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Synthesis, Structural Characterization and DNA Studies of Nickel (II) Complexes of (2*E*)-^{4}*N*-Substituted-2-[4-(propan-2-yl) Benzylidene]Hydrazinecarbothioamide Schiff's Bases

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ABSTRACT

This paper describes the synthesis of nickel (II) complexes of (2E)-^{4}N-substituted-2-[4-(propan-2-yl)benzylidene]hydrazinecarbothioamide Schiff bases derived from ^{4}N substituted thiosemicarbazides and cuminal. The prepared ligands and complexes were characterized using various physicochemical techniques viz. elemental analysis, molar conductance, magnetic susceptibility measurements, IR, electronic absorption spectral studies and cyclic voltammetry. The spectral data indicates that the complexes are square planar geometry in solid state while in coordinating solvents like DMSO solvent exhibits octahedral geometry suggesting coordination of solvent molecules presumably in axial position. The absorption titration studies revealed that each of these complexes is an avid binder to calf thymus-DNA. The apparent binding constants are in the order of 10^7–10^8 M^{-1}. The nucleolytic cleavage activities of the ligands and their complexes were assayed on pUC18 plasmid DNA using gel electrophoresis in the presence and absence of H2O2. The ligands showed increased nuclease activity when administered as copper complexes. All these nickel (II) complexes behave as efficient chemical nucleases with hydrogen peroxide activation. These studies revealed that the complexes exhibit both oxidative and hydrolytic chemistry in DNA cleavage.

Keywords: Cuminal; Thiosemicarbazones; Nickel (II) complexes; DNA studies

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INTRODUCTION

Besides enhancing the flavour and aroma of food, spices have also been long recognized to possess physiological effects supposed to be beneficial to human system. Those spices containing medicinal compounds [1] having carbonyl groups have evoked interest in the preparation of novel Schiff bases and their metal complexes. In the of view of this, it is interest to study thiosemicarbazone derivatives of culinary compounds such as cuminal which is main constituent of the most typical spices for India, Cumin. Thiosemicarbazones and their derivatives have been emerged as an important class of sulphur and nitrogen containing ligands in the last few decades due to extensive investigation in chemistry and biology owing to their broad spectrum of certain kinds of tumors [2-6], and in many other applications including corrosion inhibition of metals [7-9]. In many cases, coordination of these ligands to metal ions increases their bioactivity, suggesting that complexation could be an interesting strategy for dose reduction. The choice on the substances was made to find out which of the molecule is determinant in endowing the complex of activity and also in the light of the considerations reported literature on Pd(II), Pt(II) [10,11], Zn(II), Cd(II) [12] and Cu(II) [13], Cu(I) [14] complexes of ^{4}N substituted cuminaldehyde thiosemicarbazones.

To extend further our knowledge of the chemical and biological behavior of thiosemicarbazones and to widen our comprehension of the mechanism of action and of the possible biological targets, we synthesized Continued interest in new copper—thiosemicarbazone complexes [15-19] prompted us to synthesize nickel(II) complexes of a series of new thiosemicarbazones derived from a culinary carbonyl compound, viz. cuminaldehyde (p-isopropyl benzaldehyde), which may be isolated from Indian spice viz. Cuminum cymium Linn (cumin).

EXPERIMENTAL SECTION

Materials and methods

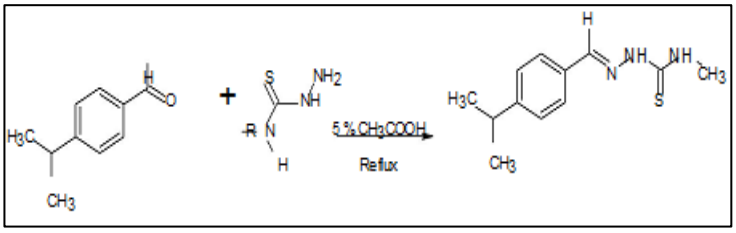
Thiosemicarbazide, 4-methyl-3-thiosemicarbazide, 4-ethyl-3-thiosemicarbazide, 4-phenyl-3-thiosemicarbazide and cuminaldehyde (p-isopropyl benzaldehyde) were of reagent grade purchased from Sigma-Aldrich. All other chemicals were of AR grade and used as supplied. The solvents were distilled before use. Calf thymus DNA was purchased from Genie Bio labs, Bangalore, India. The plasmid pUC18 DNA was isolated from E. coli DH5a strains in Lusbria Broth (LB) medium supplemented by ampicillin cells from 5 ml culture by Qiagen column following the manufacturer's protocol.

Physical measurements

Elemental analysis was carried out on a Perkin-Elmer 2400 CHNS elemental analyzer. Magnetic susceptibility measurements were carried out on a magnetic susceptibility balance (Sherwood Scientific, Cambridge, England), high purity CuSO4.5H2O was used as a standard. Molar conductance (10^{-3}M) in DMF at 30±2^{o}C was measured with a CC180 model (ELICO) direct reading conductivity bridge. The electronic spectra were recorded in DMSO with a Shimadzu UV-160A spectrophotometer. FT-IR spectra were recorded in the range 4,000–270 cm^{-1} in KBr discs on a Nicolet protege460 IR Spectrometer. The cyclic voltammetric measurements were performed on a Bio Analytical System (BAS) CV-27 assembly equipped with an X-Y recorder. Measurements were made on degassed (N2 bubbling for 5 min) ligand/complex solutions (10-3 M) in DMF and ethanol containing tetrabutylammonium perchlorate (0.1 M) as a supporting electrolyte. The three-electrode system consisted of a glassy carbon (working), platinum wire (auxiliary) and Ag/AgCl (reference). The ^{1}H- and ^{13}C{1H}-NMR spectra were recorded on a Bruker Spectrospin DPX-300 NMR spectrometer at 300.13 and 75.47 MHz, respectively.

Preparation of the thiosemicarbazones

The ligands were prepared (Scheme 1) according to published procedure [13].



Where R = H (CTH), CH3 (CMTH), C2H5 (CETH), C6H5 (CPTH)

Scheme 1: Preparation of the ligands

Preparation of the complexes

To a methanolic solution of appropriate ligand (2mol) added 1 gm of sodium acetate to maintain pH (8-9) of the solution. Then added a solution of nickel (II) chloride **(**1mol**)** in methanol. The reaction mixture was refluxed for about 1 hr., during which time a solid complex formed was cooled to room temperature, the resulting product was washed with hot water and finally with diethyl ether and dried in vacuum desiccators over anhydrous CaCl2.

DNA binding experiments

A solution of CT-DNA in 0.5mM NaCl/5mM Tris–HCl (pH 7.0) gave a ratio of UV absorbance at 260 and 280 nm (A260/A280) of 1.8–1.9, indicating that the DNA was sufficiently free of proteins [20]. A concentrated stock solution of DNA was prepared in 5 mM Tris–HCl/50 mM NaCl in water at pH 7.0 and the concentration of CT-DNA was determined per nucleotide by taking the absorption coefficient (6,600 $dm^{3}mol^{-1}cm^{-1}$) at 260 nm [21]. Stock solutions were stored at 4^{o}C and were used after no more than 4 days. Doubly distilled water was used to prepare buffer solutions. Solutions were prepared by mixing the complex and CT-DNA in DMF medium. After equilibrium was reached (ca. 5 min) the spectra were recorded against an analogous blank solution containing the same concentration of DNA.

The data were then fitted into Equation 1 to obtain the intrinsic binding constant (Kb) [22];

$$[DNA] / (\varepsilon A-\varepsilon F) = [DNA] / (\varepsilon B-\varepsilon F) + 1 / Kb\ (\varepsilon B-\varepsilon F) \qquad (1)$$

Where [DNA] is the concentration of DNA in base pair, εA, εB, εF corresponds to the molar extinction coefficients of apparent, bound and

free metal complexes respectively. A plot of [DNA]/(εA-εF) Vs [DNA], gave a slope 1/(εB-εF) and a Y-intercept equal to 1 / Kb (εB-εF); Kb is the ratio of slope to the intercept

Assay of nuclease activity

DMF solutions of the complexes were placed in clean Eppendorf tubes and 1 lg of pUC18 DNA was added. The contents were incubated for 30 min at 37^0C and loaded on 0.8% Agarose gel after mixing 5 µl of loading buffer (0.25% bromophenol blue + 0.25% Xylene cyanol + 30% glycerol sterilized distilled water). Electrophoresis was performed at constant voltage (100 V) until the bromophenol blue reached to the $3/4^{th}$ of the gel. The gel was stained for 10 min by immersing in an ethidium bromide solution. The gel was then destained for 10 min by keeping in sterilized distilled water and the plasmid bands visualized by photographing the gel under a UV Transilluminator. The efficiency of DNA cleavage was measured by determining the ability of the complex to form open circular (OC) or nicked circular (NC) DNA from its super coiled (SC) form. The reactions were carried out under oxidative and/or hydrolytic conditions. Control experiments were done in the presence of hydroxyl scavenger DMSO.

RESULTS AND DISCUSSION

Characterization of the free thiosemicarbazones

The characterization of the ligands was reported in detail from same group [13]. The thiosemicarbazones are colourless air stable solids. Their analytical data are given in Table 1. The IR spectra of the free thiosemicarbazones showed two medium bands at 3,412–3,253 cm-1 due to terminal –NH2/NHR vibrational modes. Strong bands observed at 1,177–1,196 and 1,544–1,590 cm-1 are assigned to t(C=S) and [C=N– stretching vibrations, respectively.

No band was observed near 2,575 cm-1 suggesting the thione form in solid state. In their cyclic voltammetric scans the presence of only cathodic peaks at -1.51(-1.54), -1.64(-1.20), -1.42(-1.20), -1.50(-1.33) for CTH, CMTH, CETH, CPTH, respectively, in ethanol (DMF) suggests an irreversible reduction of the azomethine group. The peak presumably corresponds to two electron reduction.

Characterization of the complexes

All complexes are green in colour, stable at room temperature, non-hygroscopic, sparingly soluble in methanol, and readily soluble in chloroform, pyridine, dimethylformamide (DMF) and dimethylsulphoxide (DMSO). The analytical data suggest 1:2 (M: L) composition for the complexes. The melting point and analytical data of all these complexes are given in Table 1.

Conductivity and Magnetic Susceptibility measurements

The present nickel complexes are readily soluble in DMF solvent. Therefore, these complexes were dissolved in DMF to perform conductivity experiments. A 30 mg of solid complex was transferred into 25-ml standard flask and dissolved in DMF. Using DMF, the contents were made up to the mark. The DMF solution of metal complex was transferred into a clean and dry 100-ml beaker.

The conductance of this solution was measured. The molar conductance data of these nickel complexes are given in Table 1. The conductivity data suggest non-electrolytic nature [23] of complexes. The room temperature magnetic susceptibility of the complexes indicates that the complexes are diamagnetic in nature and favours the square planar geometry

Electronic spectra

The electronic spectra of present nickel (II) complexes are given in figure 1. The electronic spectra of complexes are recorded in both DMSO (coordinating) and CHCl3 (non-coordinating) solvent. In non-coordinating solvent (chloroform) electronic spectra [Figure 1A] gives strong bands in 29411–23255 cm^{-1} region are assigned to π→π* transition. Another less intense band is observed in 19230–17543 cm^{-1} region suggesting square planar geometry. While in DMSO solvent a different spectrum is obtained indicating coordination of solvent molecules presumably in axial position.

Three (3) bands are observed in the spectra of nickel complexes recorded in DMSO [Figure 1B]. These bands are respectively assigned to $^3A2g \rightarrow {}^3T2g$ (υ1), $^3A2g \rightarrow {}^3T1g(F)$ (υ2) and $^3A2g \rightarrow {}^3T1g(p)$ (υ3) transitions.

The Racah interelectronic repulsion parameters are calculated using υ1, υ2 and υ3 and following methods given below

$$10Dq = \upsilon 1 \qquad (2)$$

$$(\upsilon 2 + \upsilon 3) - 3\,\upsilon 1/\,15 \qquad (3)$$

Table 1: The physical, analytical and electronic spectral data of the ligand and its metal complexes

Compound	M.P (˚C)	Elemental analysis Cal (Found)%				Magnetic susceptibility(χg)x10-6#	M*
		C	H	N	S		
CTH	144–147	59.5 (59.7)	6.2 (6.8)	18.9 (18.9)	14.4 (14.5)	-	-
[Ni(CT)2]	185–186	52.96 (52.89)	5.62 (5.65)	16.22 (16.83)	12.5 (12.84)	-0.463	20
CMTH	145–147	60.9 (61.2)	7.1 (7.3)	17.4 (17.8)	13.6 (13.6)	-	-
[Ni(CMT)2]	171–173	55.03 (54.66)	6.25 (6.11)	15.03 (15.93)	11.61 (12.16)	-0.128	25
CETH	115–118	62.9 (62.6)	7.6 (7.7)	16.9 (16.8)	14.1 (14.1)	-	-
[Ni(CET)2]	178–180	56.13 (56.22)	6.25 (6.53)	15.05 (15.13)	11.61 (11.55)	-0.299	13
CPTH	140–142	68.5 (68.6)	6.2 (6.4)	13.9 (14.1)	10.7 (10.8)	-	-
[Ni(CPT)2]	208–209	62.66 (62.27)	5.35 (5.57)	12.48 (12.9)	9.61 (9.84)	-0.237	21

#cgs units *Ohm-1cm-2mol-1

The values of 10Dq and Racah interelectronic repulsion parameter (B) are employed to calculate υ2 and υ3 and results are given in Table 2 leading to the following conclusions.

(a) Comparison of 10Dq and B values for the nickel complexes indicates that the ligands give reasonably strong covalent bonds. The high values of Dq and B are also consistent with the coordination of thiosemicarbazone nitrogen. The B values of the present complexes were found in the range of 73-81% that of free ion (B0 = 1030 cm^{-1}) [24] indicating considerable overlap with strongly covalent nickel – ligand bond character [25]. The decrease in B values most likely associated with reduction in the nuclear charge of the cation.

(b) The ratio of υ2 and υ1 lies between 1.54-1.68 range as expected for octahedral nickel (II) complexes [26]. The usual range is 1.5-1.76 for octahedral symmetry [27].

(c) Racah interelectronic repulsion parameters (B) are used for establishing the position of the present ligands in nephelauxetic series. The data for these nickel complexes gave h values from 1.42 to 2.33, which suggest that the present ligands may be placed between ammine (NH3) and azide ($N3^-$).

(d) The LFSE values for nickel complexes are nearly same and reflect the presence of identical coordination around the central metal ion.

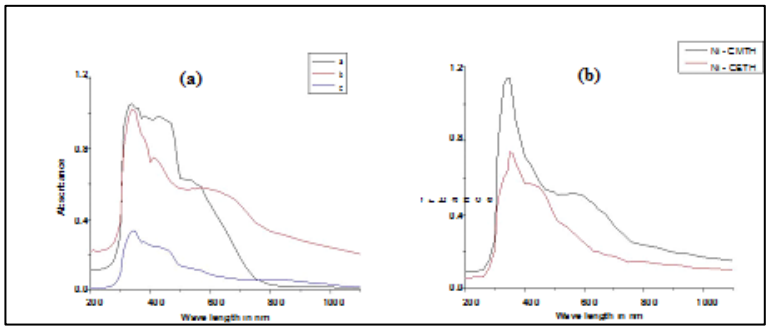


Figure 1: Electronic spectra (A) in chloroform of (a) Ni(CTH)2 (b) Ni(CMTH)2 (c) Ni(CETH)2 (B) in DMSO of (a) Ni(CMTH)2 (b) Ni(CETH)2

Table 2: Electronic spectral data and ligand field parameter of nickel complexes

Complex	Method of Evaluations	υ1	υ2	υ3	B	β	Δυ	10Dq	υ2-υ1	υ2/υ1	LFSE	hx
[Ni(CT)2]	Observed	12658	21505	29411	862.8	0.83	1772	12658	8847	1.69	36.16	1.42
	Calculated	10Dq	19733	31183					7075	1.56		
[Ni(CMT)2]	Observed	12987	21739	28985	784	0.76	1935	12987	8752	1.67	37	2
	Calculated	10Dq	19800	30920					6813	1.52		
[Ni(CET)2]	Observed	12903	21276	28571	742	0.72	1780	12903	8373	1.64	36.8	2.33
	Calculated	10Dq	19487	30351					6584	1.51		
[Ni(CPT)2]	Observed	12578	22222	27777	817.6	0.79	216	12578	9644	1.8	35.9	1.75
	Calculated	10Dq	22438	27560					9860	1.78		

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Infrared Spectra

The IR spectra of the complexes are compared with the ligands spectra. Important infrared spectral data and their tentative assignments are presented in Table 3. IR spectra of ligands show bands in 3412–3280 cm^{-1} region. These are assigned to terminal NH2/NHR group vibrations. These bands are not affected in complexes suggesting non-participation of terminal -NH2 group in coordination. In the spectra of ligands a strong band is observed in 1177–1196 cm^{-1} region due to υ(C=S) stretching vibration, No band is observed near 2575cm^{-1} suggesting that the ligands remain in thione form at least in solid state. In IR spectra of complexes this band disappeared indicating the bond formation between nickel and enolic sulphur. Further, new bands in 677–690 cm^{-1} are observed in the IR spectra of metal complexes. These are assigned to υ(C - S) stretching vibration. These vibrations are possible only when sulphur binds to metal in the thiol form [28,29]. A strong band is observed in 1590 - 1608 cm^{-1} region due to υ(C=N) stretching vibration. These bands are shifted to lower frequencies (Δυ = ± 7-12 cm^{-1}), suggesting coordination of azomethine nitrogen to nickel atom in all the complexes [30,31].

Table 3: Selected I.R. bonds (cm^{-1}) of Nickel (II) complexes with tentative assignment.

Ligand/Complex	υ(NH2 /NHR)	υ(NH)	υ(C=N)	υ(C = S)	υ(C-S)	υ(M–S)	υ(M–N)
CTH	3412(s), 3280(s)	3156(s)	1590(s)	1181(m)	-	-	-
[Ni(CTH)2]	3432(br), 3274 (s)		1602 (s)	-	670	537 (s)	436 (s)
CMTH	3316(br)	3159(m)	1608(s)	1177(m)	-	-	-
[Ni (CMTH)2]	3312(br)		1596 (m)	-	684	549	420 (s)
CETH	3300(br)	3143(br)	1607(s)	1178(m)	-	-	-
[Ni (CETH)2]	3304(br)		1584 (m)	-	697	540 (s)	480 (s)
CPTH	3306(s)	3133(br)	1596(s)	1196(s)	-	-	-
[Ni (CPTH)2]	3307(br)		1600 (s)	-	692	538 (s)	499 (s)

Based on the molar conductance, magnetic moment, electronic and I.R. data, it is suggested that all the nickel complexes to have square planar structure (Figure 2) in solid state. In coordinating solvents like DMSO, these complexes presumably have octahedral structure, due to coordination of solvent molecule in axial position (Figure 3).

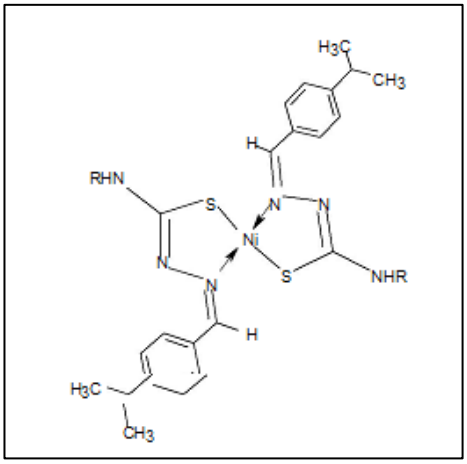

Figure 2: A general tentative structure for nickel (II) complexes

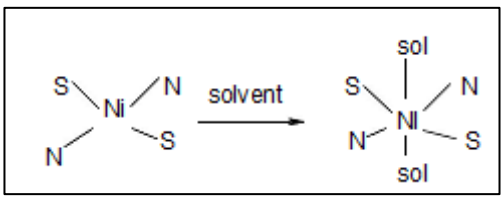

Figure 3: Coordination of solvent molecules in axial sites

Cyclic voltammetric studies

The redox potentials of nickel complexes are determined using cyclic voltammetry. Cyclic voltammograms of nickel (II) complexes were recorded in DMF and in ethanol in tetrabutyl ammonium perchlorate (0.1M) as supporting electrolyte. The cyclic voltammetric profiles of [Ni CPT) 2] complexes are given in Figure 4. The electrochemical data of all complexes obtained at the glassy carbon electrode are given in Table 4. Cyclic voltammorams of nickel (II) complexes showed only one respond in ethanol and two active responds in DMF. The E1/2 values of nickel complexes are observed in -1.33 to -1.18 V potential ranges are assigned to $NiI^{II/I}$ couple and the potential range of -0.40 to -0.30 V range are assigned to $Ni^{III/II}$ .Repeated scans as well as various scan rates showed that dissociation does not takes place in these complexes. The non-equivalent current intensity of cathodic and anodic peaks has large difference indicating quasi reversible behaviour of these complexes. The ΔEp values are greater than the Nernstian values (ΔEp ≈ 59mV) for one electron redox system. ΔG* values of complexes in ethanol are higher than those values obtained in DMF. These data (Table 4) suggest that the complexes are more stable in ethanol solvent.

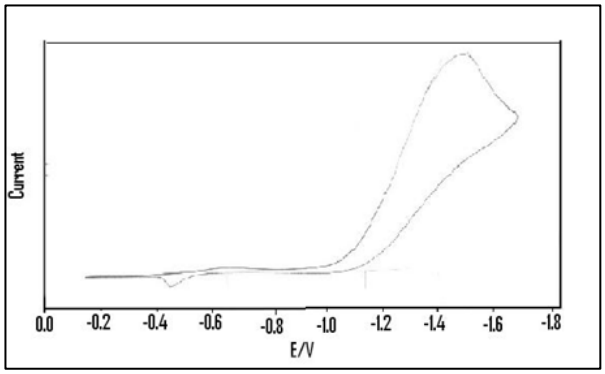

Figure 4: Cyclic voltammetric profile of Ni (CPT) 2 complex in DMF DNA binding studies of nickel complexes

The Interactions of nickel complexes with CT-DNA was monitored by absorption titrations using UV-Visible spectrophotometer in 360-371 nm [except Ni(CMT)2 at 416-420 nm] region. In the presence of increasing amount of DNA, the spectra of all complexes showed increase in the intensity of band, but the bands are shifted either lower wavelength or higher wavelength region.The change in absorbance values with increasing amounts of CT-DNA were used to calculate binding constant of the complex. Typical absorption spectra of [Ni(CMT)2] was given in Figure 5. According to the literature report, hypochromism is usually observed when a complex binds to DNA through intercalation as a consequence of strong staking interaction between an aromatic chromophore and a base pair of DNA. The extent of the hypochromism commonly reflects the intercalative binding strength [32]. The observed large hypochromism in our experiment strongly suggests a close adjacency of complex to the DNA bases. From the data (Table 5), in increasing amount of CT-DNA, absorption of cuminaldehyde thiosemicarbazone complexes showed hypercromism [hypercromicity: -12.48 for Ni(CT)2 , -12.79 for Ni(CMT)2 , -7.79 for Ni(CET)2 and -29.47 for Ni(CPT)2] and binding constants of the complexes are 2.19 x 10^7, 6.65 x 10^7, 9.22 x 10^7 and 1.03 x 10^8 respectively.

Table 4 Cyclic voltommetric data of nickel complexes

Complex	Redox couple	Epc/V		Epa/V		ΔEp/mV		E1/2		log Kc[b]		-ΔG° [c]	
		EtOH	DMF	EtOH	DMF	EtOH	DMF	EtOH	DMF	EtOH	DMF`	EtOH	DMF
[Ni(CTH)2]	III/II	-	-1	-	-0.22	240	350	-	-0.4	-	0.093	802	548
	II / I	-1.3	-	-1	-	-	-	-1.2	-	0.136	-	-	-
[Ni(CMTH)2]	III/II	-	-0	-	-0.18	-	310	-	-0.3	-	0.105	-	619
	II / I	-1.3	-1	-1	-1.04	210	400	-1.21	-1.2	0.155	0.081	914	477
[Ni (CETH)2]	III/II	-	-0	-	-0.16	-	320	-	-0.3	-	0.102	-	601
	II / I	-1.4	-1	-1	-1.07	90	385	-1.33	-1.3	0.363	0.085	2140	501
[Ni (CPTH)2]	III/II	-	-0	-	-0.17	-	250	-	-0.3	-	0.13	-	766
	II / I	-1.4	-1	-1	-1.02	130	310	-1.31	-1.2	0.252	0.105	1486	619

***Recorded at room temperature with Et4NClO4 as supporting electrolyte; glassy carbon as working electrode; Pt wire as auxiliary electrode and Ag/AgCl as reference electrode; Scan rate 50 mVs-1 blog Kc=0.434ZF/RTΔEp , c ΔG° = -2.303RTlogKc**

Table 5 Electronic absorption data upon addition of CT-DNA to nickel complex

Complex	λmax/nm		Δλ /nm	H (%)	Kb (M-1)
	Free	Bound			
Ni(CT)2	365	366	1	-12.48	2.19 x 107
Ni(CMT)2	420	416	4	-12.79	6.65 x 107
Ni(CET)2	365	360	5	-7.79	9.22 x 107
Ni(CPT)2	365	361	4	-29.47	1.03 x 108

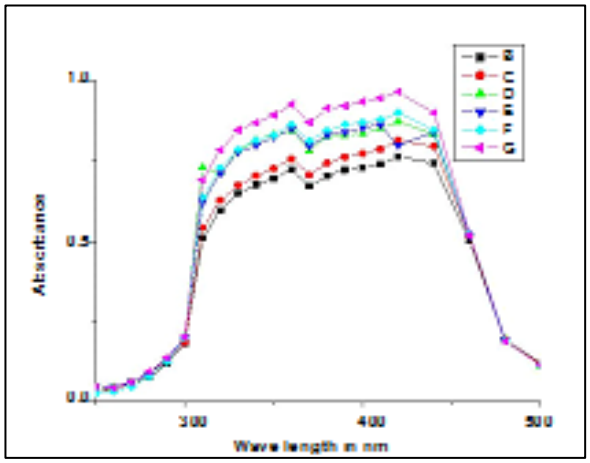

Figure 5: Absorption spectra of Ni(CMT)2 in the absence [Bottom curve in each] and presence [subsequent curve] of increasing concentration of CTDNA

Nuclease activity of ligands and their complexes

Gel electrophoresis experiments using plasmid pUC18 DNA were performed with nickel complexes in the presence/absence of oxidant (H2O2). Nickel complexes are capable of cleaving plasmid pUC18 DNA at the physiological temperature and pH.

Figure 6: Agarose gel (0.8%) showing results of electrophoresis of 3 µL of pUC18 DNA; 2 µL 0.1M TBE buffer (pH 8); 2 µL complex in DMF (10^{-3}M); 10 µL water, 2 µL H2O2 (Total volume 20 µL) were added respectively, incubated at 37 ^{0}C (30 min): Lane 1: DNA control, Lane 2. DNA+H2O2, Lane 3. Ni(CT)2 + DNA, Lane 4. Ni(CT)2 + DNA + H2O2, Lane 5. Ni(CMT)2 + DNA, Lane 6. Ni(CMT)2 + DNA + H2O2, Lane 7. Ni(CET)2 + DNA, Lane 8. Ni(CET)2 + DNA + H2O2, Lane 9. Ni(CPT)2 + DNA, 10. Ni(CPT)2 + DNA + H2O2

At micro molar concentration solution for 30 min. incubation time all nickel complexes show significant cleavage activity in the presence and absence of oxidant. Figure 6 shows cleavage pattern of nickel complexes. Ni(CET)2 and Ni(CPT)2, complexes show higher DNA cleavage activity in presence of oxidant (Lanes 8 and 10). To reveal cleavage mechanism control experiments are performed in the presence of free radical scavenger, DMSO and singlet oxygen quencher, azide ions. Nuclease activity of Ni(CTM)2 and Ni(CET)2 complexes (Lanes 7 and 10) is diminished in the presence of free radical scavenger (DMSO) indicating the involvement hydroxyl free radicals in the DNA cleavage.

CONCLUSION

Four new Schiff base complexes have been synthesized and characterized using various spectroscopic techniques like IR, electronic, ESR spectroscopy. In this work, we explored the binding interaction of the synthesized Ni(II) complexes with CT-DNA in physiological buffer using UV–Vis spectroscopic technique. The intercalative binding of mentioned complex with DNA was deduced by taking account of relevant UV–Vis

absorption spectra. The nuclease activity of Schiff bases and their Ni(II) complexes were monitored using gel electrophoresis method.

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