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**Studies on Structure and DNA interaction of Nickel(II) complexes of
NO donor Schiff base**

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Abstract

A series of Nickel(II) complexes ligated by 2,3-Dimethyl-4-formyl-[2'-(aminomethyl)pyridine]-1-phenyl-3-pyrazolin-5-one (DFAPP), $[\text{Ni}(\text{DFAPP})_2\text{X}_2]$ (where X = Cl^- or Br^-) (**1**) (**2**), $[\text{Ni}(\text{DFAPP})_2(\text{NO}_3)]\text{NO}_3$ (**3**), and $[\text{Ni}(\text{DFAPP})_2(\text{ClO}_4)]\text{ClO}_4$ (**4**) has been synthesized and characterized with the help of elemental analysis, molar conductance magnetic moments and IR and UV spectroscopic data. The Schiff base is found to act as bidentate ligand using NO donor set of atoms leading to an octahedral geometry around central metal ion in all the complexes. The interaction of the complexes with calf thymus DNA (CT-DNA) has been investigated by UV absorption method and viscometry method. The mode of binding of the complexes with DNA was evaluated and is found to be groove binding.

Keywords

Nickel(II) complexes, Schiff base, Spectra, Magnetic Susceptibility, DNA binding behavior, intercalation, hyperchromism, Viscosity.

Introduction

Transition metal complexes with Schiff base as ligands have been amongst the widely studied coordination compounds in the past few years, since they are found to be widely applicable in biochemical, analytical and antimicrobial fields [1, 2, 3]. The metal ions present in complexes can accelerate the drug action and efficacy of the organic

therapeutic agents [4]. Transition metal complexes are currently being used to bind and react at specific sequences of DNA in a search for novel chemotherapeutic agents and better anticancer drugs [5]. Herein, we have synthesized and characterized a series of novel Nickel(II) complexes of Schiff base ligand 2,3-Dimethyl-4-formyl-[2'-(aminomethyl)pyridine]-1-phenyl-3-pyrazolin-5-one and investigated their DNA binding activity.

Materials and Methods

High purity 4-antipyrine carboxaldehyde, 2-amino methylpyridine, Calf thymus DNA (CT DNA) (Aldrich,USA), Nickel(II) chloride hexahydrate, Nickel(II) nitrate hexahydrate, *Tris*-HCl (E.Merck,India) was purchased from respective concerns and used as such. Bromide and perchlorate of Nickel(II) were prepared by dissolving Analar Nickel carbonate in the respective 50% acids and crystallizing the salts after concentrating the resulting solutions on a steam bath. All other chemicals and solvents were of AR grade.

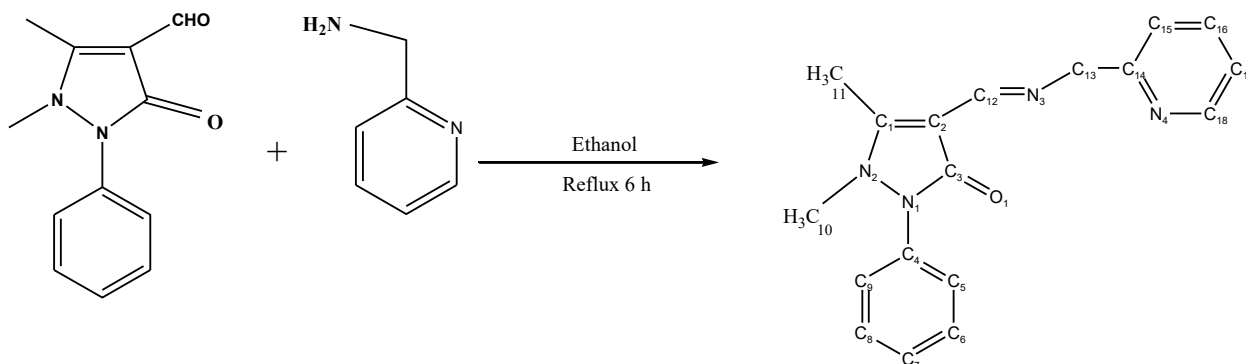
The C, H and N contents in the complexes were determined on a perkin –Elmer 240 CHN analyser. All the complexes were analyzed for their metal, halide and perchlorate contents by standard methods [6, 7]. Molar conductivities were measured using freshly prepared 10^{-3} M solutions dimethyl formamide, acetonitrile, nitrobenzene and methanol at room temperature using a Thoshniwal conductivity bridge with dip type conductance cell (cell constant 0.9741) which was calibrated with 0.01M KCl solution [8]. The infrared spectra were recorded in the range $4000-100\text{ cm}^{-1}$ on a Shimadzu IR 470 spectrometermeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrophotometer using acetone- d_6 as solvent. Magnetic susceptibility measurements were performed on pulverized samples at room temperature on a Sherwood Magwy MSB MK1 balance. The diamagnetic corrections were calculated using pascal's constants.

All experiments involving the interaction of the complex with DNA were carried out in twice distilled buffer (5 mM *Tris*-HCl, 50 mM NaCl, pH 7.2) at room temperature. Stock solutions were stored at $4\text{ }^\circ\text{C}$ and used after no more than 4 days. A solution of calf thymus DNA in the buffer gave a ratio of UV absorbance at 260 and 280 nm of 1.8-1.9

indicating that the DNA was sufficiently free of protein. The DNA concentration per nucleotide was determined by absorption spectroscopy using molar absorption coefficient (6600 cm^{-1}) at 260 nm. Viscometry measurements were carried out on semimicro dilution capillary viscometer with a thermostatic bath at room temperature.

Synthesis of 2,3-Dimethyl-4-formyl-[2'-(aminomethyl)pyridine]-1-phenyl-3-pyrazolin-5-one

The ligand, DFAPP, was prepared by the condensation of antipyrine-4-carboxaldehyde and 2-(aminomethyl)pyridine in ethanolic medium. To a boiling solution of 10 mmol (1.0815 g) 2-(aminomethyl)pyridine in ethanol (20 ml), 10 mmol (2.1624 g) antipyrine-4-carboxaldehyde in ethanol (30 ml) was added and refluxed on a steam bath for about 6 h. The light brown crystals that obtained after cooling the resulting solution were filtered out and washed with cold ethanol to remove the unreacted reactants if any. It was then recrystallised from ethyl acetate and dried over phosphorus(V)oxide under vacuum. DFAPP is light yellow in colour, its molecular formula is $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}$, molecular mass is 306.37.



Scheme1. 2,3-dimethyl-4-formyl-[2'-(aminomethyl)pyridine]-1-phenyl-3-pyrazoline-5-one (DFAPP)

The yield: 85%. m.p. 148°C . Anal. Cal. for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}$ (306.37) C, 70.57; H, 5.92; N, 18.29. Found: C, 70.47; H, 5.87; N, 18.26%. IR(cm^{-1}): 1660 ($-\text{C}=\text{O}$), 1562 ($-\text{CH}=\text{N}-$), 1460, 698 (Pyridyl N). ^1H NMR(δ): 8.42 (s, 1H, $-\text{CH}=\text{N}-$), 7.23-7.67 (m, -Ph), 7.14-8.67 (m, py. ring), 3.71 (s, 2H, $-\text{N}-\text{CH}_2-$), 3.34 (s, 3H, $-\text{N}-\text{CH}_3$), 2.55 (s, 3H, $=\text{C}-\text{CH}_3$). ^{13}C NMR (δ): 166.71 (C_{12}). UV-VIS ($\lambda_{\text{Max/nm}}$): 335 ($\text{n} - \pi^*$), 247 ($\pi - \pi^*$).

Synthesis of complexes

A solution of NiCl₂.6H₂O, NiBr₂.6H₂O, Ni(ClO₄)₂.6H₂O or Ni(NO₃)₂.6H₂O in methanol (1 mmol, 10 mL) was added drop wise to a hot solution of DFAPP (2 mmol, 20 mL) in ethyl acetate and refluxed for about 3h on a water bath. The precipitated complexes were filtered and washed repeatedly with hot benzene. The complexes were recrystallized from methanol and dried under vacuum over phosphorous(V) oxide. Yield: **1** = 85%, **2** = 75%, **3** = 77%, **4** = 78%.

Results and discussion

Physical characterization

The metal, chloride, bromide (6), perchlorate (7), carbon, hydrogen and nitrogen content in the complexes were determined. The elemental analysis data of the Ni(II) complexes are presented in the Table 1. The data suggest that the complexes **1- 4** may be formulated as [Ni(DFAPP)₂X₂] (where X = Cl⁻ or Br⁻) (**1**) (**2**), [Ni(DFAPP)₂(NO₃)]NO₃ (**3**), and [Ni(DFAPP)₂(ClO₄)]ClO₄(**4**). The molar conductance data reveal that the complexes [Ni(DFAPP)₂Cl₂](**1**) and [Ni(DFAPP)₂Br₂](**2**) behave as non- electrolytes, [Ni(DFAPP)₂(NO₃)]NO₃(**3**) and [Ni(DFAPP)₂(ClO₄)]ClO₄(**4**) behave as 1:1 electrolytes (8). All the complexes are soluble in acetonitrile, dimethylformamide, methanol and ethanol. All of them are insoluble in acetone, toluene, benzene, carbon tetrachloride, ethyl acetate, and chloroform.

Infrared spectral studies

The important infrared spectral bands of DFAPP and its Ni(II) complexes together with the tentative assignments are given in Table 2.

The infrared spectrum of the ligand exhibits a strong absorption at 1660 cm⁻¹ corresponding to stretching vibrations of the pyrazolone ring carbonyl oxygen. The band observed at 1562 cm⁻¹ is attributable to -C=N stretching vibrations. The absorptions at 1460 and 698 cm⁻¹ in the ligand are assigned respectively to ring stretching and out of plane deformation modes of pyridine moiety of DFAPP [9].

In the complexes, the band at 1660 cm^{-1} is shifted to 1650 cm^{-1} indicating coordination of carbonyl oxygen. At the same time strong band at 1562 cm^{-1} is shifted to the region $1573\text{-}1581\text{ cm}^{-1}$ suggesting coordination of imine nitrogen. The bands at 1460 and 698 cm^{-1} remain unaltered indicating non participation of pyridyl nitrogen in coordination [10]. Thus DFAPP acts as a neutral bidentate ligand coordinating through carbonyl oxygen and imine nitrogen.

The nitrate complex exhibits the vibrational frequencies characteristic of uncoordinated nitrate ions. A very strong band at 1384 cm^{-1} and a medium band at 829 cm^{-1} are attributable to ν_3 and ν_2 vibrations of uncoordinated nitrate ion of D_{3h} symmetry [11]. The two medium bands at 1492 and 1315 cm^{-1} are attributable to ν_4 and ν_1 vibrations respectively of coordinated nitrate ion of C_{2v} symmetry. Since $(\nu_4 - \nu_1) = 177\text{ cm}^{-1}$, the nitrate ion is coordinated in a bidentate fashion [12].

In perchlorate complex, the triply split band maxima at 1148 , 1115 and 1022 cm^{-1} are due to ν_8 , ν_6 and ν_1 vibrations, respectively of perchlorate ion of C_{2v} symmetry, indicating coordination of perchlorate ion in a bidentate fashion [13]. The very strong band at 1087 cm^{-1} is attributable to the ν_3 vibration of uncoordinated perchlorate ion of T_d symmetry. The bands observed at 944 and 630 cm^{-1} due to ν_2 and ν_3 vibrations respectively of the coordinated perchlorate (C_{2v}) ion and band at 624 cm^{-1} due to ν_4 vibration of uncoordinated perchlorate (T_d) ion [14] also support the co-existence of both coordinated and uncoordinated perchlorate ions in the complex.

There are two low frequency skeletal vibrations in the range $554\text{-}562\text{ cm}^{-1}$ and $440\text{-}461\text{ cm}^{-1}$ are due to M-O and M-N stretching respectively provide direct evidence for complexation.

In the infrared spectra of the halide complexes **1** and **2** the bands at 287 cm^{-1} and 302 cm^{-1} were due to the $\nu(\text{Ni-Cl})$ and $\nu(\text{Ni-Br})$ vibrations which are absent in the spectrum of the ligand.

Electronic spectra and Magnetis2

The electronic spectral data with tentative assignments and magnetic moments of Ni(II) complexes of DFAPP are presented in the Table 3.

The electronic spectrum of DFAPP exhibits two main peaks at about 335 and 247 nm which are assignable to the $n-\pi^*$ and $\pi-\pi^*$ transitions respectively. In the complexes **1-4**, the $n-\pi^*$ band is red shifted to 339-342 nm region and $\pi-\pi^*$ band is blue shifted to 234-240 nm compared to DFAPP.

In complexes **1, 2, 3** and **4** the three main bands in the regions $\nu_1 = 1037-1068$ nm, $\nu_2 = 618-686$ nm and $\nu_3 = 474-500$ nm corresponds to ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transitions and are indicative of an octahedral geometry around nickel(II) ion. Besides the room temperature magnetic moments of the complexes **1, 2, 3** and **4** are 2.91, 2.96, 2.94 and 2.80 BM respectively indicating an octahedral geometry around nickel(II) ion [15, 16].

Furthermore, the complexes **1-4** show an intense absorption band in the 390-410 nm region which may be due to charge transfer transition [17].

Table 1 Analytical data of Ni(II) complexes of DFAPP

Complex Molecular Formula/Weight	Analytical data. Obs.(Cal.)					M.P. (°C)	Yield (%)
	Carbon (%)	Hydrogen (%)	Nitrogen (%)	Metal (%)	Anion (%)		
[Ni(DFAPP) ₂ Cl ₂](1) C ₃₆ H ₃₆ N ₈ O ₂ Cl ₂ Ni (742.31)	58.18 (58.25)	4.82 (4.88)	15.01 (15.09)	7.82 (7.90)	9.47 (9.55)	212	76
[Ni(DFAPP) ₂ Br ₂](2) C ₃₆ H ₃₆ N ₈ O ₂ Br ₂ Ni (831.22)	51.92 (52.01)	4.30 (4.36)	13.39 (13.47)	6.97 (7.06)	19.16 (19.22)	211	82
Ni(DFAPP) ₂ (NO ₃)]NO ₃ (3) C ₃₆ H ₃₆ N ₁₀ O ₈ Ni (795.42)	54.23 (54.35)	4.41 (4.56)	17.49 (17.60)	7.28 (7.37)	27.32 (27.43)	221	77
[Ni(DFAPP) ₂ (ClO ₄)]ClO ₄ (4) C ₃₆ H ₃₆ N ₈ O ₁₀ Cl ₂ Ni (870.31)	49.59 (49.68)	4.08 (4.16)	12.80 (12.87)	6.66 (6.74)	22.67 (22.85)	280	79

Table 2 Important Infrared Spectral bands of Ni(II) complexes of DFAPP

DFAPP	(1)	(2)	(3)	(14)	Assignment
1660	1650	1650	1650	1650	$\nu(-C=O)$
1562	1581	1577	1577	1577	$\nu(-CH=N-)$
1460	1462	1459	1460	1461	ν_{py} ring str.
698	698	698	698	698	ν_{py} out plane str.
				1384	ν_3 - uncoordinated NO_3
				829	ν_2 - uncoordinated NO_3
				1492	ν_4 - coordinated NO_3
				1315	ν_1 - coordinated NO_3
			1148		ν_8 - coordinated ClO_4
			1115		ν_6 - coordinated ClO_4
			1022		ν_1 - coordinated ClO_4
			944		ν_2 - coordinated ClO_4
			630		ν_3 - coordinated ClO_4
			1087		ν_3 - uncoordinated ClO_4
			624		ν_4 - uncoordinated ClO_4
	562	557	554	562	$\nu(Ni-O)$
	440	448	455	460	$\nu(Ni-N)$
	287				$\nu(Ni-Cl)$
		302			$\nu(Ni-Br)$

Table 3 Electronic Spectral data and Magnetic Moments of Ni(II) complexes of DFAPP

Complex	Abs. Max (nm)	Tentative Assignments	μ_{eff} (BM)
DFAPP	335 247	$n-\pi^*$ $\pi-\pi^*$	
$[Ni(DFAPP)_2Cl_2](1)$	342 240	$n-\pi^*$ $\pi-\pi^*$	

	390 500 620 1054	Charge Transfer ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$	2.91
[Ni(DFAPP) ₂ Br ₂](2)	341 236 392 476 685 1038	n- π^* π - π^* Charge Transfer ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$	2.96
[Ni(DFAPP) ₂ (NO ₃)] NO ₃ (3)	339 234 400 500 618 1068	n- π^* π - π^* Charge Transfer ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$	2.80
[Ni(DFAPP) ₂ (ClO ₄)]ClO ₄ (4)	342 238 410 474 686 1037	n- π^* π - π^* Charge Transfer ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ ${}^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$	2.94

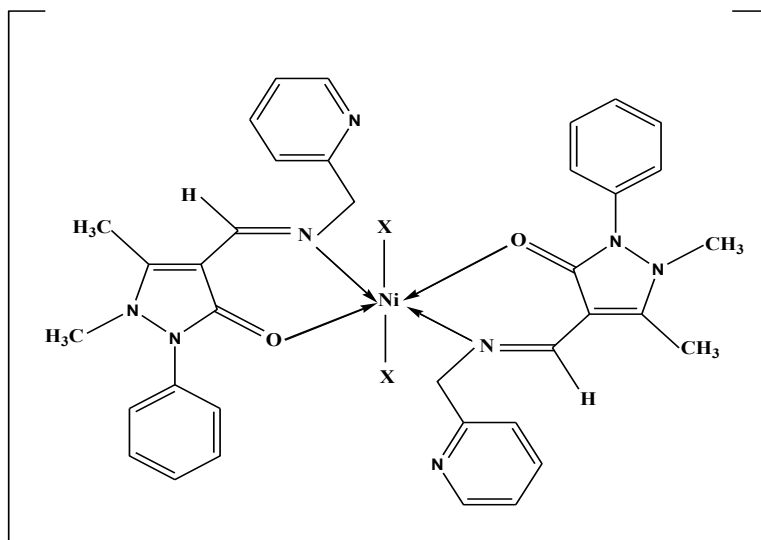


Fig 1 [Ni(DFAPP)₂X₂] (where X = Br⁻ or Cl⁻) (1 and 2)

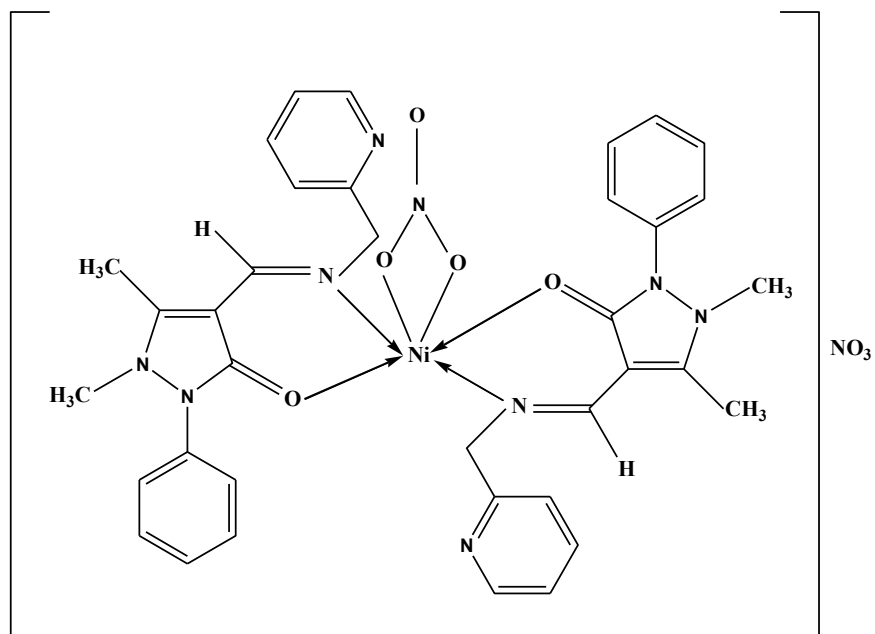


Fig. 2 [Ni(DFAPP)₂(NO₃)]NO₃(3)

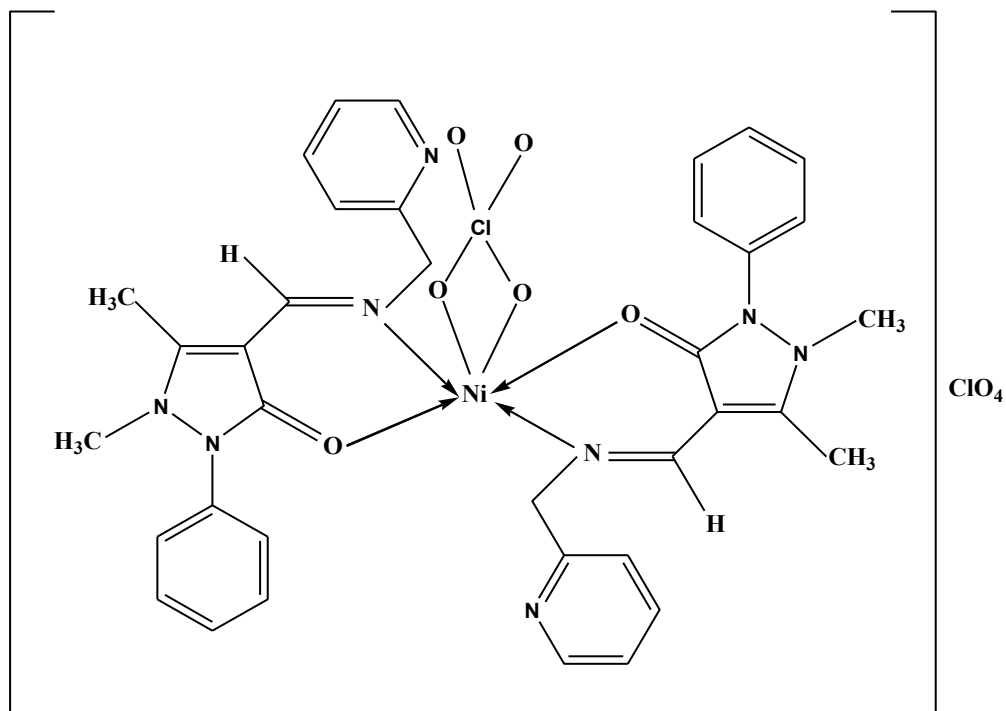


Fig. 3 [Ni(DFAPP)₂(ClO₄)]ClO₄(4)

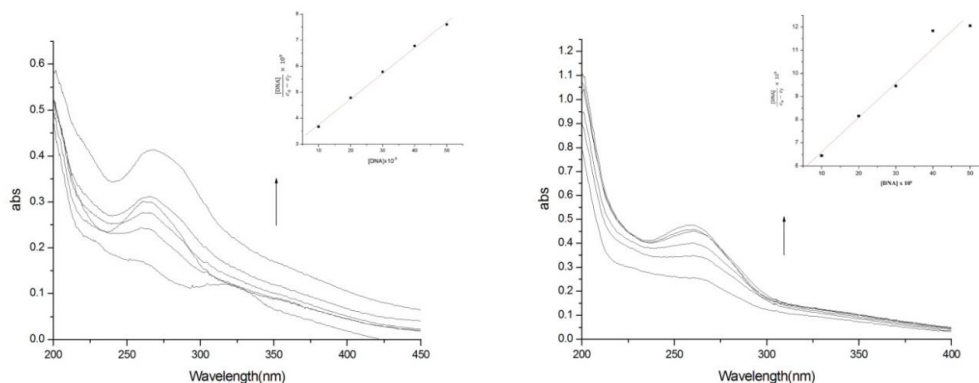
DNA binding experiments

Electronic spectral studies

The binding of complexes **1** - **4** were investigated by the technique of UV-Visible absorption titrations upon addition of increasing amount of DNA solution from 0 to 50 μM to a constant concentration of complex (25 μM) the intense ligand based $\pi\text{-}\pi^*$ absorption band of the complexes were used to monitor the interaction of present Nickel(II) complexes with CT DNA. The complexes exhibited hyperchromism in $\pi\text{-}\pi^*$ absorption band which indicates that the complexes underwent a non-intercalative binding with DNA [18]. The absorption spectra of the complexes in the absence and in presence of CT-DNA (with constant concentration of complex) is given in Fig 4. The absorption data were analyzed to evaluate the intrinsic binding constant K_b which can be determined by the eqn.

$$[\text{DNA}]/(\epsilon_a - \epsilon_f) = [\text{DNA}]/(\epsilon_0 - \epsilon_f) + K_b/(\epsilon_0 - \epsilon_f)$$

Where $[\text{DNA}]$ is the concentration of DNA in base pairs, the apparent absorption coefficients ϵ_a , ϵ_0 and ϵ_f correspond to $A_{\text{obsd}}/[\text{M}]$. The extinction coefficient for the free copper complex and the extinction coefficient for the complex in fully bound form. The ratio of slope to intercept in plots of $[\text{DNA}]/(\epsilon_a - \epsilon_f)$ versus $[\text{DNA}]$ (Fig 4) gives the value of intrinsic binding constant K_b . The value of K_b for **1**, **2**, **3** and **4** are 2.905×10^5 , $3 \times 10^4 \text{ M}^{-1}$, 7.03×10^6 and 1.44×10^4 respectively.



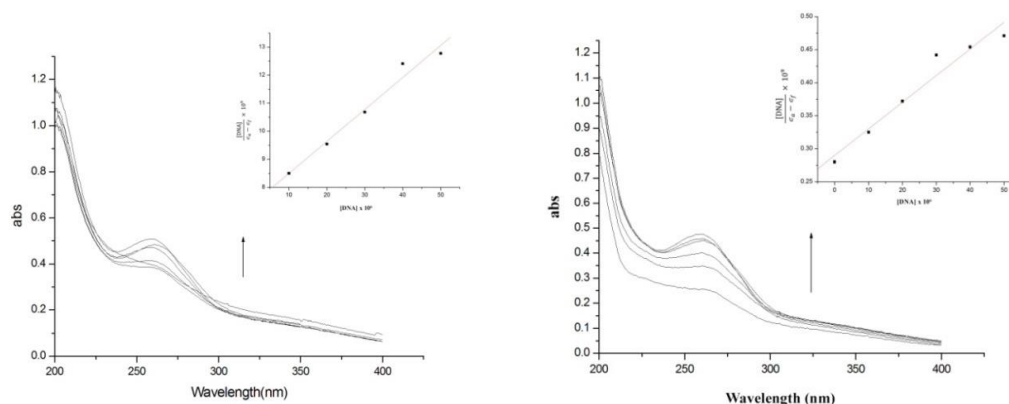


Fig. 4 The absorption spectra of the complexes in the absence and in presence of CT-DNA
Viscosity measurements

The viscosity measurements of CT-DNA are regarded as the least ambiguous and most essential analysis of DNA binding mode in solution. In the absence of crystallographic structural data, viscosity measurements are regarded as most critical test of a binding model in solution. To clarify further the mode of interaction between the complexes and DNA, viscosity measurements were performed. The values of relative viscosities of complexes $(\eta/\eta_0)^{1/3}$ (where η is the viscosity of DNA in presence of complex and η_0 is the viscosity of DNA alone) is plotted against $[\text{complex}]/[\text{DNA}]$ with increase in the amount of complex, the DNA viscosity shows only a small increase with increase of concentration of complex but the increase is less when compared to a classical intercalator. This observation is consistent with DNA groove binding [19]. The plots of $(\eta/\eta_0)^{1/3}$ vs $[\text{complex}]/[\text{DNA}]$ of the complexes is shown in Fig 5.

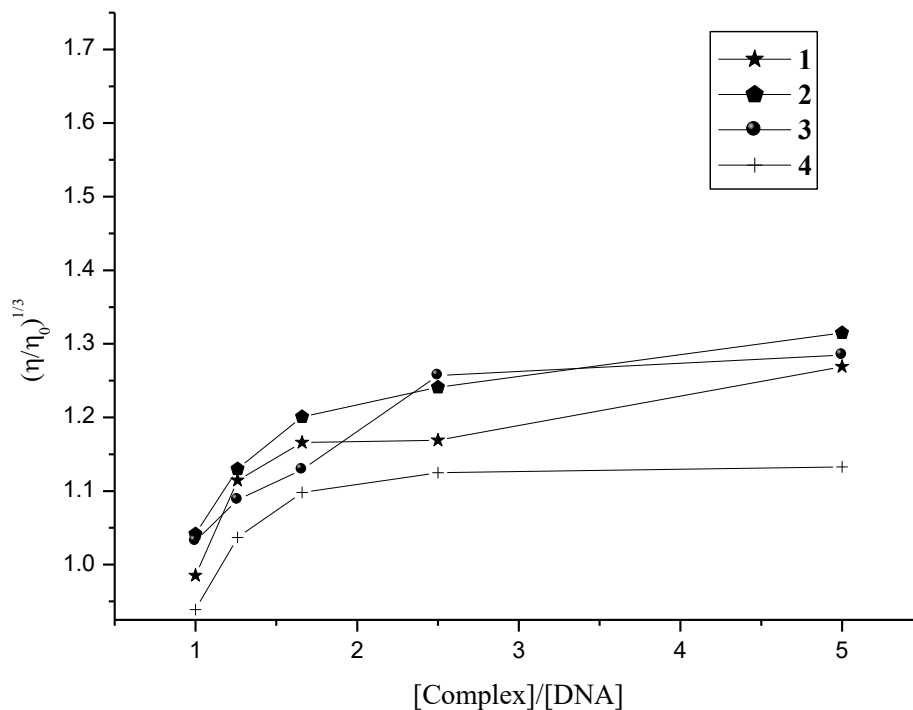


Fig 5 Effect of increasing amounts of complexes on viscosity of CT DNA ($5 \times 10^{-5}M$).
[Complex]/[DNA] = 1, 1.25, 1.66, 2.50, 5.

Conclusions

Elemental studies and magnetic moment and spectral data reveal that DFAPP acts as a neutral bidentate ligand coordinating through pyrazolone carbonyl oxygen and imine nitrogen in all the complexes and both the anions are coordinated in chloride and bromide complexes, while only one of the anions is coordinated to the metal ion in nitrate and perchlorate complexes suggesting an octahedral geometry around central metal ion in all complexes. The interaction studies of the complexes with calf thymus DNA (CT-DNA) by UV absorption method and viscometry method suggest that the mode of binding is groove binding.

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