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Chemistry of Some Amino Acid Complexes of Ruthenium. Synthesis, Characterization, and DNA Binding Properties

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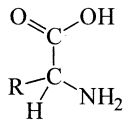
Introduction

There has been considerable current interest toward the synthesis of molecular species with potential for functioning as DNA intercalators,[1] and the present study was also initiated with a similar target. Metallointercalators are very useful in probing nucleic acid structure and function, and the intercalation process itself. There are two desirable properties for a complex to function as an intercalator: (i) presence of planar aromatic ligands in the complex and (ii) solubility of the complex in water. It is now well documented in the literature that transition metal complexes of polypyridyl ligands can effectively interact with DNA.[1] Studies on the binding of such complexes to DNA revealed that complexes of this type are mutagenic, and some serve as clinically useful chemotherapeutic agents of which the anticancer agents deserve special mention.[1] In this study, we report the design and synthesis of mixed-ligand polypyridyl complexes of ruthenium using 2,2′-bipyridine (bpy) and α-amino acids (**1**). 2,2′-Bipyridine (bpy) was used as a model ligand to study the coordination chemistry which could be applied to related established pyridyl−DNA intercalators. The α-amino acids (abbreviated in general as HL where H stands for the dissociable carboxylic proton) are known to bind to metal ions, via dissociation of the acidic proton, as bidentate N,O-donor forming five-membered chelate rings (**2**).[2] They have been chosen as one of the ligands because their complexes are usually soluble in water owing to intermolecular hydrogen bonding between the uncoordinated carbonyl oxygen and the water molecules. Among the transition metals, ruthenium

R = H, CH_3, CH_2-C_6H_5,
CH_2-C_6H_4-OH(*para*), $CH_2CH(CH_3)_2$



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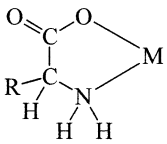

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has been picked up because of our interest in the chemistry of ruthenium in general[3] and its remarkable role in DNA intercalation reactions in particular.[4] It may be mentioned here that while the chemistry of amino acid complexes of many transition metals has received considerable attention,[5] the ruthenium chemistry of amino acids appears to remain much less explored.[3c,6] Herein, we report the chemistry of a family of complexes of type $[Ru(bpy)_2(L)]ClO_4$, with special

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reference to their synthesis, characterization, and DNA-binding properties.

Experimental Section

Materials. Commercial ruthenium trichloride was purchased from Arora Matthey, Kolkata, India and was converted to $RuCl_3 \cdot 3H_2O$, by repeated evaporation with concentrated hydrochloric acid. 2,2′-Bipyridine (bpy) and the α-amino acids were obtained from Loba Chemie, Mumbai, India. $[Ru(bpy)_2Cl_2]\cdot 2H_2O$ was synthesized by following a reported procedure.[7] Calf thymus (CT) DNA and Tris buffer were procured from Sigma Chemical Company. The dry powder of CT DNA was dissolved in 10 mM Tris buffered saline, pH 7.8 (TBS), and dialyzed overnight against the same buffer so that the A_{260}/A_{280} of the dialyzed solution was >1.90. The DNA concentrations were adjusted according to its absorbance at 260 nm using $\epsilon_{260} = 6.6\ mM^{-1}\ cm^{-1}$. Plasmid pBR322 and agarose were purchased from Bangalore Genei Pvt Ltd, Bangalore, India. Purification of acetonitrile and preparation of tetrabutylammonium perchlorate (TBAP) for electrochemical work were performed as reported in the literature.[8] All other chemicals and solvents were reagent grade commercial materials and were used as received.

Preparation of Complexes. All the $[Ru(bpy)_2(L)]ClO_4$ complexes were prepared by following a general procedure. Specific details are given in the following paragraph for a particular complex.

$[Ru(bpy)_2(L^1)]ClO_4$. To a solution of $[Ru(bpy)_2Cl_2]\cdot 2H_2O$ (100 mg, 0.19 mmol) in ethanol (30 mL) was added $AgNO_3$ (65 mg, 0.38 mmol). The mixture was refluxed for 15 min, and the deposited AgCl was separated by filtration. To the filtrate was added glycine (16 mg, 0.21 mmol) and NEt_3 (0.03 mL, 0.21 mmol). The resulting solution was heated at reflux for 3 h. It was then concentrated to ~15 mL, and a saturated aqueous solution of $NaClO_4$ (0.5 mL) was added to afford a red precipitate of $[Ru(bpy)_2(L^1)]ClO_4$, which was collected by filtration, washed with cold water, and dried in vacuo over P_4O_{10}. Recrystallization from 1:3 acetonitrile−benzene solution gave $[Ru(bpy)_2(L^1)]ClO_4$ as a dark red crystalline solid. Yield, 79%.

Physical Measurements. Microanalyses (C, H, N) were performed using a Perkin-Elmer 240C elemental analyzer. IR spectra were obtained on a Perkin-Elmer 783 spectrometer with samples prepared as KBr pellets. Electronic spectra were recorded on a Jasco V-570 spectrophotometer. Magnetic susceptibilities were measured using a PAR 155 vibrating sample magnetometer fitted with a Walker scientific L75FBAL magnet. ^1H NMR spectra were recorded on a Brucker AC-200 NMR spectrometer using TMS as the internal standard. Solution electrical conductivities were measured using a Philips PR 9500 bridge with a solute concentration of 10^{-3} M. Electrochemical measurements were made using a CH Instruments model 600A electrochemical analyzer. A platinum-disk or graphite working electrode, a platinum wire auxiliary electrode, and an aqueous saturated calomel reference electrode (SCE) were used in a three electrode configuration. Electrochemical measurements were made under a dinitrogen atmosphere. All electrochemical data were collected at 298 K and are uncorrected for junction potentials. Fluorescence studies were performed with a Perkin-Elmer spectrofluorimeter (MPF 40). Electrophoresis experiments were carried out on a BIORAD electrophoretic system using TBS containing EthBr. The DNA binding studies were carried out as follows: (i) Fluorescence studies were performed with the complex and DNA dissolved separately in TBS, and the samples were excited at 330 nm. (ii) Photometric reaction of $[Ru(bpy)_2(L^4)]ClO_4$ with CT DNA involved monitoring $[Ru(bpy)_2(L^4)]ClO_4$ spectrophotometrically with and without irradiation at 254 nm for 20 min both in the presence and absence of CT DNA. (iii) For the DNA−agarose gel studies, plasmid pBR322 was incubated in the presence of different concentrations of $[Ru(bpy)_2(L^4)]ClO_4$. These solutions were monitored on agarose gel. The DNA was visualized under UV light.

Table 1. Crystallographic Data for $[Ru(bpy)_2(L^4)]ClO_4\cdot C_6H_6$

empirical formula	$C_{35}H_{32}N_5O_7ClRu$
fw	771.18
space group	monoclinic, $P2_1$
a, Å	8.9299(16)
b, Å	18.308(4)
c, Å	10.3473(17)
β, deg	91.905(13)
V, Å^3	1690.7(5)
Z	2
λ, Å	0.71073
cryst size, mm	0.54 × 0.42 × 0.23
T, K	298
μ, mm^{-1}	0.599
R1[a]	0.0414
wR2[b]	0.0902
GOF[c]	1.036

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum\{w(F_o^2 - F_c^2)^2\}/\sum\{w(F_o^2)\}]^{1/2}$. [c] $GOF = [\sum(w(F_o^2 - F_c^2)^2)/(M - N)]^{1/2}$, where M is the number of reflections and N is the number of parameters refined.

Crystallography of $[Ru(bpy)_2(L^4)]ClO_4\cdot C_6H_6$. Single crystals of $[Ru(bpy)_2(L^4)]ClO_4\cdot C_6H_6$ were grown by slow diffusion of benzene into an acetonitrile solution of the complex. Selected crystal data and data collection parameters are given in Table 1. Data were collected on a Bruker P4S diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) by ω scans. X-ray data reduction and structure solution and refinement were done using the SHELXS-97 and SHELXL-97 packages.[9] The structure was solved by the direct methods.

Results and Discussion

Reaction of the five α-amino acids (**1**; viz. glycine (HL^1), alanine (HL^2), phenyl alanine (HL^3), tyrosine (HL^4), and leucine (HL^5)) with $[Ru(bpy)_2(EtOH)_2]^{2+}$, generated in situ from $[Ru(bpy)_2Cl_2]$ by displacing the chlorides with the help of Ag^+ in ethanol medium, in the presence of a base afforded the desired $[Ru(bpy)_2(L)]^+$ complex cations, which have been

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Table 2. Microanalytical, Electronic Spectral, and Cyclic Voltammetric Data of the $[Ru(bpy)_2(L)]ClO_4$ Complexes

complex	microanalytical data[a] %C	%H	%N	electronic spectral data[b] λ_{max}, nm (ϵ, M^{-1} cm^{-1})	cyclic voltammetric data[c] $E_{1/2}$, V (ΔE_p, mV)
$[Ru(bpy)_2(L^1)]ClO_4$	45.60 (45.01)	3.37 (3.41)	11.87 (11.94)	511(7800), 362(8300), 292(34000), 244(23900)	0.67(75), −1.50(73), −1.74(194)
$[Ru(bpy)_2(L^2)]ClO_4$	45.29 (45.96)	3.69 (3.66)	11.56 (11.66)	511(9700), 362(10200), 292(34700), 244(28500)	0.67(71), −1.51(147), −1.76(188)
$[Ru(bpy)_2(L^3)]ClO_4$	51.08 (51.44)	3.89 (3.84)	10.30 (10.35)	502(6100), 353(7900), 292(33900), 244(22400)	0.65(66), −1.52(110), −1.73(192)
$[Ru(bpy)_2(L^4)]ClO_4$	50.36 (50.25)	3.68 (3.75)	10.00 (10.11)	511(7400), 362(9000), 292(45900), 244(27900)	0.67(75), −1.53(68), −1.80(162)
$[Ru(bpy)_2(L^5)]ClO_4$	48.84 (48.56)	4.42 (4.36)	10.78 (10.89)	502(6500), 353(8100), 288(30200), 239(25200)	0.66(74), −1.51(96), −1.76(133)

[a] Calculated values are in parentheses. [b] In acetonitrile solution. [c] Conditions: solvent, acetonitrile; supporting electrolyte TBAP; reference electrode SCE; $E_{1/2} = 0.5(E_{pa} + E_{pc})$, where E_{pa} and E_{pc} are anodic and cathodic peak potentials respectively; $\Delta E_p = E_{pa} - E_{pc}$; scan rate 50 mV s^{-1}.

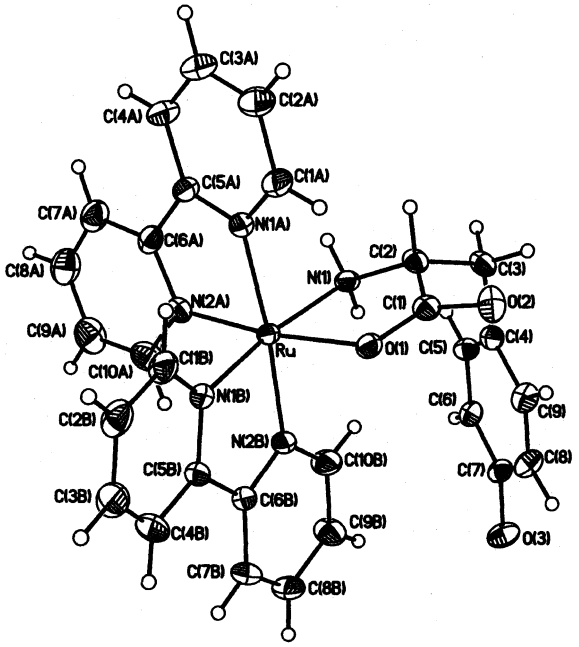

Figure 1. View of the $[Ru(bpy)_2(L^4)]ClO_4$ molecule.

isolated as perchlorate salts in decent yields. Elemental (C, H, N) analytical data of the complexes agree well with their compositions (Table 2). Though α-amino acids are known to bind to metal ions usually as a bidentate N,O-donor (**2**), other coordination modes are also possible for these ligands. To find out the coordination mode of the α-amino acids in these $[Ru(bpy)_2(L)]ClO_4$ complexes, the structure of a representative member of this family, viz. $[Ru(bpy)_2(L^4)]ClO_4$, has been determined by X-ray crystallography. The structure is shown in Figure 1, and selected bond parameters are listed in Table 3. The amino acid (tyrosine) is coordinated to ruthenium in the expected fashion, through one carboxylate oxygen and the amine-nitrogen with a bite angle of 79.5(2)°. The N_5O coordination sphere around ruthenium is significantly distorted from ideal octahedral geometry, which is reflected in the bond parameters around ruthenium. The bond distances in the $Ru(bpy)_2$ fragment are all quite normal. The Ru−O(1) distance is also usual. The Ru−N(1) length is a bit longer than the other four Ru−N(bpy) lengths, and the difference is attributable to the difference in the nature of the nitrogens. The C(1)−O(1) and C(1)−O(2) lengths indicate the expected charge delocalization in this carboxylate fragment. As all five $[Ru(bpy)_2(L)]ClO_4$ complexes have been prepared by following similar synthetic procedures and as all these complexes show similar properties (vide infra), the other four $[Ru(bpy)_2(L)]^+$ complexes are assumed to have a similar structure to that of $[Ru(bpy)_2(L^4)]^+$.

Table 3. Selected Bond Distances and Bond Angles for $[Ru(bpy)_2(L^4)]ClO_4$

Bond Distances (Å)			
Ru−O(1)	2.083(5)	C(1)−O(1)	1.257(8)
Ru−N(1)	2.114(6)	C(2)−O(2)	1.246(8)
Ru−N(1A)	2.045(5)	C(1)−C(2)	1.523(10)
Ru−N(2A)	2.029(5)	C(2)−N(1)	1.471(9)
Ru−N(1B)	2.038(6)	C(2)−C(3)	1.546(10)
Ru−N(2B)	2.065(5)	C(3)−C(4)	1.505(9)
		C(7)−O(3)	1.359(8)

Bond Angles (deg)			
N(1)−Ru−O(1)	79.5(2)	N(1)−Ru−N(1B)	171.6(2)
N(1A)−Ru−N(2A)	79.5(2)	N(2A)−Ru−O(1)	173.1(2)
N(1B)−Ru−N(2B)	79.3(2)	N(1A)−Ru−N(2B)	174.3(2)

The $[Ru(bpy)_2(L)]ClO_4$ complexes are diamagnetic, which corresponds to the bivalent state of ruthenium (low-spin d^6, $S = 0$) in these complexes. ^1H NMR spectra of the complexes, recorded in CD_3CN solution, are complex in nature because of the lack of any C_2 symmetry in these complexes. However, intensity measurement of the signals corresponds to the total number of protons in the respective complexes. The bpy signals appear within 6.5−9.3 ppm. Most of the expected signals from the coordinated amino acid have been detected in all these complexes. For example, in the $[Ru(bpy)_2(L^2)]ClO_4$ complex, three signals are expected from the coordinated alanine (viz. the methyl signal, the C−H signal, and the NH_2 signal), and all of them have been observed at 1.30, 1.96, and 7.13 ppm, respectively. Infrared spectra of the $[Ru(bpy)_2(L)]ClO_4$ complexes show a broad and very strong vibration near 1610 cm^{-1} and a sharp and strong vibration near 1380 cm^{-1}, which are assigned respectively to the $\nu_{as(CO)}$ stretching and $\nu_{s(CO)}$ stretching of the coordinated carboxylate groups.[10] The distinct peaks observed near 3200 cm^{-1} in all these complexes are attributed to the N−H stretching vibrations. Vibrations due to the coordinated bpy ligands (near 810, 770, 660, and 425 cm^{-1}) and the perchlorate ion (near 1100 and 625 cm^{-1}) are also observed in all the complexes. The NMR and infrared spectral data of the $[Ru(bpy)_2(L)]ClO_4$ complexes are therefore consistent with their compositions.

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The $[Ru(bpy)_2(L)]ClO_4$ complexes are soluble in water and organic solvents such as ethanol, methanol, acetonitrile, and so forth to produce pinkish-red solutions. Conductance measurement in acetonitrile solution shows that these complexes behave as 1:1 electrolytes ($\Lambda_M = 140-150\ \Omega^{-1}\ cm^2\ M^{-1}$), as expected. Electronic spectra of these complexes have been recorded in acetonitrile solution. Each complex shows four intense absorptions, two in the visible region and two in the ultraviolet region (Table 2). The absorptions in the ultraviolet region are assignable to transitions within the ligand orbitals. The intense absorptions in the visible region are probably due to allowed metal-to-ligand charge-transfer transitions. Multiple charge-transfer transitions in such mixed-ligand complexes may result from lower symmetry splitting of the metal level, the presence of different acceptor orbitals, and the mixing of singlet and triplet configurations in the excited state through spin−orbit coupling.[11] To have a better insight into the nature of transitions observed in the visible region, qualitative EHMO calculations have been performed[12] on computer generated models of the $[Ru(bpy)_2(L)]^+$ complexes. The results obtained are similar for all the complexes. A partial MO diagram for a representative complex is shown in Figure 2. The top three filled orbitals, viz. the highest occupied molecular orbital (HOMO) and the next two filled orbitals (HOMO − 1 and HOMO − 2), are close in energy, and they have major (>74%) contributions from the ruthenium t_2 orbitals. The lowest unoccupied molecular orbital (LUMO) and the next vacant orbital (LUMO + 1) are also close in energy, and they are localized almost entirely on different parts of the bpy ligands. The absorptions in the visible region may therefore be assigned to transitions occurring from the filled ruthenium t_2 orbitals to the vacant π^*-orbitals of the bpy ligands.

Electrochemical properties of the $[Ru(bpy)_2(L)]ClO_4$ complexes have been studied by cyclic voltammetry in acetonitrile solution (0.1 M TBAP). Voltammetric data are given in Table 2. Each complex shows an oxidative response near 0.67 V versus SCE, which is assigned to the ruthenium(II)−ruthenium(III) oxidation. This oxidation is reversible, characterized by a peak-to-peak separation (ΔE_p) of ∼70 mV which does not vary with variation in scan rates, and the anodic peak current (i_{pa}) is almost equal to the cathodic peak current (i_{pc}), as expected for a reversible electron-transfer process. The one-electron nature of this oxidation has been established by comparing its current height with that of the standard ferrocene/ferrocenium couple under identical experimental conditions. The ruthenium(II)−ruthenium(III) oxidation potential in these $[Ru(bpy)_2(L)]ClO_4$ complexes is much lower than that in $[Ru(bpy)_3]^{2+}$ (1.30 V),[13] which shows that, compared to the bpy ligand, anions of the α-amino acids are better stabilizers of the trivalent state of ruthenium. Two successive one-electron reductions within −1.49 to −1.78 V are displayed by all these complexes, which are assigned to reductions of the two bpy ligands. It is well-known that each bpy can successively accept two electrons in the lowest unoccupied molecular orbital.[14] Hence, in the $[Ru(bpy)_2(L)]ClO_4$ complexes, four successive one-electron reductions are expected. Only two of these have been experimentally observed, and the other two have not been observed because of solvent cutoff.

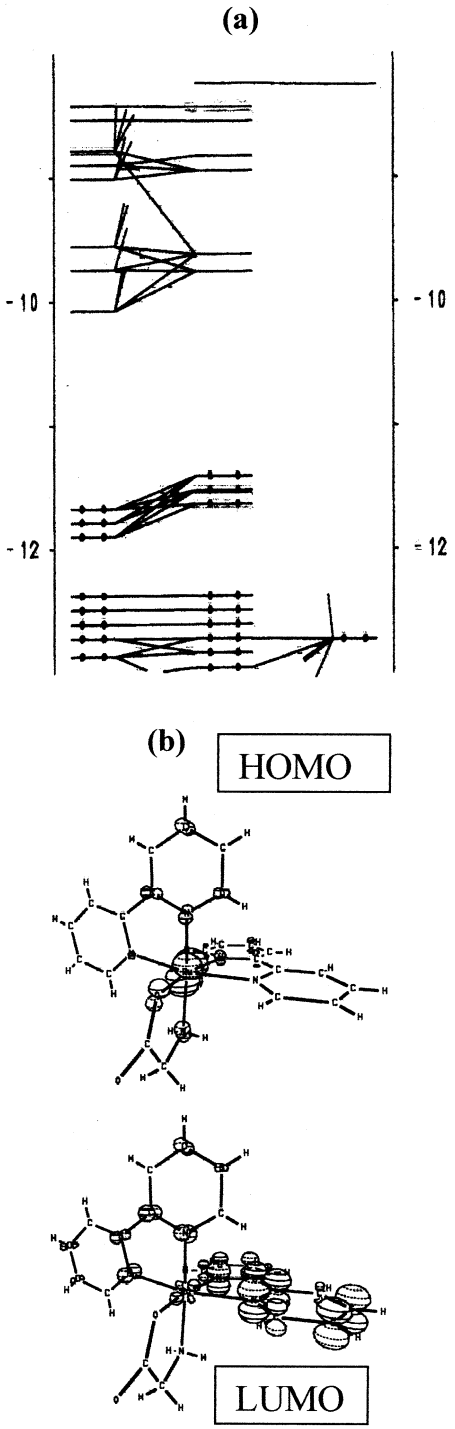

Figure 2. Partial molecular orbital diagram of $[Ru(bpy)_2(L^1)]ClO_4$: (a) the interaction diagram and (b) the highest occupied molecular orbital and the lowest unoccupied molecular orbital.

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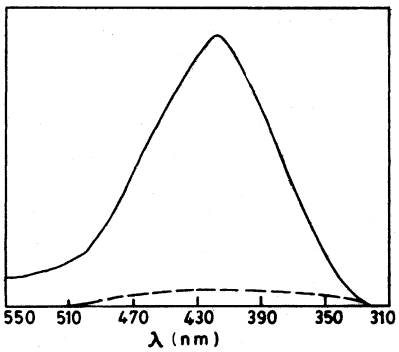

Figure 3. Fluorescence spectrum of $[Ru(bpy)_2(L^2)]ClO_4$ in TBS solution in the absence (- - -) and presence (—) of CT DNA (λ_{ex} = 330 nm, [DNA]/[complex] = 1:44).

As transition metal complexes containing polypyridyl ligands are known to display DNA intercalation properties, we have also explored such possibilities in these $[Ru(bpy)_2(L)]ClO_4$ complexes. Interaction of the $[Ru(bpy)_2(L)]ClO_4$ complexes with DNA has been monitored by fluorescence studies. Solutions of DNA and the $[Ru(bpy)_2(L)]ClO_4$ complexes were made by dissolving the respective solute in TBS. The complexes as well as DNA excited at 330 nm in this medium do not show any detectable fluorescence. However, all the $[Ru(bpy)_2(L)]ClO_4$ complexes show intense fluorescence near 410 nm in the presence of DNA while excited at the same energy. A representative case is shown in Figure 3. This dramatic change in luminescence property of the complexes in the presence of DNA suggests that these complexes are definitely binding to DNA. The fluorescence intensity is observed to vary with the [DNA]/[complex] ratio, and it reaches its optimum value when [DNA]/[complex] = 1:44. The fluorescence intensity also varies with the nature of amino acid. At [DNA]/[complex] = 1:44, the ratio of the fluorescence intensities is 2.0:2.3:1.0:3.7:3.0 for the glycine, alanine, phenyl alanine, tyrosine, and leucine complexes, respectively. The fluorescence studies suggest that binding to DNA protects the bipyridine rings of these complexes from interaction with water molecules, and thus, the photochemical excited states of the complexes are stabilized which leads to the observed fluorescence.

Transition metal complexes of polypyridyl ligands are known to cleave DNA when irradiated by UV light.[15] The irradiation of CT DNA in the presence of the $[Ru(bpy)_2(L)]ClO_4$ complexes was studied so as to determine their efficiency in DNA cleavage. This has been achieved by monitoring the absorption spectra of solutions of the complexes and complex−DNA systems in TBS in the UV region after irradiation for ∼20 min with 254 nm light. It was found that the complex itself incurred a hyperchromic shift after irradiation at 254 nm. Absorption spectra of the complex−DNA systems also show a similar hyperchromic shift upon irradiation. This indicates that there has been no damage of DNA double-helix structure on binding with the complex. This was further supported by the electrophoresis

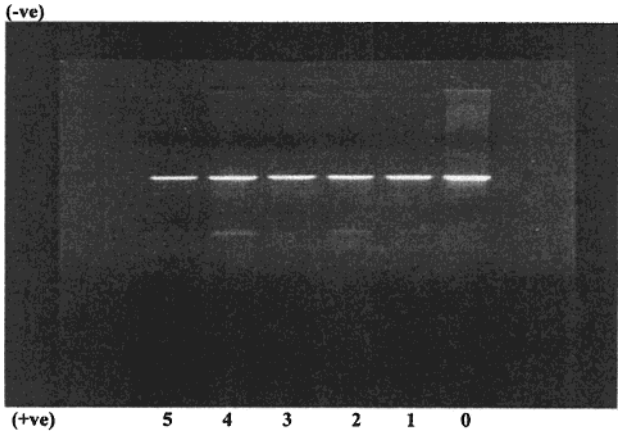

Figure 4. Results of the gel electrophoresis experiment for $[Ru(bpy)_2(L^4)]ClO_4$. The [complex]/[pBR322 DNA] ratio is 0, 10, 20, 30, 40, and 50 for lanes 0, 1, 2, 3, 4, and 5, respectively.

experiments where plasmid pBR322 was incubated in the presence of different concentrations of the five $[Ru(bpy)_2(L)]ClO_4$ complexes. These solutions were then monitored on agarose gel. The DNA was visualized under UV light. It was found that there was no gel electrophoretic separation of pBR322 DNA after incubation with the concerned complexes and irradiation (irradiation was done for variable times). A selected example is shown in Figure 4. The extreme left lane is for pBR322 showing a beautiful band of the supercoiled form, and in the following five lanes are the bands for complex−DNA systems ([complex]/[DNA] = 10, 20, 30, 40, and 50). No band for relaxed coil or linear structure was found. This again shows that, on binding with the complex, the plasmid pBR322 does not break into either relaxed coil or linear structures; that is, conformational characteristics of the DNA remain intact.

Conclusions

The present study shows that, in combination with π-acid ligands such as bpy, α-amino acids can form stable complexes with ruthenium(II) which can effectively bind to DNA without causing any damage to the DNA double helix.

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Supporting Information Available: Crystal data and details of structure determination, atomic coordinates, anisotropic thermal parameters, and bond distances and angles for $[Ru(bpy)_2(L^4)]ClO_4 \cdot C_6H_6$. This material is available free of charge via the Internet at http://pubs.acs.org.

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