 μM) at 260 nm various temperatures in the presence (5–10 μM) and absence of each complex. As such, the melting temperature (T_m), at which 50% of double-stranded DNA be converted into single-stranded (absorption increase was noticed in the curve width (σ_T) and temperature range between 10% and 90%) occurred and was calculated as reported [20].

DNA cleavage experiments

The cleavage of DNA was performed using agarose gel electrophoresis. Supercoiled pUC19DNA (0.5 μg) in *Tris*-HCl buffer (50 μM) with 50 μM NaCl (pH 7.2) was treated with metal complex (50 and 100 μmol/L) followed by dilution with *Tris*-HCl buffer to a total volume of 20 μL. The samples were incubated for 1 h at 37 $^\circ$C. A loading buffer containing 25% bromophenol blue, 0.25% xylene cyanol, 30% glycerol and H_2O_2 was added to a final concentration of 2.5 μmol/L were added and electrophoresis was performed at 50 V for 3 h in TBE buffer(45 μmol/L *Tris*-borate, 1 μmol/L EDTA) using 0.8% agarose gel containing 1.0 μg/ml ethidium bromide. The samples were incubated for 60 min inside the sample chamber. Bands were visualized using UV light and photographed. The cleavage efficiency was deliberated by determining

the capability of the complex to convert the SC DNA to nicked circular form (NC) and linear form (LC) [21,22].

RESULTS AND DISCUSSION

Characterization of Metal Complexes

Each synthetic step involved in the synthesis of complexes was straightforward and provided good-to-moderate yield of the desired product in pure form. These new complexes are insoluble in water, but they are soluble in DMF, DMSO, and in buffer (pH 7.2) solution at room temperature. The complexes employed in this work have been characterized by elemental analyses as well as UV-Visible, IR, and ^{1}H NMR spectroscopic these are summarized in the experimental section. The formula of the complexes $[Ru(cq)_3](PF_6)_2$, $[Ru(phen)_2(cq)](PF_6)_2$, $[Ru(bpy)_2(cq)](PF_6)_2$ respectively. The molar conductance values of the complexes in DMF solutions fall in the range 189–212 ohm^{-1} cm^2 mol^{-1}, demonstrating their electrolytic nature.

In IR spectra of the complexes, the characteristic frequencies exhibit significant changes as compared with those of the parent ligands. The spectrum of the ligands show absorption bands in the region 1570–1640 cm^{-1} ν(C=N) and 1357 cm^{-1} ν(C-O), which can be assigned to *ν*(C-N) and *ν*(C-O) vibrations, respectively. The complexes **(1)**, **(2)** and **(3)** clearly exhibited strong band ν(C=N) in the range of 1518-1542 cm^{-1} and 1310-1325 cm^{-1} which shows a shifting to the lower frequencies in compared with ligands. Besides, the metal chelates also show some new bands in the region 418-428 cm^{-1} and 468-486 cm^{-1} which are due to formation of M-N and M-O bands respectively. In addition, the IR spectrum of the PF_6 salt of each complex showed a strong band in the region 830-850 cm^{-1} ascribable to the counter anion and this band was absent for the corresponding chloride salts [23-26].

The electronic spectrum for complexes are characterized by intense π→π* ligand transitions in the UV region, in addition metal-to-ligand charge transfer (MLCT) transition. The broad MLCT absorption bands appear at 458 to 497 nm which are attributed to Ru(dπ) → ligand (π*) transitions. The magnetic measurements results of new ruthenium(II) complexes recommended diamagnetic behavior, indicating the presence of ruthenium in the +2 oxidation state. The ground state of ruthenium(II) is $^1A_{1g}$ arising from the t^6_{2g} configuration in an octahedral environment. The excited state corresponding to the t^5_{2g} e_{1g} configuration are $^3T_{1g}$, $^3T_{2g}$, $^1T_{1g}$ and $^1T_{2g}$. Hence, four bands corresponding to the transitions $^1A_{1g} \rightarrow {}^3T_{1g}$, $^1A_{1g} \rightarrow {}^3T_{2g}$, $^1A_{1g} \rightarrow {}^1T_{1g}$, $^1A_{1g} \rightarrow {}^1T_{2g}$ are possible in the order of increasing energy [27]. Finally, complexes also confirmed by ^{1}H NMR spectroscopic data. The ^{1}H NMR spectral data are reported along with the possible assignments in the experimental section. Based on the above analytical data, the following structure is anticipated for the complexes (Fig. 1).

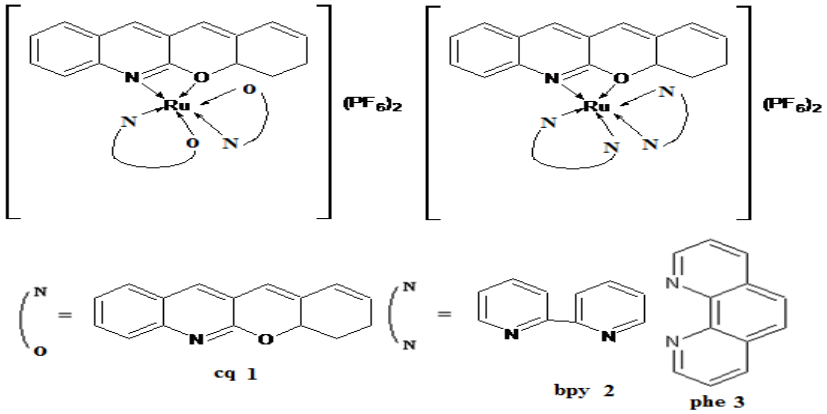

Fig. 1. Structures of Ru(II) complexes

DNA binding studies

Absorption spectral features of DNA binding

Absorption spectroscopy is one of the expedient tools for examining the interaction between complex and nucleic acids. Binding of complexes to DNA persuade changes of the absorption spectrum. Binding of complexes to DNA through intercalation generally results in hypochromism and red shift (bathochromic shift). The extent of the hypochromism in the charge transfer band is commonly consistent with the strength of intercalative binding [28]. The absorption spectra of Ru(II) complexes were recorded separately in the presence of increasing amounts of CT- DNA (Fig. 2). The absorption results have revealed that, as the DNA concentration was increased the absorbance of the complexes were decreased. The hypo chromism increased up to 13.5, 17.4 and 26.2% for Ru(III) complexes The hypocromism observed for the peaks of complexes are accompained by small red shift. The K_b values for complexes **1**, **2** and **3** were $3.4x10^5$, $5.1x10^5$ and $7.3x10^5$ M^{-1} respectively. The binding constants of these metal complexes are analogous to the classical intercalators [29].

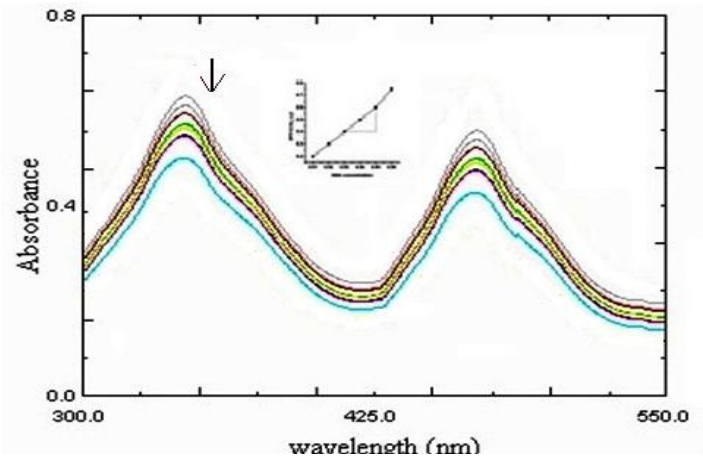

Fig. 2. Absorption spectral traces showing the decrease in absorption intensity on gradual addition of CT-DNA (0-100 μM) to the solution of Ruthenium complexes (0.5 μM) in *Tris*-HCl buffer. Inset shows the plot of [DNA]/ε_a-ε_f *vs* [DNA] for the titration of complexes **2** with CT-DNA.

Viscosity measurements: To further elucidate the nature of the interaction between the complexes and DNA, viscosity of CT-DNA by varying the concentration of complexes were recorded. Hydrodynamic measurements that are sensitive to length change (i.e, viscosity, sedimentation) are considered as the most fundamental tests of binding in solution in the absence of crystallographic structure data [30]. A classical intercalation model demands that the DNA helix elongate as base pairs are separated to hold the binding ligand, leading to an increase in DNA viscosity. In contrast, a partial, non-classical intercalation of compound could bend (or kink) the DNA helix, sinking its effective length and concomitantly, its viscosity [31].

In this study, by plotting the graph of values of relative viscosity (η/η_0) (where η and η_0 are the specific viscosities of DNA in the presence and absence of the Ru(II) complexes) against [M]/[DNA]. The viscosity of DNA is increased with the increment of each complexes (Fig. 3) and it is similar to the behavior of well-known DNA-intercalator ($[Ru(bpy)_2(dppz)]^{2+}$) [32]. This result further suggested an intercalative binding mode of the complex with DNA and also similar to the spectroscopic results, such as hypochromism and bathochromism (red-shift) of complexes in the presence of DNA.

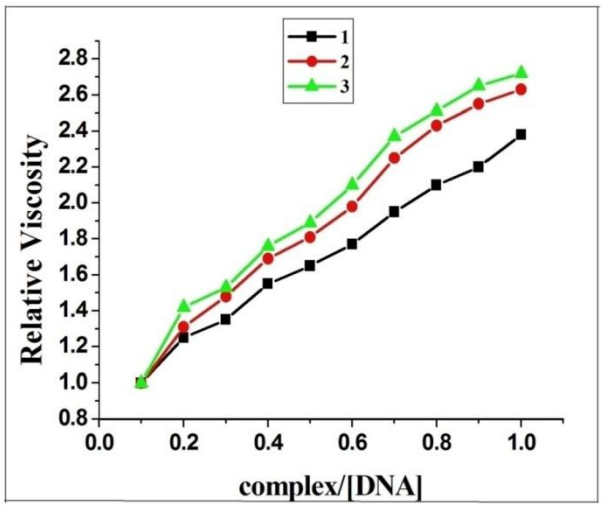

Fig. 3. Plot of relative viscosity vs [Complex]/[DNA]. Effect of Ru(II) complexes on the viscosity of CT-DNA at 25 ^{0}C. Complex = 0-100 μM, [DNA] = 50 μM.

Thermal denaturation measurements: The DNA melting experiments were conducted by examining the absorption intensity of CT-DNA at 260 nm at various temperatures both in the absence and presence of the complexes. Thermal denaturation studies of DNA are useful in establishing the extent of intercalation. It is well known that when the temperature in the solution increases, the double stranded DNA gradually dissociates to single strands and produce a hypochromic effect on the absorption spectra of DNA bases (λ_{max} = 260 nm) [33]. In order to identify this transition process, the melting temperature T_m, which is defined as the temperature at which half of the total base pairs is bounded, is usually introduced. According to the literature, the intercalation of natural or synthesized organic compounds and metal-intercalators usually results in a substantial increase in melting temperature (T_m). As shown in Fig. 4, the T_m, DNA was found to be 60 ± 1 ^{o}C under experimental conditions. Under the same set of conditions, addition of Ru(II) complexes increased T_m (±1 ◦C) by 5 ^{o}C to 7 ^{o}C, which indicate that these compounds stabilize the double helix of DNA. The advantage of this method is as it is much easier to identify when more than one transition occurs [34]. These variations in DNA melting temperature strongly supported the intercalation Ru(II) complexes into the double helix DNA.

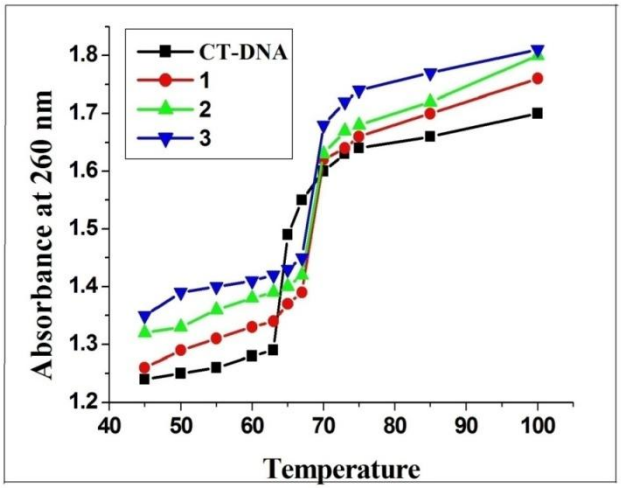

Fig. 4. Thermal denaturation of CT-DNA in the absence and presence of Ru(II) complexes. [DNA]= 50 μM, [complex] = 10 μM, Buffer: Phosphate.

DNA Cleavage Studies: There has been substantial interest in DNA endonucleolytic cleavage reactions which are activated by metal [35]. The delivery of high concentrations of metal complexes to the helix, in locally producing oxygen or hydroxide radicals, yields an efficient DNA cleavage reaction. DNA cleavage was monitored by relation of SC circular pUC19 DNA (Form I) into nicked circular (Form II) and linear (Form III). When circular pUC19 DNA is subjected to electrophoresis, relatively fast migration will be observed for the SC form (Form I). If scission occurs on one strand (nicking), the supercoils will relax to give a slower-moving open circular form (Form II). If both strands are cleaved, a linear Form (III) will be generated that migrates between Forms I and II.

In the current study, all the complexes exhibit significant nuclease activity. Control experiments do not show any apparent cleavage of DNA (Fig. 5, lane1). As shown in fig. 5, when the complex concentration increased, the intensity of the circular SC DNA (FORM-I) decreases while that for the NC DNA (FORM-II) apparently increases. The complexes at 100 μ mol L^{-1} (lanes 3, 5 and 7) concentration under the same experimental conditions, exhibit more effective nuclease activity than 50 μmol L^{-1} (lanes 2, 4 and 6) concentration of complexes. From these experimental results, we infer that the complex **3** containing planar phenanthroline ligand shows more cleavage activity than the complexes **1** and **2**. The cleavage efficiency follows the order 3 > 2 >1. The reason for dissimilarity in the cleavage activity also depends on the DNA binding capabilities [36, 37].

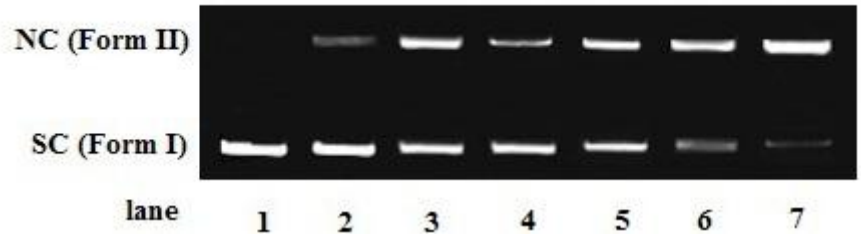

Fig. 5. Clevage of supercoiled pUC19 DNA (0.5 µg) by the complexes **1**, **2** and **3** at the concentrations of 50 μM and 100 μM. Lane 1, untreated DNA (control); lane 2: DNA+ 50 μM complex **1** + H_2O_2; lane 3: DNA+ 100 μM complex **1**+ H_2O_2; lane 4: DNA+50 μM complex **2** + H_2O_2; lane 5: DNA+ 100 μM complex **2** + H_2O_2; lane 6: DNA+50 μM complex **3**+ H_2O_2; lane 7: DNA+ 100 μM complex **3** + H_2O_2

APPLICATIONS

The complexes in the presence of H_2O_2 act as an efficient cleaving agent. Hence, these complexes may be useful as tool for probing DNA.

CONCLUSIONS

In conclusion, we have synthesized and characterized new complexes of the type, $[Ru(cq)_3](PF_6)_2$, $[Ru(phen)_2(cq)](PF_6)_2$, $[Ru(bpy)_2(cq)](PF_6)_2$. The binding propensity of complexes with (ds) DNA was investigated by absorption spectra, viscosity and thermal denaturation. The results obtained by binding studies revealed that the complexes bind in intercalating manner to the CT-DNA.

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