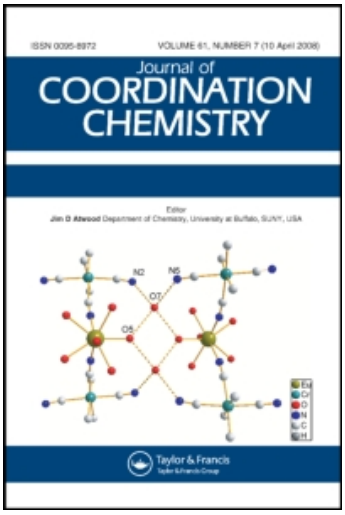

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Synthesis, characterization, and DNA-binding of $[Co(phen)_2(CPIA)]^{3+}$, $[Co(phen)_2(BIP)]^{3+}$, and $[Co(phen)_2(CIP)]^{3+}$

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Three ligands, 2-(3-(carboxymethyl)-1,10-phenanthroline-[5,6-d]imidazole-1-yl)acetate (CPIA), 2-(benzo[d][1,3]dioxol-4-yl)-1H-imidazo[4,5-f][1,10]phenanthroline (BIP), and 2-(9H-carbazol-3-yl)-1H-imidazo[4,5-f][1,10]phenanthroline (CIP), and their complexes, $[Co(phen)_2(CPIA)]^{3+}$ (**1**) (phen = 1,10-phenanthroline), $[Co(phen)_2(BIP)]^{3+}$ (**2**), and $[Co(phen)_2(CIP)]^{3+}$ (**3**), have been synthesized and characterized. Binding of the three complexes with calf thymus DNA (CT-DNA) has been investigated by spectroscopic methods, cyclic voltammetry, and viscosity measurements. The three complexes bind to DNA through an intercalative mode, and the size and shape of the intercalative ligands have significant effects on the binding affinity of complexes to CT-DNA.

Keywords: Cobalt(III) complexes; UV-Vis spectroscopy; Fluorescence spectroscopy; DNA-binding

1. Introduction

Deoxyribonucleic acid (DNA) bears heritage information and instructs the biological synthesis of proteins and enzymes through replication and transcription of genetic information in living cells. DNA is particularly a good target for metal complexes as it offers a wide variety of potential metal-binding sites [1–4]. Metal complexes have diversity in size and structure, and have useful photophysical and electrochemical properties. Furthermore, they offer a unique modular system, easily designed *via* the facile interchange of ligands. Transition metal complexes have potential as structure-selective binding agents for nucleic acids [5–11]. Since it was reported that inert platinum complexes containing aromatic ligands binding with DNA are coplanar with the metal coordination sites, these have aroused a great deal of interest [12]. Applications of polypyridine metal complexes require that the complex should bind

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to DNA through an intercalative mode with the ligand intercalating into the π-stack between two base pairs [13–15].

Increasing interest has focused on substitutionally inert octahedral transition metal complexes through non-covalent binding with DNA. Octahedral polypyridine complexes of ruthenium and rhodium exhibit interesting spectroscopic and luminescence properties on binding to DNA [16–18]. Complexes $[Ru(phen)_2(dppz)]^{2+}$ [19], $[Rh(bpy)_2(phi)]^{3+}$, $[Rh(phen)_2(phi)]^{3+}$, and $[Rh(phi)_2(bpy)]^{3+}$ [20] have been reported, binding with DNA strongly. Cobalt is an integral part of vitamin B12 and its polypyridyl complexes can also interact with DNA [21]. Chemistry of Co(III) metallointercalators has attracted much interest due to relevance in various redox processes in biological systems and therapeutic properties for anti-tumor [21], anti-fungal [22], anti-viral [23], and anti-microbial activities [24]. Varying ligands can create interesting differences in the space configuration and the electron density distribution of Co(III) polypyridine complexes, resulting in different spectral properties and DNA-binding of the complexes [25, 26]. Therefore, further studies using different ligands to evaluate and understand the factors that determine the DNA-binding are necessary.

Intercalative ligands of many polypyridine complexes have π-conjugated aromatic coplanar configuration [27, 28]. Actually, the DNA groove is unsymmetrical and it may be interesting if the intercalative ligand is unsymmetrical or its ends do not preserve aromatic coplanar configuration. Herein, we choose three different intercalative ligands and their cobalt complexes for interaction with DNA. The proposed structures of these cobalt complexes are shown in scheme 1. DNA-binding of these complexes was investigated by spectroscopic methods, viscosity, and cyclic voltammetry measurements.

2. Experimental

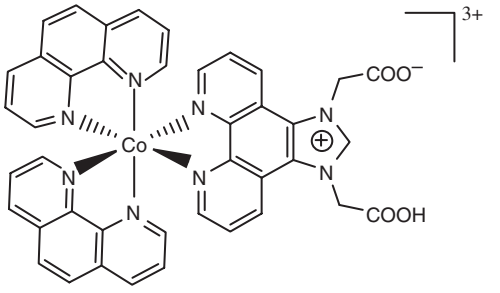
2.1. *Materials*

Calf thymus DNA (CT-DNA) was obtained from the Sino-American Biotechnology Company. A solution of 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 of protein [29]. The DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient ($6600\,mol^{-1}\,cm^{-1}$) at 260 nm [30]. Stock solutions were stored at 4°C.

All other reagents and solvents were purchased commercially and used without purification.

2.2. *Syntheses*

2.2.1. Synthesis of 2-(3-(carboxymethyl)-1,10-phenanthroline-[5,6-d]imidazole-1-yl) acetate. Chloroacetic acid was added to a solution of imidazo[4,5-f][1,10]phenanthroline (IP) (26.20 g, 0.12 mol) dissolved in sodium hydroxide (NaOH) ($1.20\,mol\,L^{-1}$, 30 mL) at room temperature [31]. Under strong stirring, the mixture was heated for 4 h.



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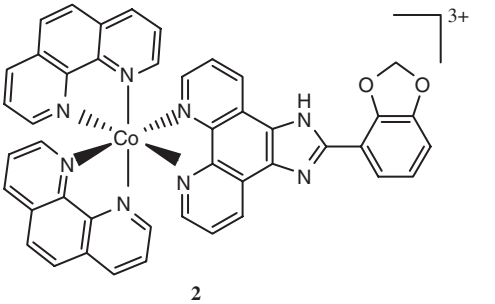

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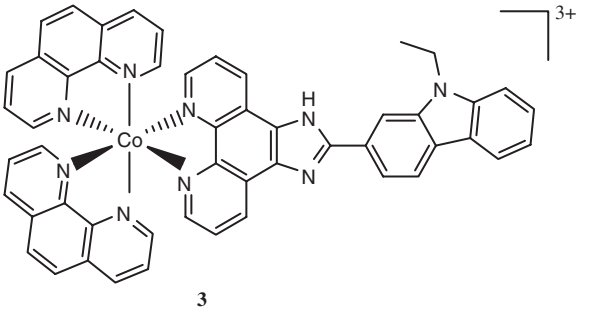

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Scheme 1. Structures of $[Co(phen)_2(CPIA)]^{3+}$ (**1**), $[Co(phen)_2(BIP)]^{3+}$ (**2**), and $[Co(phen)_2(CIP)]^{3+}$ (**3**).

NaOH was added to the mixture and pH was kept at 8–10. Then, hydrochloric acid was added to the solution and pH was decreased to 2–3. The solvent was evaporated in vacuum and the residue was re-precipitated from water to give white solid of 2-(3-(carboxymethyl)-1,10-phenanthroline-[5,6-d]imidazole-1-yl)acetate (CPIA). Yield: 30.70 g, 89%. Anal. Calcd for $C_{17}H_{13}N_4O_4$ (%): C, 60.5; H, 3.9; and N, 16.6. Found (%): C, 60.9; H, 3.5; and N, 16.3. ^{1}H-NMR (400 MHz, DMSO-d_6, tetramethylsilane (TMS); d, doublet; s, singlet; t, triplet; m, multiplet): 9.10(d, 2H), 8.70(d, 2H), 8.00(m, 2H), 5.80(s, 2H), and 3.83(s, 4H).

2.2.2. Synthesis of 2-(benzo[d][1,3]dioxol-4-yl)-1H-imidazo[4,5-f][1,10]phenanthroline. 2-(Benzo[d][1,3]dioxol-4-yl)-1H-imidazo[4,5-f][1,10]phenanthroline (BIP) was synthesized using the method described in [32] and confirmed by microanalyses and

NMR. Anal. Calcd for $C_{20}H_{12}N_4O_2$ (%): C, 70.6; H, 3.5; and N, 16.5. Found (%): C, 70.2; H, 3.9; and N, 16.4. ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): 9.15(dd, 2H), 8.84(d, 2H), 7.78(m, 2H), 7.72(m, 2H), 7.18(d, 1H), 6.27(s, 2H), and 2.44(s, 6H).

2.2.3. Synthesis of 2-(9H-carbazol-3-yl)-1H-imidazo[4,5-f][1,10]phenanthroline. A mixture of N-ethyl-3-formylcarbazole [33] (0.20 g, 1 mmol), 1,10-phenanthroline-5,6-dione [34] (0.22 g, 1 mmol), ammonium acetate (4.62 g, 60 mmol), and glacial acetic acid (30 mL) was refluxed with stirring for 2 h. After cooling, the solution was filtered, diluted with water, and neutralized with concentrated aqueous ammonia. The yellow precipitate was collected and purified by column chromatography on alumina with ethanol : toluene (4 : 1, v/v) as the eluant to afford 2-(9H-carbazol-3-yl)-1H-imidazo[4,5-f][1,10]phenanthroline (CIP) as an amorphous yellow solid. Yield: 0.21 g, 41%. Anal. Calcd for $C_{27}H_{19}N_5$ (%): C, 78.5; H, 4.6; and N, 16.9. Found (%): C, 78.1; H, 4.9; and N, 16.4. ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): 9.75(d, 2H), 9.71(d, 2H), 9.35(d, 1H), 8.12(m, 3H), 7.98(d, 1H), 7.87(m, 2H), 7.43(m, 2H), 3.72(m, 2H), and 1.24(t, 3H).

2.2.4. Synthesis of $[Co(phen)_2(CPIA)](ClO_4)_3 \cdot 2H_2O$ (1). A mixture of CPIA (0.34 g, 1 mmol) dissolved in 30 mL of ethanol was added to a solution of *cis*-$[Co(phen)_2Cl_2]Cl \cdot 3H_2O$ [35] (0.58 g, 1 mmol) in 30 mL of water. The mixture was heated at 85°C for 10 h. After being warmed, an equal volume of saturated aqueous sodium perchlorate solution was added under vigorous stirring. A yellow solid was collected, washed with small amounts of water and ethanol, and dried under vacuum. Yield: 0.74 g, 68%. Anal. Calcd for $C_{41}H_{33}N_8Cl_3O_{18}Co$ (%): C, 45.1; H, 3.0; and N, 10.3. Found (%): C, 44.3; H, 2.4; and N, 10.1. Infrared (IR), KBr pellets (cm^{-1}): 475 (Co–N), 1372 (C–H), 1607 (C=N), 1714 (C=O), 2592 (O–H), and 3083 (C–H). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): 9.12(d, 2H), 8.83(d, 4H), 8.40(d, 4H), 8.08(d, 2H), 8.06(d, 2H), 7.80(d, 2H), 7.76(t, 2H), 7.65(d, 4H), and 6.12(s, 2H). Electrospray ionization-mass spectrometry (ESI-MS): $m/z = 991$ $[M - ClO_4]$, 891 $[M - 2ClO_4]$, and 792 $[M - 3ClO_4]$.

2.2.5. Synthesis of $[Co(phen)_2(BIP)](ClO_4)_3 \cdot 2H_2O$ (2). This complex was synthesized using the same procedure described for **1**, but using BIP (0.34 g, 1 mmol) in place of CPIA. Yield: 0.68 g, 62%. Anal. Calcd for $C_{44}H_{32}N_8Cl_3O_{16}Co$ (%): C, 48.3; H, 2.9; and N, 10.2. Found (%): C, 48.1; H, 3.1; and N, 10.5. IR, KBr pellets (cm^{-1}): 472 (Co–N), 932 (C–O), 1363 (C–H), 1582 (C=N), 2778 (C–H), and 3058 (C–H). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): 9.19(d, 2H), 8.84(d, 4H), 8.46(s, 4H), 8.22(d, 4H), 8.02(d, 2H), 7.83(m, 2H), 7.65(m, 4H), 7.33(d, 2H), 7.15(d, 1H), and 6.54(s, 2H). ESI-MS: $m/z = 994$ $[M - ClO_4]$, 894 $[M - 2ClO_4]$, and 795 $[M - 3ClO_4]$.

2.2.6. Synthesis of $[Co(phen)_2(CIP)](ClO_4)_3 \cdot 2H_2O$ (3). This complex was synthesized using the same procedure described for **1**, but using CIP (0.38 g, 1 mmol) in place of CPIA. Yield: 0.65 g, 55%. Anal. Calcd for $C_{51}H_{39}N_9Cl_3O_{14}Co$ (%): C, 52.5; H, 3.3; and N, 10.8. Found (%): C, 52.1; H, 3.9; and N, 11.3. IR, KBr pellets (cm^{-1}): 476 (Co–N), 1402 (C=C), 1607 (C=N), 2364 (N–H), and 3074 (C–H). ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): 9.82(d, 2H), 9.07(m, 4H), 8.83(d, 4H), 8.51(m, 4H), 8.37(d, 2H), 7.73(m, 4H),

7.68(t, 1H), 7.54(m, 2H), 7.46(m, 3H), 7.23(m, 3H), 3.56(d, 2H), and 1.82(t, 3H). ESI-MS: $m/z = 1067$ [M − ClO_4], 967 [M − $2ClO_4$], and 868 [M − $3ClO_4$].

Caution: Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of the material should be prepared and handled with great care.

2.3. *Physical measurements*

^{1}H-NMR spectra were recorded on an Avance-400 spectrometer in trichloromethane with TMS as the internal standard. Microanalyses (C, H, and N) were carried out on a Perkin Elmer 240Q elemental analyzer. UV-Vis spectra were recorded on a Perkin Elmer Lambda-25 spectrophotometer and emission spectra were recorded on a Perkin Elmer LS-55 luminescence spectrometer at room temperature. ESI-MS was obtained on a Finnigan spectrometer.

Cyclic voltammograms were performed on a CHI 660A electrochemical workstation in a one-compartment cell using a glassy carbon (area, 0.088 cm^2) working electrode, a Pt flag counter electrode, and a saturated calomel reference electrode (SCE). The supporting electrolyte was 10 mmol Tris-HCl, 50 mmol NaCl, pH 7.2, Tris = Tris-(hydroxymethyl)methylamine) at room temperature. All samples were purged with nitrogen prior to measurement.

The viscosity experiments were carried out with an Ubbelodhe viscometer maintained at 28.0 ± 0.1°C in a thermostated bath. DNA samples of *ca.* 200 bp average length were prepared by sonication [36]. The flow time was measured with a digital stopwatch, and each sample was tested thrice to get an average calculated time. Data are presented as $(\eta/\eta_0)^{1/3}$ *versus* binding ratio [37], where η is the viscosity of DNA in the presence of the appropriate complex, η_0 being the viscosity of free DNA. The relative viscosity values were calculated from the flow time of DNA containing solution t and the flow time of buffer alone t_0, using the equation: $\eta = (t - t_0)/t_0$.

3. Results and discussion

3.1. *Synthesis and characterization*

IR and ^{1}H-NMR data of **1**–**3** have been mentioned in section 2. Absorption spectra and redox potential data are provided in table 1. The IR spectrum of each complex showed a strong band in the 1097–1102 cm^{-1} region ascribable to the counter anion [38]. In ^{1}H-NMR spectra of the three Co(III) complexes, signals due to phen, CPIA, BIP, and CIP are shifted in comparison with the corresponding free ligands, suggesting complexation.

The absorption spectra are characterized by intense π–π^* ligand transitions in the UV band. The band below 300 nm is attributed to intraligand (IL) π–π^* transitions at 272, 285, and 277 nm for **1**, **2**, and **3**, respectively. No charge-transfer transitions are discernable from the spectra of these complexes unlike the corresponding Ru(II) complexes [39], which show metal-to-ligand charge transfer (MLCT) bands at 440–465 nm in CH_3CN.

Electrochemical behaviors have been determined in acetonitrile. Each complex exhibits one oxidation and one reduction wave from −1.8 to +1.6 V (table 1).

Table 1. Electrochemical and absorption data of the Co(III) complexes.

Complex	$E_{1/2}$(V *vs.* SCE)[a]		λ_{max} (nm)[b]
	$Co^{III/II}$	Ligand	
1	−1.33	−0.50	354 (2074), 271 (34215)
2	−1.28	−0.43	325 (52634), 286 (56589), 218 (34620)
3	−1.10	−0.49	392 (13590), 371 (15905), 277 (71795)

[a]All complexes were measured in 0.1 mol NBu_4ClO_4–CH_3CN, scan rate = 100 mV s^{-1}.
[b]In CH_3CN.

The electrochemical behavior of the Co(III) polypyridyl complex has been rationalized in terms of a metal-based oxidation and reduction occurring in a stepwise manner for each π^* system. Reduction processes for **1**–**3** are based on the cobalt center and are assigned to the Co(III) → Co(II). The oxidation is assigned to the oxidation of the ligand on the electrode surface [40].

3.2. *Absorption spectra studies*

Electronic absorption spectroscopy is the most common way to study the interaction of complexes with DNA. Complex binding with DNA through intercalation usually results in hypochromism and bathochromism due to the intercalative mode involving a strong stacking interaction between an aromatic chromophore and DNA base pairs. The extent of hypochromism commonly parallels the intercalative binding strength.

Addition of increasing amounts of CT-DNA results in hyperchromism (figure 1). Intense absorption bands observed in the Co(III) complexes are attributed to the IL π–π^* transition of the coordinated groups. The hypochromism increases with increasing CT-DNA concentration. The percentages of hypochromism in the UV band for **1**–**3** in the presence of DNA at saturation are 9.06% at 270, 14.81% at 291, and 18.8% at 272 nm, respectively, compared with that of $[Co(phen)_3]^{3+}$ (10.9% hypochromism at 274 nm) [41].

The intrinsic binding constants of the complexes with DNA, K_b, could be determined by electronic absorption titration. These were obtained by monitoring changes in absorbance at 270 nm for **1**, 291 nm for **2**, and 272 nm for **3** with increasing the concentration of DNA according to the following equation [42]:

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

where, ε_a, ε_f, and ε_b correspond to A_{obsd}/[Co], the extinction coefficient for the free cobalt complex, and the extinction coefficient for the free cobalt complex in the fully bound form, respectively. [DNA] is the concentration of DNA in base pairs. K_b is given by the ratio of the slope to the intercept. The intrinsic binding constants of **1**–**3** were thus determined as $4.50 \times 10^3\,mol^{-1}$, $1.03 \times 10^5\,mol^{-1}$, and $1.47 \times 10^5\,mol^{-1}$, respectively. The DNA-binding affinity of **2** and **3** are higher than those of the metallointercalators (K_b, $[Co(phen)_2(pdtp)]^{3+}$, $4.01 \times 10^4\,mol^{-1}$ [43], $[Ru(phen)_2(MIP)]^{2+}$, $3.96 \times 10^4\,mol^{-1}$ [33]). The binding constants show the order **3** > **2** > **1**. In general, a planar extension of the intercalative ligand would increase the strength of the interaction of complexes with DNA [33]. Complex **3** shows much higher

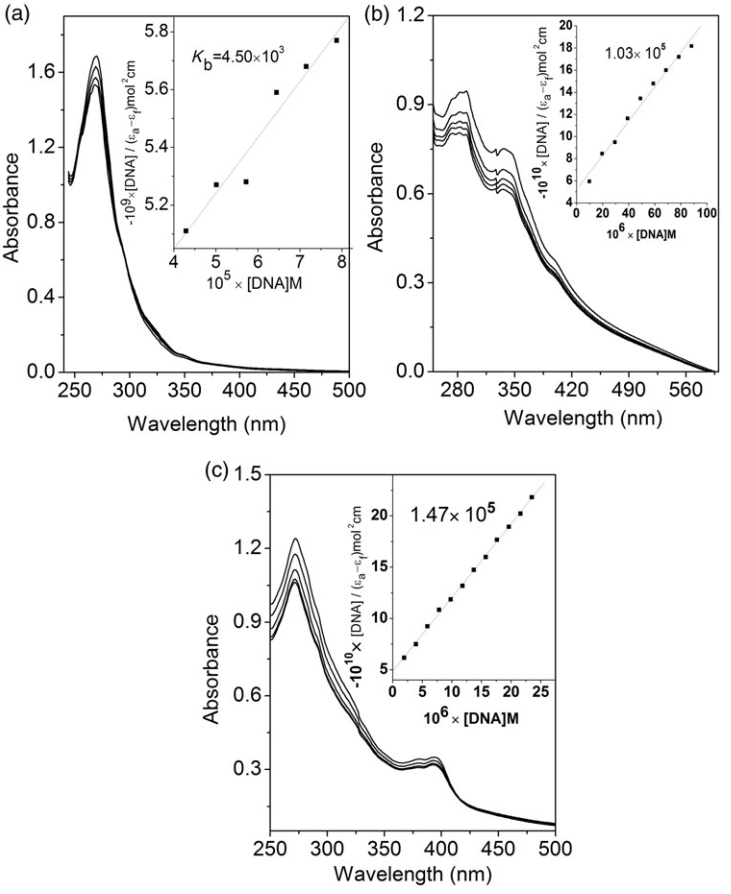

Figure 1. Absorption spectra of **1** (a), **2** (b), and **3** (c) in the presence of CT-DNA. $[Co] = 2 \times 10^{-5}$ mol, $[DNA] = (0\text{–}20.6) \times 10^{-5}$ mol. Inset: plots of $-10^9 \times [DNA]/(\varepsilon_a - \varepsilon_f)$ (in mol^2 cm) *vs.* [DNA] (in mol) for the titration of DNA with Co(III) complex.

affinity for DNA than **2** due to more π-conjugated aromatic area and there is repulsive interaction with methylene of BIP and a base pair. There may be repulsion between internal salt CPIA and the DNA polyanion backbone. BIP displays a more planar conjugate system than CPIA ligand. In addition, the shapes of the intercalated ligand have a significant effect on the strength of DNA binding.

3.3. *Steady-state emission titration*

Steady-state emission is also common to investigate the interactions of complexes with DNA. As shown in figure 2, in the absence of DNA, **1** is luminescent in Tris-buffer at ambient temperature with a fluorescence maximum at 364 nm. In the presence of DNA, the luminescence decreases in peak intensities, attributed to photoelectron transfer from the guanine base of DNA to the excited MLCT state of the complex. Similar results were reported for $[Co(bzimpy)_2]^{2+}$ (bzimpy = 2,6-bis(benzimidazol-2-yl)pyridine) [44],

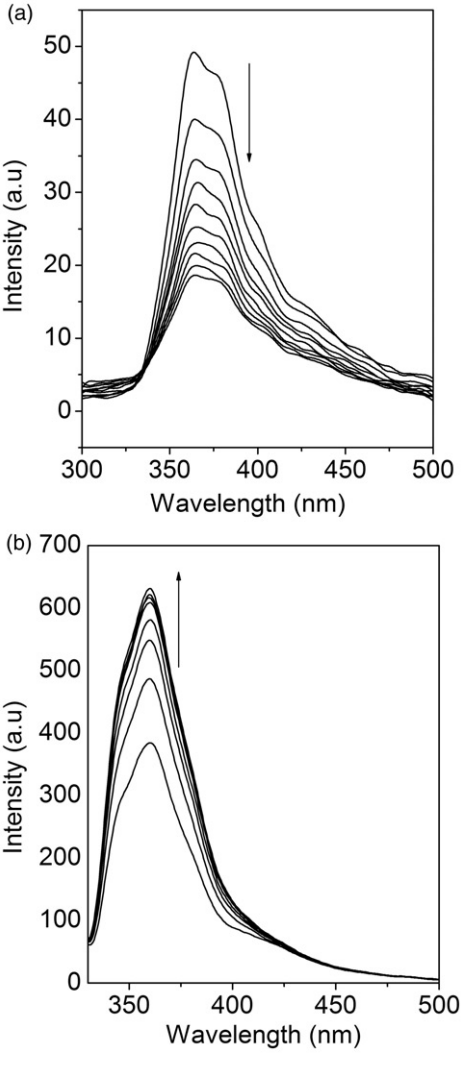

Figure 2. Fluorescence emission spectra of **1** (a) and **3** (b) in Tris–HCl buffer at 298 K in the absence and presence of CT-DNA. Arrow shows the absorbance changing upon increasing the DNA concentration.

$[Ni(HL)_2(L)]$ (HL = 2-phenylquinoline-4-carboylhydrazide) [45], and $[Ru(bzimpy)_2]^{2+}$ [46]. However, no luminescence was observed for **2** in the absence or presence of CT-DNA. Similar phenomena were observed for $[Co(phen)_2(L)]^{3+}$ (L = 3-(pyridine-2-yl)-5,6-diphenyl-as-triazine, 3-(pyridine-2-yl)-as-triazino[5,6-f]acenaphthylene, 3-(pyridine-2-yl)-as-triazino[5,6-f]-phenanthroline) [43]. Complex **3** is luminescent in Tris-buffer at ambient temperature with a fluorescence maximum at 359 nm in the absence of DNA and the fluorescence emission intensity increases with the increase of DNA. The emission result powerfully supports that **3** binds to double-stranded DNA, because stacking of the overall complex with the base pairs leads to electron and energy transfer from phenanthroline-based emission to the base pairs, decreasing the vibrational modes of relaxation and thus higher emission intensity [47].

3.4. *Cyclic voltammetry*

Application of electrochemical methods to the study of metallointercalation and coordination of metal ions and chelates to DNA provides a useful complement to other methods of investigation, such as UV-Vis spectroscopy. Voltammetric methods have been used to probe the interaction (electrostatic or intercalative) of metal complexes with CT-DNA [48]. Bard [49] thinks that shifts in E can be used to differentiate intercalative interactions, which involve hydrophobic interactions with the interior of the DNA molecule from electrostatic ones, which involve the outer anionic coat of DNA.

The cyclic voltammograms of the complexes in the absence and in the presence of CT-DNA are shown in figure 3. The cyclic voltammograms of **1**–**3** in the absence of DNA featured irreversible reduction peaks ($E_1 = -0.117$; $E_2 = -0.161$; and $E_3 = -0.107$ V). Cyclic voltammograms of **1**–**3** in the presence of DNA featured reduction peaks ($E_1' = -0.087$; $E_2' = -0.149$; and $E_3' = -0.0901$ V) [50].

The above-mentioned research suggests that **1**–**3** intercalate into the base pairs of DNA by their different structures. The drop of the voltammetric currents in the presence of CT-DNA is given from the concentration of free complex reducing and the complex moving to electrode surface decreasing [46]. The obvious shift of peak potentials indicates strong association of the complex and DNA [51] through intercalative mode.

3.5. *Viscosity measurements*

Optical photophysical probes provide necessary, but not sufficient, evidence to support the binding model of Co(III) complexes with DNA. In the absence of crystallographic structure data and hydrodynamic methods, which are sensitive to DNA length increases, viscosity measurements are regarded as the least ambiguous and most critical tests of binding in solution [52, 53]. A classical intercalation model results in lengthening the DNA helix, as base pairs are separated to accommodate the binding ligand, leading to the increase of DNA viscosity. However, a partial and/or non-classical intercalation of ligand may bend (or kink) DNA helix, resulting in the decrease of its effective length and, concomitantly, its viscosity [53, 54].

The viscosity on CT-DNA is shown in the presence of **1**–**3** in figure 4. With increasing the amounts of complex, the relative viscosities of CT-DNA increase, suggesting that complexes bind to DNA through a classical intercalation model. The change in relative viscosity, expected to correlate with DNA-intercalating potential, followed the order $\mathbf{3} > \mathbf{2} > \mathbf{1}$. Due to the greater planar area and higher hydrophobicity, **3** binds with DNA more strongly than **2** and **1**; due to carboxyl steric effect, **2** can intercalate into DNA base pairs deeper and has stronger DNA-binding affinity than **1**.

4. Conclusions

$[Co(phen)_2(CPIA)]^{3+}$, $[Co(phen)_2(BIP)]^{3+}$, and $[Co(phen)_2(CIP)]^{3+}$ have been synthesized and characterized. The DNA-binding properties of these three complexes were investigated. The results show that the three complexes bind to DNA in an intercalative

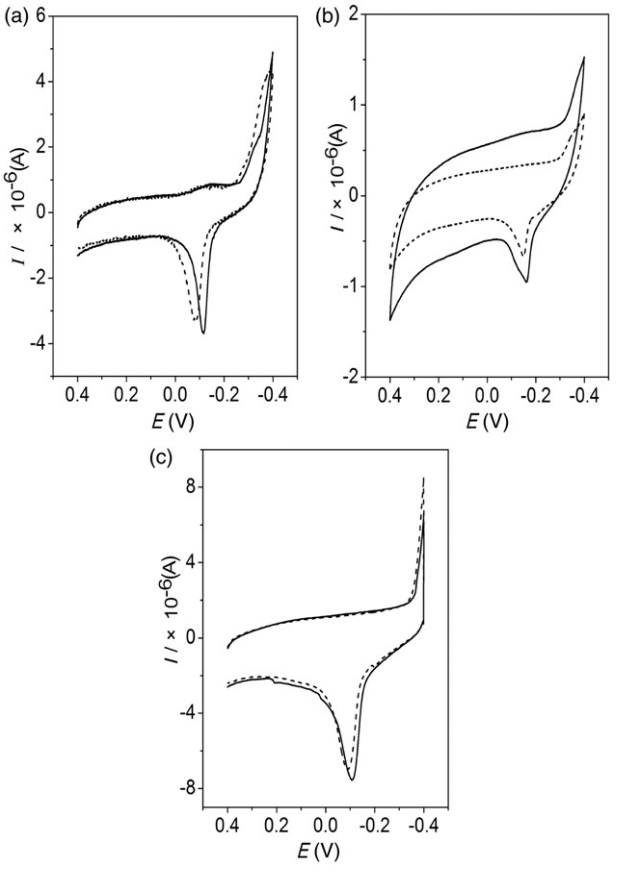

Figure 3. Cyclic voltammograms of **1** (a), **2** (b), and **3** (c) in the absence (—) and presence (- - - -) of DNA in Tris-buffer. [Co] = 100 μmol, [DNA]/[Co] = 20. Scan rates, 50 mV s^{-1}.

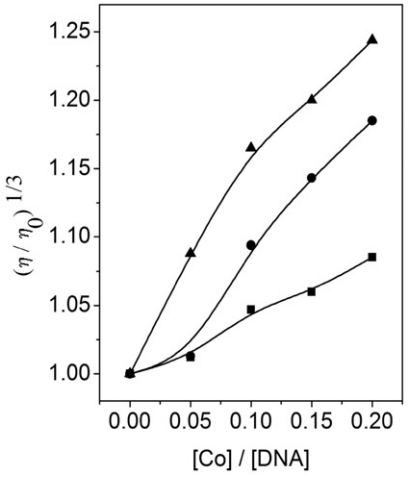

Figure 4. Effect of increasing amounts of **1** (■), **2** (●), and **3** (▲) on the relative viscosity of CT-DNA. Total DNA concentration: 0.1 mmol, $T = 28 \pm 0.1$°C.

mode with DNA-binding constants of $4.50 \times 10^3\,mol^{-1}$, $1.03 \times 10^5\,mol^{-1}$, and $1.47 \times 10^5\,mol^{-1}$, respectively. Cyclic voltammetry and viscosity support that the complexes bind to CT-DNA by intercalation.

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