

Synthesis, Characterization, DNA binding and Microbial Activity of Cobalt (III) Complexes of Mixed Ligands, Hydroxamic Acid and 1,10-Phenanthroline

Rakesh K. Sahu

Department of Chemistry, National Institute of Technology (NIT) Raipur, hhattisgarh, 492010, India
E-mail: rakesh.sahu13@gmail.com

Dr. (Mrs.) F. Khan*

Department of Chemistry, National Institute of Technology (NIT) Raipur, hhattisgarh, 492010, India
E-mail: fkhan.chy@nitrr.ac.in

Kush Nayak

Department of Biotechnology, National Institute of Technology (NIT) Raipur, hhattisgarh, 492010, India

Abstract

New Co(III) complexes of mixed ligands, hydroxamic acid (L1 = AHA (acetohydroxamic acid), L2 = BHA (benzohydroxamic acid) and L3 = OHA (oxalohydroxamic acid) and 1, 10-phenanthroline (phen) were synthesized and characterized by NMR, IR, UV-visible, mass spectrometer, and elemental analysis. In the complexes, $[\text{Co}(\text{phen})_2\text{L}]\text{ClO}_4$ (L = L1, L2, L3), the metal ion is coordinated by six atoms, two oxygen atoms from hydroxamic acid and 4N atoms from co-ligand 1, 10-phenanthroline to form octahedral Co(III) complexes. The interaction of these complexes with calf thymus DNA (CT-DNA) has been investigated by absorption spectroscopy measurement. The DNA-binding constants for complexes 1, 2, 3 are $2.47 \times 10^6 \text{ M}^{-1}$, $4.02 \times 10^6 \text{ M}^{-1}$, $2.23 \times 10^6 \text{ M}^{-1}$ respectively. Detailed analysis shows that these complexes bind with DNA through interaction binding. And the study of microbial activity against Gram positive and Gram negative bacteria.

Keywords: DNA binding, hydroxamic acid, cobalt complexes, 1, 10-phenanthroline, microbial activity.

1. Introduction

Cancer is most serious health concerns faced by our society and it is the primary targets for the medicinal chemist [1, 2]. DNA is an important cellular receptor [3, 4]. Many chemicals exhibit antitumor effect by binding with DNA and inhibiting the growth of tumor cells. On the basis of it new and powerful antitumor drugs are designed [5-7]. The effectiveness of drugs mainly depends on two things binding affinity and modes of binding [8, 9]. Metal ion and their complexes play an important role in the life science processes and very tremendously in their function and complexity [10]. Metal complex-DNA interaction identification is the fundamental importance of molecular basis of therapeutic activity [11]. Pharmacological activity is highly dependent of metal ion as well as donor atoms of ligands [9, 12-13]. In the metal complex, different ligands show different type of biological properties [14, 15]. In recent year non-platinum based complexes are widely used for research in this field [16].

In the present work a new Co(III) complexes of mixed ligands, 1, 10-phenanthroline (phen) and hydroxamic acid (L1 = AHA (acetohydroxamic acid), L2 = BHA (benzohydroxamic acid) and L3 = OHA (oxalohydroxamic acid) were synthesized and characterized by NMR, IR, UV-visible, mass spectrometer, and elemental analysis. The hydroxamic acid (AHA, BHA and OHA), -NR-OH group (here R = H), appear to be amenable to biotransformation such as reduction, oxidation, hydrolysis and conjugation with organic and inorganic molecules. N-OH containing compound and also metal complexes were further reported to be effective antibacterial, antifungal [17], antidiabetic [18], antitumor [19], antiproliferative [20], anticancer [12], herbicidal [22], antimalarial drugs, to possess antioxidant and anti-inflammatory activity [23, 24]. And the development of coordination chemistry, 1, 10-phenanthroline plays an important role, it is a classic chelating bidentate ligand for transition metal ions [14, 15, 25].

In the complexes, $[\text{Co}(\text{phen})_2\text{L}]\text{ClO}_4$ (L = L1, L2, L3) metal ion is coordinated by six atoms, two oxygen atom from hydroxamic acid and 4N atom from co-ligand 1, 10-phenanthroline to form octahedral Co(III) complexes. The interaction of these complexes with CT-DNA has been investigated by electronic absorption spectroscopy and studied microbial activity.

2. Materials and instrumentations

All reagents and chemicals including CT-DNA and plasmid were purchased from Merck products and used as such. Hydroxamic acids were prepared and purified according to the literature procedure, for AHA [26], BHA [27], and OHA [28]. $[\text{Co}(\text{phen})_2\text{Cl}_2]\text{Cl}$ complex was prepared and purified according to the literature procedure,

2 mole of 1, 10-phenanthroline was reacted with 1 mole of cobalt (II) chloride followed by chlorine oxidation [29]. Solvents used for electrochemical and spectroscopic studies were purified by standard procedures. The spectroscopic titration was carried out in the buffer (50 mM NaCl-5 mM Tris-HCl, pH 7.2) at room temperature. A solution of CT-DNA in the buffer gave a ratio of UV absorbance 1.9 at 260 and 280 nm, indication that the DNA was sufficiently free of protein [30]. Millipore water was used to prepare the solutions.

Molar conductivities in DMSO (10^{-3} M) at room temperature were measured using Labard LI-CON 01 micro digital conductivity meter. Carbon, hydrogen and nitrogen analyses of the complexes were carried out on a CHN analyzer Carlo Erba (Fisons) 1108 analyzer. The infrared spectra (KBr disks) of the samples were recorded on a FTIR-Thermo Nicolet, Avatar 370 spectrophotometer. NMR spectra were recorded on a Bruker AVANCE 500 FT-NMR spectrometer using DMSO- d_6 as solvent and chemical shift values are reported in ppm (δ scale) relative to TMS as a reference, and the mass spectra were recorded on a WATERS micromass Q-ToFmicroTM instrument. The electronic absorption spectra in the region 200-1100 nm were obtained on a Shimadzu model UV-1800 spectrophotometer at room temperature.

2.1 Synthesis of $[Co(phen)_2AHA]ClO_4$ complex (1)

The $[Co(phen)_2Cl_2]Cl$ (0.3 g, 0.57 mmol) was dissolved in water-ethanol (20 cm³, 1:1 v/v) then basic solution of AHA (0.05 g, 0.67mmol) dissolved in 15 mL ethanol was added to the solution. The reaction was catalyzed by base. The resulting mixture was refluxed for 2h, then allowed to cool at room temperature and then the desired complex was precipitated out upon the addition of NaClO₄ solution, dissolved in dil. HClO₄ acid. The purple-gray solid was filtered and washed with small portion of water and ethanol respectively, then dried under vacuum. Yield 0.27g (78%) (Anal. Found C 63.23, H 3.56, N 14.04. Calc. for C₂₆H₁₉N₅O₆ClCo: C 63.42, H 3.89, N 14.22%), Molar conductance, Λ_m (1×10^{-3} M, DMSO): 116 $\Omega^{-1}cm^2 mol^{-1}$ (1:1 electrolyte). ESI-MS (m/z): 492.06(M⁺), UV-Vis. (H₂O, nm) ($\epsilon/M^{-1} cm^{-1}$): 271, 498(89). IR (cm⁻¹): 479.41, ν (Co-O); 587.31, ν (Co-O); 622.22, ν (ClO₄⁻); 718.56, 846.50 (phen); 1089.64, ν (N-O); 1429.91, 1519.69 ν (C-N, phen); 1488.75 ν (C-N, OCN), ¹H-NMR, ppm, (DMSO, TMS): 9.32 (d, 2H), 9.22 (d, 1H), 9.10 (d, 1H), 8.98 (d, 1H), 8.94 (d, 1H), 8.57 (m, 3H), 8.46 (m, 3H), 7.94 (d, 1H), 7.84 (dd, 1H), 7.76 (dd, 1H), 7.69 (d, 1H), 2.03 (s, 3H). ¹³C NMR, ppm, (DMSO, TMS): 169.31, 154.32, 154.27, 151.60, 151.41, 146.97, 146.68, 146.50, 141.27, 141.18, 140.47, 131.15, 131.08, 130.35, 128.14, 128.06, 127.99, 127.96, 127.32, 127.25, 14.28.

2.2 Synthesis of $[Co(phen)_2BHA]ClO_4$ complex (2)

The complex 2 was synthesized according to the procedure outlined above with ligand BHA (0.09g, 0.66 mmol) instead of AHA. Yield: 0.32g (82%), (Anal. Found C 67.05, H 3.56, N 12.44. Calc. for C₃₁H₂₁N₅O₆ClCo: C 67.15, H 3.82, N 12.63%), Molar conductance, Λ_m (1×10^{-3} M, DMSO): 110 $\Omega^{-1}cm^2 mol^{-1}$ (1:1 electrolyte). ESI-MS (m/z): 554.99 (M⁺), UV-Vis. (H₂O, nm) ($\epsilon/M^{-1} cm^{-1}$): 271, 495(107). IR (cm⁻¹): 440.57, ν (Co-N); 566.14, ν (Co-O); 622.46, ν (ClO₄⁻); 713.73, 837.99 (phen); 1090.55, ν (N-O); 1430.11, 1520.92 ν (C-N, phen); 1468.87 ν (C-N, OCN), ¹H-NMR, ppm, (DMSO, TMS): 9.29 (dd, 3H), 9.01 (d, 2H), 8.96 (d, 1H), 8.43-8.57 (m, 6H), 8.01 (d, 1H), 7.89 (dd, 1H), 7.78 (dd, 1H), 7.72 (d, 1H), 7.70 (dd, 2H), 7.52 (t, 1H), 7.39 (dd, 2H). ¹³C NMR, ppm, (DMSO, TMS): 154.23, 151.55, 151.18, 146.99, 146.74, 146.61, 146.53, 141.15, 141.05, 140.37, 131.11, 131.04, 130.39, 130.28, 128.69, 128.35, 128.07, 128.00, 127.94, 127.34, 127.26, 126.83.

2.3 Synthesis of $[Co(phen)_2OHA]ClO_4$ complex (3)

The complex 3 was synthesized by employing same procedure as described above for 1 with ligand OHA (0.083g, 0.69mmol) instead of AHA. Yield 0.3g (78%), (Anal. Found C 57.31, H 3.02, N 14.12. Calc. for C₂₆H₁₈N₆O₈ClCo: C 58.11, H 3.38, N 15.64%), Molar conductance, Λ_m (1×10^{-3} M, DMSO): 113 $\Omega^{-1}cm^2 mol^{-1}$ (1:1 electrolyte). ESI-MS (m/z): 537 (M⁺), UV-Vis. (H₂O, nm) ($\epsilon/M^{-1} cm^{-1}$): 271, 510(109). IR (cm⁻¹): 443.99, ν (Co-N); 509.40, ν (Co-O); 624.50, ν (ClO₄⁻); 717.96, 847.56 (phen); 1089.06, ν (N-O); 1430.28, 1520.90 ν (C-N, phen); 1461.49 ν (C-N, OCN).

2.4 Reaction mechanism

Reaction catalyzed by the base, without base it does not occur, because mesomeric effect (+M) of lone pair electron of N-atom, electron density delocalized towards both the oxygen atom. It is hard to substitute H atom of OH group. The mechanism is given in Figure 1 (scheme 1)

2.5 NA binding and cleavage experiments

The interaction between metal complexes and DNA was studied using absorption spectra. Millipore water was used to prepare all the solutions. The experiments involving interaction of the complexes with CT-DNA were done in buffer solution containing 5 mM Tris-HCl/50 mM NaCl, pH 7.2 at room temperature. In UV absorbance at 260 and 280 nm, solution of CT-DNA in the buffer gave a ratio of about 1.9, it indicates the CT-DNA sufficiently free from protein [30]. The DNA concentration was measured using its extinction coefficient at 260 nm ($6600 M^{-1} cm^{-1}$). Stock solution were stored at 4°C and were used within 4 days. For the preparation of

complex solution, minimum amount of DMSO was used for dissolving the complex and diluting with Tris-HCl buffer to the required concentration for all the experiment.

The absorption titration was performed by using a fixed concentration of the complexes in Tris-buffer to which varying concentration of the DNA solution were added. The solutions of complex-DNA were allowed to stand for 30 min. for binding properly before the absorption spectra were recorded. The intrinsic binding constant K_b of the complexes to DNA was calculated using the following formula [31]:

$$\frac{[DNA]}{(\epsilon_a - \epsilon_f)} = \frac{[DNA]}{(\epsilon_b - \epsilon_f)} + \frac{1}{K_b(\epsilon_b - \epsilon_f)} \quad \dots\dots\dots (1)$$

Where [DNA] is the concentration of DNA in base pairs, ϵ_a , ϵ_f and ϵ_b are the apparent, free and bound metal complex extinction coefficients, respectively. In plots of $[DNA]/(\epsilon_a - \epsilon_f)$ versus [DNA], K_b is given by the ratio of slope to the intercept.

2.6 Microbial assay

The *in vitro* antimicrobial study of the cobalt (III) complexes were studied for their effect on Gram positive (*Bacillus subtilis*) and Gram negative (*Escherichia coli*) bacteria by well diffusion method [32, 33]. The complexes were stored in dry at room temperature and dissolved in DMSO (1%). In a typical procedure both the Gram positive and Gram negative bacteria were grown in nutrient agar medium and incubated at 37°C for 48h followed by frequent subculture to fresh medium and were used as test bacteria. Then the petri dishes were inoculated with a loop full of bacterial culture and spread throughout the petri dishes uniformly with a sterile glass spreader then a well was made on the agar medium inoculated with microorganisms. The well was then filled with the test solution (2.5 µg/mL) using a micropipette and reference Ciprofloxacin disc was added. The plates were then incubated at 37°C for 48h. Plates with disc containing respective solvents served as control. During this period, the test solutions were diffused and the growth of the inoculated microorganisms was affected. The inhibition zone developed on the plate was measured the diameter of the inhibitory zone after the period of incubation. All the experiments were repeated twice and the average values are presented.

3. Results and discussion

The complexes were synthesized by reacting 1:2:1 stoichiometric amounts of hydroxamic acid (L), 1, 10-phenanthroline and cobalt chloride. All the complexes were stable towards air and moisture and are soluble in DMSO and DMF. The complexes were thoroughly characterized from analytical and spectroscopic data. On the basis of spectral studies, the coordination geometry of central metal ion, cobalt (III) is octahedral. The structure of complexes are shown in Figure 2.

3.1 Elemental analysis and molar conductivity measurements

The elemental analysis result of the cobalt complexes are in good agreement with the calculated values showing that the complexes of stoichiometry $[Co(phen)_2(L)]ClO_4$ [34]. The cobalt (III) complexes were dissolved in DMSO and the molar conductivities of 10^{-3} M of their solution at room temperature were measured. The result of higher conductance values of the complexes indicate their electrolytic nature.

3.2 Infrared spectra

The IR spectra of ligand and complexes were recorded in the region of 4000-400 cm^{-1} by using the KBr pellet. The IR spectrum of the free ligand exhibited the characteristic band of the carbonyl (C=O) at 1684 – 1642(s) cm^{-1} and broad band of the hydroxyl (-OH) group at 3300 – 3200(b) which was disappeared in the complexes, which supports that the oxygen of carbonyl and hydroxyl group are coordinated to central metal, Co(III) with pair of bonding electron. The medium intensity bands around 440 – 479 and 509 – 587 cm^{-1} were attributed to $\nu(Co-O)$ and $\nu(Co-O')$, respectively.

3.3 Electronic absorption spectra

The electronic spectrum of $[Co(phen)_2(L)]ClO_4$ complexes showed one broad bands in the visible region and one in the UV region at ~ 20000 cm^{-1} (500 nm) and 36900 cm^{-1} (271 nm), which are assigned to $^1A_1g(I) \rightarrow ^1T_1g(I)$ and $^1A_1g(I) \rightarrow ^1T_2g(I)$ transitions respectively [35]. It shows the complexes is d^6 , low spin system and cobalt has +3 oxidation state.

3.4 DNA binding studies

3.4.1 Absorption spectral studies

Titration with electronic absorption spectroscopy is an effective method to investigate the binding mode of DNA with metal complexes [36]. Transition metal complexes can bind to DNA via both covalent and/or non-covalent interactions. In the case of covalent binding, the labile ligand of the complexes can be replaced by a nitrogen base of DNA such as guanine N7, while the non-covalent DNA interactions include interactive, electrostatic and

groove (surface) binding of metal complexes outside of DNA helix, along major or minor groove. The absorption titration experiment was carried out upon addition of CT-DNA to metal complexes 1, 2, and 3 of fixed concentration, an increase in the absorbance hyperchromic effect was observed, which reflects greater binding propensity of the complexes for DNA (Fig. 3). However, there was practically no change in the position of the absorption bands of the complexes in the presence of DNA, suggesting the possibility of electrostatic and groove (surface) binding of metal complexes outside of DNA helix, along major or minor groove. The “hyperchromic effect” arises due to the electrostatic interaction between positively charged complexes involving ligand with extended hydrophobic region or surfaces and the negatively charged oxygen phosphate backbone of the double helix CT-DNA non-covalently, thereby causing a contraction and overall damage to the secondary structure of DNA [37]. This was substantiated by quantitative calculation of intrinsic binding constant (K_b) using Wolfe-Shimer Eq. (1), through a plot of $[DNA]/(\epsilon_a - \epsilon_f)$ vs $[DNA]$, where $[DNA]$ represents the concentration of DNA, and ϵ_a , ϵ_f and ϵ_b the apparent extinction coefficient ($A_{obs}/[M]$), the extinction coefficient for free metal complex (M), and the extinction coefficient for the metal complexes were determined by the plots of $[DNA]/(\epsilon_a - \epsilon_f)$ vs $[DNA]$, K_b is given by the ratio of slope to the intercept Eq. (1). The binding constant (K_b) were given in Table 1, which followed the order complex 2 > complex 1 > complex 3. The K_b values is quite stronger. These results suggest an intimate association of the compounds with CT-DNA and it is also likely that compounds bind to the helix via intercalative mode.

3.5 Antibacterial screening

The cobalt(III) complexes (1-3) were screened *in vitro* for their microbial activity against Gram positive (*Bacillus subtilis*) and Gram negative (*Escherichia coli*) bacteria and compared with standard drugs Ciprofloxacin by well diffusion method using agar nutrient as the medium [32, 33]. These complexes were found to exhibit activity against Gram positive (*Bacillus subtilis*) but not found in Gram negative bacteria (*Escherichia coli*). The results of the antimicrobial activities are showed in Table 2. All complex possess moderate activity, in the order of three cobalt(III) complexes is complex 2 > complex 3 > complex 1.

4. Conclusion

In this work, mixed ligand cobalt(III) complexes i.e. hydroxamic acid and 1, 10-phenanthroline have been synthesized and characterized by spectral and analytical data. Binding of these complexes to CT-DNA has been investigated by electronic absorbance titrations, the result suggest an intimate association of the compounds with CT-DNA and it is also likely that compound bind to the helix via intercalative mode. The binding constant is found to be in the following order complex 2 > complex 1 > complex 3. All the metal complexes are found to moderate antibacterial activity again Gram positive (*Bacillus subtilis*) bacteria but it is not affected in Gram negative bacteria (*Escherichia coli*).

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Table 1: The intrinsic binding constants (K_b) of cobalt (III) complexes with calf thymus DNA

Complex	Complex Concentration	Binding Constant (K_b)
[Co(phen) ₂ AHA](ClO ₄)	5.41 x 10 ⁻⁵	2.47 X 10 ⁶
[Co(phen) ₂ BHA](ClO ₄)	2.24 x 10 ⁻⁵	4.02 X 10 ⁶
[Co(phen) ₂ OHA](ClO ₄)	3.98 x 10 ⁻⁵	2.23 X 10 ⁶

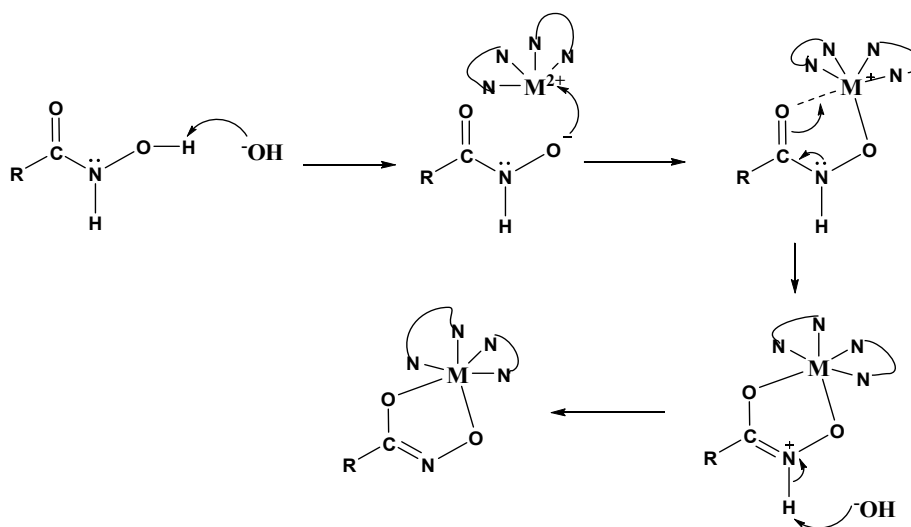
Table 2: Antimicrobial activities of cobalt (III) complexes.

Complexes	Diameter of inhibition zone (mm)		
	Test organisms		
	Gram positive (Bacillus subtilis)		Gram negative (Escherichia coli)
[Co(phen) ₂ AHA](ClO ₄)	15		F
[Co(phen) ₂ BHA](ClO ₄)	21		F
[Co(phen) ₂ OHA](ClO ₄)	18		F
Standard	34		35

Standard — Ciprofloxacin for bacteria.

Solvent — DMSO (Showed nil effect against the microorganisms under test).

F — No inhibition zone is determined.



Scheme 1

Figure 1: Scheme of reaction mechanism

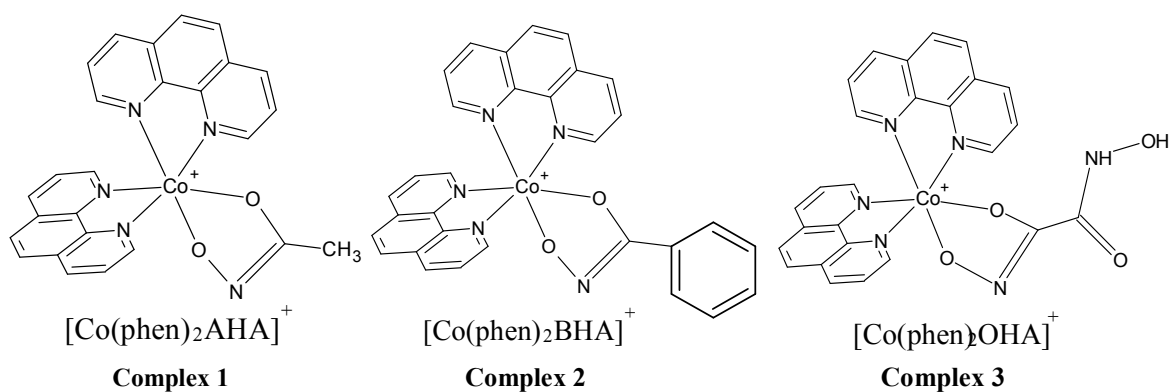


Figure 2: Structure of the Cobalt (III) complexes

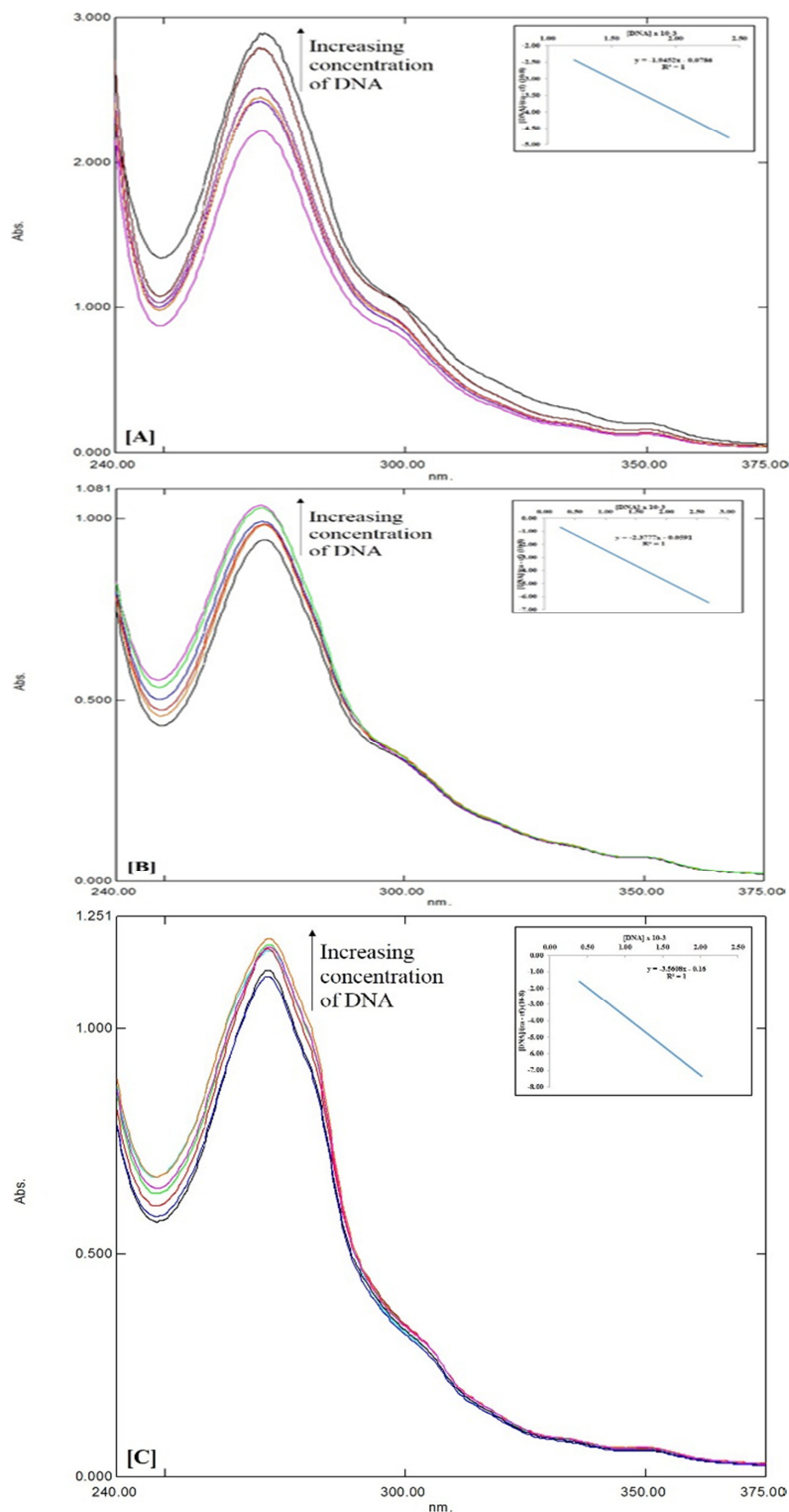


Figure 3. Absorption spectral traces of [A] complex 1, [B] complex 2, [C] complex 3 in 5 mM TrisHCl/50 mM NaCl buffer at pH 7.2 in presence of increasing amount of CT-DNA. Inset: Plots of $[DNA]/(\epsilon_a - \epsilon_f)$ vs $[DNA]$ for the titration of CT DNA with complexes; full lines, linear fitting of the data. Arrow indicates the changes in absorbance upon increasing the DNA concentration.

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