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DNA cleavage, binding and intercalation studies of drug-based oxovanadium(IV) complexes

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Abstract
The complexes of oxovanadium(IV) with ciprofloxacin and various uni-negative bidentate ligands have been prepared and their structure investigated using spectral, physicochemical and elemental analyses. The viscosity measurement suggest that the complexes bind to DNA by intercalation. The DNA binding efficacy was determined using absorption titration to obtain the binding constant (K_b). The DNA cleavage efficacy was determined using gel electrophoresis. The DNA binding and cleavage efficacy were increased in the complexes relative to the parental ligands and metal salts. Antibacterial activity has been assayed against two Gram$^{(-ve)}$ i.e. *Escherichia coli, Pseudomonas aeruginosa* and three Gram$^{(+ve)}$ *Staphylococcus aureus, Bacillus subtilis, Serratia marcescens* microorganisms using the doubling dilution technique. The results show a significant increase in antibacterial activity in the complexes compared with parental ligands and metal salts.

Keywords: *Drug based oxovanadium(IV) complexes, MIC, intrinsic binding constants (K_b), gel electrophoresis and viscometric techniques, antimicrobials*

Introduction

The interaction of transition metal complexes containing multidentate ligands with DNA has recently gained much attention followed by an important biological and medical roles played by potential metallointercalators. Vanadium occurs as an "essential trace" element in diverse living forms [1–6]. It plays active roles in many enzymatic reactions such as halogenation of organic substrate [2,5,6] and fixation of nitrogen through an alternative pathway[2,7–9]. Coordination chemistry involving vanadium is often directed towards the use of relatively hard *N*- and, in particular, *o*-based anions and to limit the growth to well-defined molecular species, chelating ligands or those containing bulky substituents are often employed. In order to gain an insight into the intricate roles of vanadium in biological system, it is advantageous to acquire information about the basic coordination chemistry of this metal employing a biologically relevant ligand donor set [10–12]. Quinolone antibacterial drugs have been frequently used to treat various bacterial infections because of their broad spectrum of activity against gram-positive and gram-negative bacteria [13]. The fluoroquinolones are antibacterial agents that act by forming ternary complexes with DNA gyrase and DNA topoisomerase IV on chromosomal DNA. Resistance to the compounds is generally associated with amino acid substitutions in portions of the GyrA (gyrase) and ParC (topoisomerase IV) proteins called the quinolone resistance-determining regions (QRDRs) [14]. Ciprofloxacin (Cip) is one of the quinolone antibacterial agents, used in the treatment of a wide range of infections, that antagonize the A subunit of DNA gyrase [14,15]. In order to continue researching DNA binding model of the fluoroquinolones and their transition metal complexes [16,17], in this paper, we prepared the VO(IV) mixed ligand complexes of ciprofloxacin and

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anthranilic acid (L^1), glycine (L^2), β-alanine (L^3), L-asparagine (L^4), DL-serine (L^5), o-aminophenol (L^6) and DL-valine (L^7). The DNA binding properties of the complexes have been investigated by ultraviolet spectroscopy, viscosity measurements and gel electrophoresis method. Experimental results indicated that complexes and ciprofloxacin can bind to DNA by intercalation modes, but the binding affinity of the complexes is much higher than that of the ligand. Antibacterial activity has been assayed against gram-positive and gram-negative bacteria using the doubling dilution technique.

Experimental

Materials and methods

All the chemicals used were of analytical grade. Vanadylsulphate, anthranilic acid (L^1), glycine (L^2), β-alanine (L^3), L-asparagine (L^4), DL-serine (L^5), o-aminophenol (L^6) and DL-valine (L^7) were purchased from, E. Merck (India) Ltd., Mumbai. Ciprofloxacin hydrochloride was purchased from Bayer AG (Wyppertal, Germany). Luria broth, ethidium bromide, sucrose, and tris(hydroxymethyl)methylamine were purchased from Hi-media Laboratories Pvt. Ltd., India. Agarose was purchased from Sisco research lab., India. Bromophenol blue, acetic acid and EDTA were purchased from Sd fine chemicals, India. The organic solvents were purified by standard methods [18].

Instrumentation physical properties

Carbon, hydrogen and nitrogen were analyzed on a model 240 Perkin Elmer elemental analyzer. Thermogravimetric analysis and differential scanning calorimetric study were performed with a model 5000/2960 SDTA, TA instrument (USA). Infrared spectra were recorded on an FT-IR Shimadzu spectrophotometer as KBr pellets in the range 4000–400 cm^{-1}. The electronic spectra of the complexes were recorded in the range 800–200 nm on UV-160A UV–Vis. spectrophotometer, Shimadzu (Japan). The magnetic moments were measured by Gouy's method using mercury tetrathiocyanatocobaltate(II) as the calibrant ($\chi_g = 16.44 \times 10^{-6}$ cgs units at 20°C), Citizen Balance. The diamagnetic correction was made using Pascal's constant [19].

UV–Vis. Spectroscopy

The electronic absorption spectroscopy is an important tool in DNA-binding studies. Concentrated solutions of metal complexes were prepared by dissolving the complexes in DMSO and diluted suitably with buffer to desire concentrations for all the experiments. The experiments were performed by maintaining a constant concentration of the complex (4 μM) while varying the nucleic acid concentration (2–20 μM). The intrinsic binding constants (K_b) for the complexes with DNA were obtained using the following equation [20,21].

$$\frac{[DNA]}{(\varepsilon_a - \varepsilon_f)} = \frac{[DNA]}{(\varepsilon_b - \varepsilon_f)} + \frac{1}{K_b(\varepsilon_b - \varepsilon_f)} \quad (1)$$

Where [DNA] is the concentration of DNA in terms of nucleotide phosphate, [NP] the apparent absorption coefficient ε_f, ε_a and ε_b correspond to the extinction coefficient of the free complex, the extinction coefficient for each addition of DNA to the complex and the extinction coefficient for the complex in the fully bound form respectively.

Viscosity measurements

Viscosity measurements were carried out using an Ubbelodhe viscometer maintained at a constant temperature 27.0 ± 0.1°C in a thermostatic bath. Flow time was measured with a digital stopwatch, each sample was measured three times, and an average flow time was considered. Data are presented as $(\eta/\eta_0)^{1/3}$ vs. binding ratio [22], where η and η_0 are the viscosity of DNA in the presence and absence of complex, respectively.

Antibacterial assays- dilution method

All the bacteria were incubated and activated at 30°C for 24 h before inoculation into Luria broth for 24 h. The compounds were dissolved in DMSO and then diluted using Luria broth. Two-fold serial concentrations of the compounds were employed to determine the Minimum Inhibitory Concentration (MIC) ranging from 100 μg/mL - 0.1 μg/mL. Test cultures were incubated at 37°C (24 h). The lowest concentrations of antimicrobial agents that resulted in complete inhibition of growth were represented as MIC (μg/mL). In each case triplicate tests were performed and the average was taken as the final value [23].

Gel electrophoresis

Plasmid DNA (pBR322) (100 μM) cleavage activity of mixed-ligand complexes (50 μM) was monitored using agarose gel electrophoresis. In a typical experiment supercoiled pBR322 DNA (2.5 μg/mL) in Tris-HCl (100 mM, pH 8.0) was treated with different mixed-ligand complexes. The samples were then incubated at room temperature and loaded with 0.5x loading buffer containing 40% sucrose and 0.02% bromophenol blue on 1.5% agarose gel. Electrophoresis was carried out at 100 V for 90 min. in TAE (Tris Acetate EDTA) buffer and run in duplicate. Same was stained with ethidium bromide. Same experimental conditions were maintained for control assays. The gels were viewed on UV transilluminator; images were captured with an attached camera and estimated using AlphaDigiDoc™ RT. Version V.4.1.0 PC-Image software.

Synthesis of the mixed-ligand complexes

An ethanolic solution (50 mL) of $VOSO_4 \cdot 3H_2O$ (0.6327 g, 5 mM) was added to an ethanolic solution of (50 mL) anthranilic acid (L^1) (0.3428 g, 5 mM), followed by a solution of (Cip.HCl) (0.917 g, 5 mM) in water and the reaction mixture was adjusted to pH 6.0 ~ 7.0 with dilute NaOH solution. The resulting green solution was refluxed with stirring for 7 h, heated on a steam bath to evaporate up to half volume and kept overnight at room temperature. A fine green coloured (**I**) product was obtained which was washed with ether and dried in a vacuum desiccators. All the remaining compounds i.e. **II-VII** was prepared according to the same method but by changing ligand L^1 by L^2–L^7 respectively. Physicochemical parameters for all the synthesised compounds are summarized in Table I.

Results and discussion

Composition and properties of the mixed-ligand complexes

All the synthesized complexes are stable to air for extended period of time and soluble in DMSO, slightly soluble in ethanol and water; insoluble in benzene, acetone, acetonitrile and diethyl ether. Elemental analyses of the complexes are in good agreement with theoretical expectation. They possess high melting points indicating that the complexes are stable in air.

Spectroscopic studies of the mixed-ligand complexes

Infrared spectroscopy. The ν(C=O) stretching vibration band appears at 1708 cm^{-1} in the spectra of ciprofloxacin, while in mixed-ligand complexes this band shifted towards lower energy at 1619–1680 cm^{-1} (Table II), suggests that coordination occurs through pyridone oxygen atom [24]. The absorption bands observed at 1624 and 1340 cm^{-1} in ciprofloxacin are assigned to be $\nu(COO)_{asy}$ and $\nu(COO)_{sym}$ respectively, while in mixed-ligand complexes these bands observed at 1585–1590 and 1370–1374 cm^{-1}. The frequency separation ($\Delta\nu = \nu(COO)_{asy} - \nu(COO)_{sym}$) in investigated mixed-ligand complexes is greater than 200 cm^{-1}, suggests that the carboxylato group posses unidentate nature [25]. The absorption bands observed at 527–531 cm^{-1} are attributed to ν(M-N). The absorption bands observed at 426–428 cm^{-1} and 513–521 cm^{-1} are attributed to $\nu(M\text{-}O)_{(Carbo)}$ $\nu(M\text{-}O)_{(Keto)}$ respectively, while in case of complex VI the observed band at 470 cm^{-1} is due to the $\nu(M\text{-}O)_{(phenolic)}$. The sharp band in ciprofloxacin at 3520 cm^{-1} [26] is due to hydrogen bonding; which is attributed to ionic resonance structure and peak observed because of stretching vibration of free hydroxyl group. This band absolutely vanished in the spectra of mixed-ligand complexes indicates deprotonation of carboxylic proton. Of particular interest are the spectroscopic features of the conformers in the 1100-850 cm^{-1} region, which after screening the bands due to ligand internal stretching, reveal interesting differences in their metal-terminal oxygen (V = O_t) vibrational modes. The metal-terminal oxygen (V = O_t) band observed at ~1000 cm^{-1} region suggesting the anti conformers and vanadium has a distorted square pyramidal structure [27]. The complexes have one unpaired electron, characteristic of vanadyl unit, and a fairly high V = O stretching frequency in the infra red spectrum about 1000 cm^{-1}, suggesting that there is no ligand (or a weakly bound solvent) in the sixth position [28]. Some prominent IR band frequencies of the compounds are provided in Table II.

Electronic spectroscopy and magnetic measurements. The UV–Vis. spectra of the complexes have been recorded using UV-160A UV–Vis. spectrophotometer, Shimadzu (Japan) (Table III). The four absorption bands are observed in mixed-ligand complexes at ~ 810 nm for $d_{xy} \rightarrow d_{xz}$(band I), ~ 590 nm for $d_{xy} \rightarrow d_{yz}$ (band II), at ~ 540 nm for $d_{xy} \rightarrow d_{x^2-y^2}$ (band III), and ~ 405 nm for $d_{xy} \rightarrow d_z^2$ (band IV). An examination of Table III substantiates that the parameter Δ (λ_1–λ_2), related to the splitting of the d_{yz} and d_{xz} levels, can be used for establishing the geometrical distortion. In particular, Δ (λ_1–λ_2), increases with increasing distortion in the following order of complexes: IV (215 nm) < II (217 nm) < VI (220 nm) = V (220 nm) < III (248 nm). The mixed-ligand complexes exhibit magnetic moment of 1.69–1.73 B.M. This value is close to the spin-only value expected for s = 1/2 system (1.73 B.M.) and may be indicative of distorted square pyramidal geometry around the VO(IV) ion.

Thermal analysis. The thermogravimetric analyses for the mixed-ligand complexes were carried out within a temperature range from 20–800°C in N_2 atmosphere at a rate of 10°C per minute in order to establish their compositional differences as well as to ascertain the nature of associated water molecules [29]. The determined temperature ranges and corresponding percent mass loss accompanying the changes in the mixed-ligand complexes on heating revealed the following things. The TG curves of mixed-ligand complexes show three-decomposition steps respectively. It has been observed that all the mixed-ligand complexes show a loss in weight corresponding to two water molecules in the range of 50–130°C which indicating that these water molecules are water of crystallization. In second step weight loss during 130–420°C is corresponding to liberation of ligands and leaving behind the oxide of metal in the temperature range 420–710°C. Suggested structure of the complexes from the above analytical facts is given in Figure 1.

Table I. Chemical and physical characteristics of the complexes.

Complexes	Found (Calcd.) %				m.p. °C	μ_{eff} (B.M.)	% Yield	Formula weight (gm/mol)
	C	H	N	M				
$C_{24}H_{27}FN_4O_8V$ [VO(Cip)L^1].2H_2O	50.59 (50.62)	4.74 (4.78)	9.80 (9.84)	8.92 (8.95)	>360	1.70	65.5	569.43
$C_{19}H_{25}FN_4O_8V$ [VO(Cip)L^2].2H_2O	44.94 (44.98)	4.90 (4.97)	11.07 (11.04)	10.00 (10.04)	>360	1.69	61.2	507.36
$C_{20}H_{27}FN_4O_8V$ [VO(Cip)L^3].2H_2O	46.06 (46.07)	5.20 (5.22)	10.70 (10.75)	9.72 (9.75)	>360	1.73	59.5	521.39
$C_{21}H_{28}FN_5O_9V$ [VO(Cip)L^4].2H_2O	44.63 (44.69)	4.98 (5.00)	12.44 (12.41)	8.99 (9.00)	>360	1.71	67.8	564.42
$C_{20}H_{27}FN_4O_9V$ [VO(Cip)L^5].2H_2O	44.72 (44.70)	5.01 (5.06)	10.40 (10.46)	9.50 (9.48)	>360	1.73	63.4	537.39
$C_{23}H_{27}FN_4O_7V$ [VO(Cip)L^6].2H_2O	51.03 (51.02)	5.05 (5.03)	10.30 (10.35)	9.42 (9.41)	>360	1.70	58.0	541.42
$C_{22}H_{31}FN_4O_8V$ [VO(Cip)L^7].2H_2O	48.06 (48.09)	5.67 (5.69)	10.21 (10.20)	9.25 (9.27)	>360	1.73	58.0	549.44

Table II. Infrared spectral data of the complexes.

Complexes	ν (C=O) $_{(pyridine)}$	ν $(COO)_{sy}$	ν $(COO)_{asy}$	$\Delta\nu$	ν(M-O)$_{(Carbo)}$	ν(M-O)$_{(Keto)}$	ν(C-F)	ν(M-N)	ν(C-N)	ν(V = O)
[VO(Cip)L^1].2H_2O	1638	1370	1590	220	426	513	1276	530	1356	1001
[VO(Cip)L^2].2H_2O	1620	1374	1586	212	426	513	1276	528	1356	1001
[VO(Cip)L^3].2H_2O	1625	1372	1585	213	427	514	1275	531	1357	1020
[VO(Cip)L^4].2H_2O	1619	1370	1587	217	428	513	1277	530	1356	1021
[VO(Cip)L^5].2H_2O	1670	1373	1589	216	427	518	1278	529	1354	1020
[VO(Cip)L^6].2H_2O	1680	1374	1586	212	426	521	1274	527	1357	1020
[VO(Cip)L^7].2H_2O	1675	1371	1588	217	428	517	1273	529	1358	1019

Table III. Electronic absorption parameters of VO(IV) complexes.

Complexes	λ_4	λ_3	λ_2	λ_1	Δ (λ_1-λ_2)
$[VO(Cip)L^1].2H_2O$	406	535	606	829	223
$[VO(Cip)L^2].2H_2O$	401	530	604	821	217
$[VO(Cip)L^3].2H_2O$	408	530	577	825	248
$[VO(Cip)L^4].2H_2O$	410	548	590	805	215
$[VO(Cip)L^5].2H_2O$	398	548	598	818	220
$[VO(Cip)L^6].2H_2O$	401	547	576	796	220
$[VO(Cip)L^7].2H_2O$	401	547	576	816	240

Antimicrobial activity

The complexes exhibit strong activities against two Gram$^{(-ve)}$ i.e. *Escherichia coli, pseudomonas aeruginosa* and three Gram$^{(+ve)}$ *Staphylococcus aureus, Bacillus subtilis, Serratia marcescens* microorganisms. The results concerning *in vitro* antimicrobial activity (MIC) of the ligands and their complexes are represented in Table IV. The ligands (L^1–L^7) exhibit no antimicrobial activity. The antimicrobial activity of all the complexes against the five microorganisms is much higher than metal salt, while in competition with the ciprofloxacin. It was observed that all the complexes were more potent bacteriostatic than the ligands. The inhibition activity seems to be governed in certain degree by the facility of coordination at the metal centre as well as bulkiness of the ligands. This may support the argument that some type of biomolecular binding to the metal ions or intercalation or electrostatic interactions causing the inhibition of biological synthesis and preventing the organisms from reproducing. The results of our study indicate that the compounds **II**, **III**, **IV** and **V** have good activity, by displaying high affinities towards most of the bacteria. While the compounds **VI** and **VII** have good activity against *S.merscences*. The strong antimicrobial activities of these compounds against tested organisms suggest further investigation on these compounds.

The studies on the binding of the title complex to DNA

Absorption spectroscopic titrations. The application of electronic absorption spectroscopy in DNA-binding studies is one of the most useful techniques [30–32].

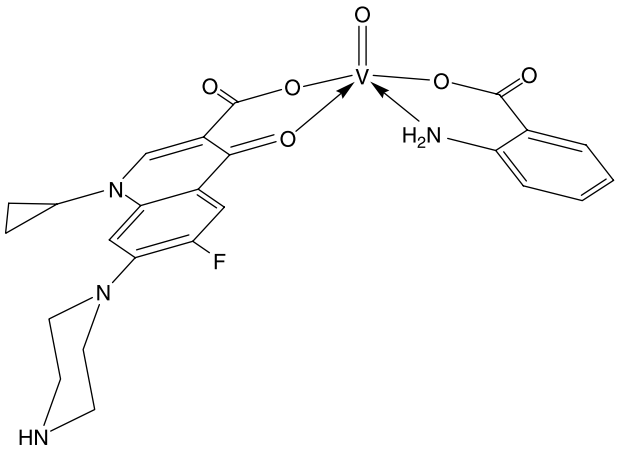

Figure 1. Probable structure of complex(I).

Complex binding with DNA through intercalation usually results in hypsochromism and bathochromism, due to the intercalative mode involving a strong stacking interaction between an aromatic chromophore and the base pairs of DNA [33]. The absorption spectra of the complex in the absence and presence of DNA are illustrated in Figure 2. Change in absorbance at peak maximum shows moderate hypsochromism shift (~ 2 nm) for each complex with increasing concentration of DNA has been monitored for an evaluation of the intrinsic binding constant, which observed in the range of 5.0×10^2 to $6.6 \times 10^5 M^{-1}$. (Inset Figure 2 for the plot for the calculation of intrinsic binding constant). The binding constants are given in Table V. The binding constant of the complexes in increasing order is **III** < **I** < **VI** < **II** ≈ **V** < **IV** < **VII**. These spectral characteristics are consistent with a mode of interaction that involves a stacking interaction between the complex and the base pairs of DNA, which means that the titled complexes can intercalate into the double helix structure of DNA.

Viscosity studies. The interaction mode between the complexes and DNA is carried out by viscosity

Table IV. *In vitro* antimicrobial activity of the compounds (MIC μg/mL).

Compounds	Gram positive			Gram negative	
	S.aureus	*B.substilis*	*S.merscences*	*P. aeruginosa*	*E.coli*
$VOSO_4.3H_2O$	650	650	650	300	300
Cpf	0.6	0.4	0.6	0.5	0.5
$[VO(Cip)L^1].2H_2O$	1.0	1.0	0.5	0.5	0.5
$[VO(Cip)L^2].2H_2O$	0.5	0.4	0.4	0.4	1.5
$[VO(Cip)L^3].2H_2O$	0.3	0.5	0.3	0.3	1.5
$[VO(Cip)L^4].2H_2O$	0.4	0.5	0.5	0.4	1.5
$[VO(Cip)L^5].2H_2O$	0.5	0.5	0.4	0.4	2.0
$[VO(Cip)L^6].2H_2O$	1.0	0.5	0.4	2.5	1.0
$[VO(Cip)L^7].2H_2O$	1.0	0.5	0.4	2.5	1.0

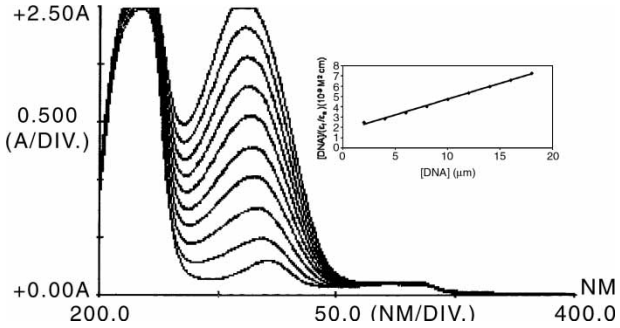

Figure 2. Absorption titration spectra of complex(I).

measurements. Hydrodynamic measurements that are sensitive to length change (i.e., viscosity and sedimentation) of DNA are regarded as the least ambiguous and the most critical tests of binding mode in solution in the absence of crystallographic structural data [34,35]. A classical intercalation mode results in lengthening the DNA helix, as base pairs are separated to accommodate the binding ligand, leading to the increase of DNA viscosity. The effect of the complexes on the viscosity of DNA is shown in Figure 3. It is found that the viscosity of DNA increases steadily with the increase of the concentration of the complex, which is similar to that of a classical intercalator EB [36]. This result demonstrates that the complexes and EB bind to DNA through the same way, i.e. the classical intercalation mode. The significant increase in viscosity of the complexes is obviously due to the partial insertion of the ligand in between the DNA base pairs leading to increase in separation of base pairs at intercalation sites and hence an increase in overall DNA contour length [37,38].

Cleavage of plasmid pBR322 DNA. The characterization of DNA recognition by transition metal complexes has been aided by the DNA cleavage chemistry that is associated with redox-active or photoactivated metal complexes. DNA cleavage is controlled by relaxation of supercoiled circular form of pBR322 DNA into nicked circular form and linear form. When circular plasmid DNA is conducted by electrophoresis, the fastest migration will be observed

Table V. The binding constants (K_b) of VO(IV) complexes with DNA in phosphate buffer pH 7.2.

Complexes	K_b (M^{-1})
$[VO(Cip)L^1].2H_2O$	2.5×10^4
$[VO(Cip)L^2].2H_2O$	5.0×10^4
$[VO(Cip)L^3].2H_2O$	5.0×10^2
$[VO(Cip)L^4].2H_2O$	2.0×10^5
$[VO(Cip)L^5].2H_2O$	5.0×10^4
$[VO(Cip)L^6].2H_2O$	3.0×10^4
$[VO(Cip)L^7].2H_2O$	6.6×10^5

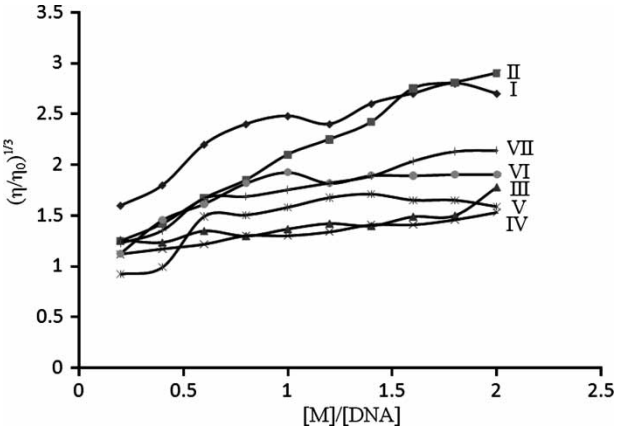

Figure 3. The effect of the complexes on the viscosity of pBR 322 DNA.

for the supercoiled form (SC). If one strand is cleaved, the supercoiled will relax to produce a slower-moving open circular form (OC). If both strands are cleaved, a nicked form (NC) will be generated that migrates in between. Figure 4 illustrates the gel electrophoretic separations showing the cleavage of plasmid pBR322 DNA induced by the complexes under aerobic conditions. With the increase of complex concentration, the circular supercoiled DNA is converted into nicked DNA via single strand cleavage (lanes 2–10). The obtained gel was analyzed for the

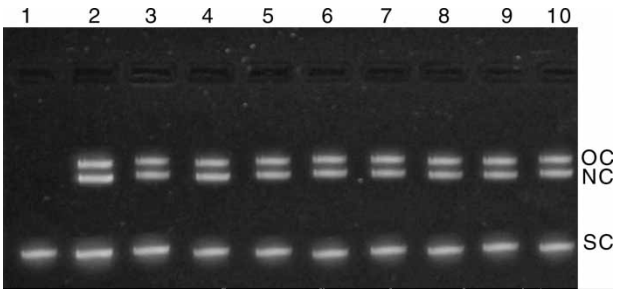

Figure 4. Gel electrophoresis data with pBR322 DNA (A) Lane 1: pBR322 (Control), Lane 2: pBR322 + $VOSO_4$, Lane 3:pBR322 + Cip HCl, Lane 4: pBR322 + I, Lane 5: pBR322 + II, Lane 6: pBR322 + III, Lane 7: pBR322 + IV, Lane 8:pBR322 + V, Lane 9:pBR322 + VI, Lane 10: pBR322 + VII.

Table VI. Gel electrophoresis data of the complexes.

Compounds	(%)(SC)	(%)(NC)	(%)(OC)
DNA Control	100	–	–
DNA + $VOSO_4$	52	23	25
DNA + Cip	56	21	23
DNA + $[VO(Cip)L^1].2H_2O$	43	31	26
DNA + $[VO(Cip)L^2].2H_2O$	49	26	25
DNA + $[VO(Cip)L^3].2H_2O$	45	30	25
DNA + $[VO(Cip)L^4].2H_2O$	48	24	28
DNA + $[VO(Cip)L^5].2H_2O$	46	27	27
DNA + $[VO(Cip)L^6].2H_2O$	42	24	34
DNA + $[VO(Cip)L^7].2H_2O$	43	29	28

relative concentration of three form of the pBR 322 DNA and the relative concentrations are mentioned in Table VI. This clearly shows that the relative binding efficacy of the complexes to DNA is much higher than the binding efficacy of metal salt itself or ciprofloxacin. The different DNA-cleavage efficiency of the complexes was due to the different binding affinity of the complexes to DNA, which has been observed in other cases [39,40,41].

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