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Research Article

Synthesis, Characterization, and Biological Studies of New Ruthenium Polypyridyl Complexes Containing Noninnocent Ligands

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Two new polypyridyl complexes $[Ru(ttp)(L^1)Cl]PF_6$ (**1**) and $[Ru(ttp)(L^2)Cl]PF_6$ (**2**) with noninnocent o-benzoquinonediimine (L^1; bqdi) and 4,5-dimethyle-o-benzoquinonediimine (L^2; 4,5-di-Mebqdi) ligands were synthesized and characterized (ttp = 4′-p-toloyle-2,2′: 6′,2″-terpyridine). Cyclic voltammetry studies suggest that noninnocent ligands are coordinated in their benzoquinonediimine form. Preliminary ruthenium complexes-induced DNA dysfunction was studied on *E. coli* GM109 DNA by means of melting temperature analysis (Tm). Our results suggest that complex (**2**) inhibited DNA function more strongly compared to (**1**). Antibacterial activities of the complexes against *E. coli* bacteria were studied, and Minimum inhibitory concentration (MIC) values were evaluated. Both complexes showed great antibacterial activities.

1. Introduction

Identifying the molecules that are capable of binding and cleaving DNA has attracted considerable interest over the last few decades [1]. In this regard, ruthenium-containing complexes have obtained great considerations [2–13]. Although the investigation of the interactions of other transition metal complexes with DNA and RNA has been the subject of several researches [14–17], more attention has been given to ruthenium complexes [18–22]. These investigations are very important in the development of new therapeutic reagents and DNA molecular probes [23, 24]. Ruthenium complexes are also well suited for medical applications due to their favorable rate of ligand exchange and their ability to mimic iron binding to certain biomolecules [25, 26]. Therefore, the studies on the interaction of ruthenium compounds with DNA have led to the development of several ruthenium-based anticancer drugs [27, 28]. As a result, a variety of Ru complexes, especially terpyridine complexes, have obtained considerable attention [29–31]. This is due to the benefit of high stability of their coordination compounds and the rich photochemical and electrochemical properties of their metal complexes which are found to promote DNA binding and cleaving. Furthermore, introduction of substituents in the 4′ position of terpyridine can be easily achieved by available procedures, which gives the opportunity of fine tuning of the coordination environment. Many useful applications of these complexes require that the complexes bind to DNA through an intercalative mode as well as outer of double strand or both of side. Therefore, the vast majority of such studies have been focused on the modification of the intercalative and outercalative ligands [32–34]. Since the octahedral polypyridyl Ru(II) complexes bind to DNA in three dimensions, the ancillary ligands can also play an important role in governing DNA binding of these complexes. At the same time, varying substitutive group or substituent position in the ancillary ligand can also create some interesting differences in the space configuration and the electron density distribution of Ru(II) polypyridyl complexes, which will result in some spectral properties and different DNA-binding behaviors of the complexes and will be helpful to more clearly understand the binding

mechanism of Ru(II) polypyridyl complexes to DNA [35, 36]. Considering the afore mentioned, herein we report the synthesis and characterization of two new polypyridyl complexes: $[Ru(ttp)(L^1)Cl]PF_6$ **(1)** and $[Ru(ttp)(L^2)Cl]PF_6$ **(2)** with noninnocent o-benzoquinonediimine (L^1; bqdi) and 4,5-dimethyle-o-benzoquinonediimine (L^2; 4,5-di-Mebqdi) ligands. The interaction of these complexes with *E. coli* GM109 DNA was also studied by means of UV-Vis spectroscopy. Our results show that complex **(2)** with two methyl groups on the bqdi-type ligand interacts with *E. coli* GM109 DNA more strongly. Antibacterial activity of the two complexes was evaluated, and minimum inhibitory concentrations were obtained by the dilution method as recommended by NCCLS (National Committee for Clinical Laboratory Standards).

2. Experimental

All chemicals were of the highest purity and were used as received. All the synthesis and purifications were conducted in aerobic condition. Ttp (4′-p-toloyle-2,2′:6′,2″-terpyridine) was synthesized as described elsewhere [37]. *E. coli* GM109 DNA was extracted as described elsewhere [38, 39]. Tris(hydroxymethyl)aminomethane-HCl (trisbuffer) was prepared with deionized and degassed triple distilled water, and all of the DNA interaction studies were performed in this buffer (pH = 7.2). Melting points were obtained on a thermoscientific 9100 apparatus. ^{1}HNMR spectra were recorded on a 500 MHz Bruker FT-NMR spectrometer using $CDCl_3$ and DMSO-d_6 solvents; chemical shifts (δ) are given in ppm. IR spectra were obtained as KBr plates using a Bruker FT-IR instrument, and UV-Vis spectra were obtained as acetonitrile solutions on a Shimadzu UV-1650PC spectrophotometer or UV-Visible Milton Roy 1201 spectrophotometer apparatus. Elemental analysis (C, H, N) was performed using a Heraeus Elemental Analyzer CHN-O-Rapid (Elementar-Analysensysteme, Gmbh, West Germany). A Metrohm 757 VA computrace instrument was employed to obtain cyclic voltammograms in acetonitrile at room temperature (25°C) using 0.1 M tetra-n-butylammonium hexafluorophosphate (TBAHFP) solution as supporting electrolyte. A platinum electrode was used as the auxiliary electrode and Ag/AgCl electrode as working electrode.

2.1. Synthesis of the Complexes. $Ru(ttp)Cl_3$ was synthesized following a similar procedure as described for $Ru(terpy)Cl_3$ [40]. The reaction of $Ru(ttp)Cl_3$ with o-phenylenediamine (opda) and 4,5-dimethyle-o-phenylenediamine gave $[Ru(ttp)(bqdi)Cl]PF_6$ **(1)** and $[Ru(ttp)(4,d\text{-}diMe\text{-}bqdi)Cl]PF_6$ **(2)**, respectively.

2.2. Preparation of $[Ru(ttp)(bqdi)Cl]PF_6{\cdot}2H_2O$ **(1)**. $[Ru(ttp)Cl_3]$ (0.7 g, 1.32 mmol), o-phenylenediamine (0.18 g, 1.67 mmol), and NEt_3 (0.5 mL, 3.1 mmol) were dissolved in 100 mL of ethanol/water (3 : 1) and were refluxed for 4 hours. 0.5 g of LiCl was then added, and the reaction mixture was refluxed for a further 30 min. The color of the solution turned to purple. The solvent of the reaction was evaporated to about 20 mL, and 1 g of NH_4PF_6 was added. After the addition of 300 mL of water, the dark precipitate was filtered off and washed thoroughly with ice-cold water and diethyl ether and air dried. It was then purified on an alumina (neutral) column. The purple target complex was obtained by elution with CH_3CN/Toluene (1 : 1). Evaporation of the solvent under reduced pressure gave analytically pure target compounds. Yield: 220 mg, 25%. ^{1}HNMR: 13.65 (s, 1H), 11.45 (s, 1H), 9.42–6.99 (m, 18p), 2.48 (s, 3p); IR (cm^{-1}): 3447, 3302, 842; UV-Vis, λ_{max}/CH_3CN, nm (ε, $M^{-1}\,cm^{-1}$): 490 (22600), 310 (59700), 284.5 (54700). Anal. calcd. for $C_{28}H_{27}N_5ClF_6PO_2Ru$: C: 45.1; H: 3.6; N: 9.4; found: C: 45.2; H: 3.8; N: 9.2.

2.2.1. Preparation of $[Ru(ttp)(4,d\text{-}diMe\text{-}bqdi)Cl]PF_6$ **(2)**. Complex two was synthesized following the same procedure as described for (1) except 4,5-dimethyle-o-phenylenediamine was used instead of o-phenylenediamine. Yield: 253 mg, 26%^{1}HNMR: 14.03 (s, 1H), 11.50 (s, 1H), 9.46–6.70 (m, 16P), 2.40 (s, 3H), 2.21 (s, 3H), 2.07 (s, 3H). IR (cm^{-1}): 3448, 3301, 840; UV-Vis, λ_{max}/CH_3CN, nm (ε, $M^{-1}\,cm^{-1}$): 529.7 (39600), 237.7 (37900), 284.1 (46600). Anal. calcd. for $C_{30}H_{27}N_5ClF_6PRu$: C: 48.7; H: 3.7; N: 9.5; found: C: 48.6; H: 3.9; N: 9.3.

2.3. Biological Studies

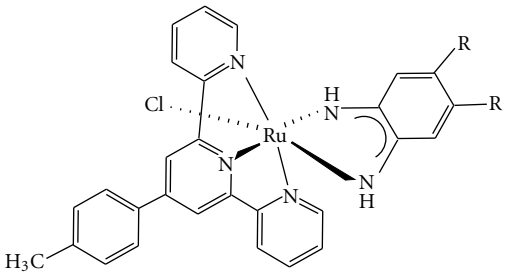
2.3.1. Melting Temperature Analysis. The temperature at which 50% of the double helix denatures into single strand DNA is known as T_m. It is shown that the interaction of small molecules with DNA increases the T_m [41, 42]. Two mL of the solutions containing 10 μL of DNA solution, 10 μL of 3 μM complex **(1)** or **(2)** and 1980 μL of tris-buffer were prepared. The temperature of the solutions was increased gradually and the absorbance at 260 nm was monitored. T_m values were obtained by plotting the absorbance versus temperature. Similar experiments were done for the control solution containing 10 μL of DNA solution and 1990 μL of trisbuffer solution.

2.3.2. Determination of Minimum Inhibitory Concentrations (MIC). In order to further investigate the interaction of the two newly synthesized complexes with *E. coli* bacteria, anti-bacterial tests were also performed. The tests were performed by microdilution assays, and minimum inhibitory concentration (MIC) values, defined as the minimal concentration of the complexes which prevents the growth of the microorganisms, were obtained by the microdilution broth method, as recommended by NCCLS standards [43]. The complexes were first dissolved in DMSO and were diluted to 200 $\mu g\,mL^{-1}$. Serial twofold dilutions to about 1.6 $\mu g\,mL^{-1}$ were performed in sterile tubes. A suspension of the microorganism was added to each dilution in a 1 : 1 ratio. The growth or lack of the *E. coli* bacteria was visually determined after 48 h of incubation at 37°C. The lowest concentration at which

Table 1: Electrochemical data for Ru complexes in acetonitrile.

	(**1**)				(**2**)			
	E^c (mV)	E^a (mV)	ΔE (mV)	E^0 (mV)	E^c (mV)	E^a (mV)	ΔE (mV)	E^0 (mV)
$Ru^{II}NIL/Ru^{III}NIL$	1510	1590	80	1550	1390	1490	100	1440
$Ru^{II}NIL/Ru^{II}NIL^{\bullet}$	−850	−998	148	−924	−1631	—	—	−1220
$Ru^{II}NIL^{\bullet}/Ru^{II}NIL^{Red}$	−1850	−1990	140	−1920	−1582	−1493	89	−1545

Data are for 10^{-3} M solutions of the complexes in acetonitrile in presence of 0.1 M of TBAHFP as supporting electrolyte. E^c: E cathodic; E^a: E anodic.



Complex	R
(**1**)	H
(**2**)	CH_3

Figure 1: Structure of the complexes **(1)** and **(2)**.

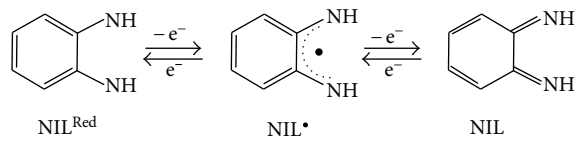


Figure 2: The coordination modes of the NIL ligands.

no visible growth was seen was chosen as the MICs. The experiments were repeated for three times. Besides, control experiments with DMSO were also done.

3. Results and Discussions

3.1. Synthesis of the Complexes. The complexes were readily prepared by the equimolar reaction between $Ru(ttp)Cl_3$ and appropriate derivative of o-phenylenediamine in the presence of NEt_3 as base and ethanol/water (3/1) as solvent (Figure 1). The complexes were purified by column chromatography. Alumina was employed as the stationary phase, and CH_3CN/Toluene (1 : 1) was used as the eluent. The complexes were isolated as hexafluorophosphate salt in good yields.

3.2. Spectroscopic and Electrochemical Determination of the Complexes. In the ^{1}HNMR spectra of the diamagnetic Ru^{II} complexes, the presence of two singlets at around 14 and 11 ppm is indicative of the formation of two benzoquinone type NHs. As it could be seen from Figure 1, these two protons are not equivalent; one of them is trans to Cl ligand while the other one is trans to the nitrogen atom of the ttp ligand. Aromatic protons of ttp and those of o-benzoquinonediimine ligands also appear in the region of 6.5–9.5 as multiplets. Protons of the CH_3 group of ttp appear in the region of the aliphatic protons at 2.48 ppm and 2.40 ppm for **(1)** and **(2)**, respectively. For complex **(2)**, two sets of signals at the region of the aliphatic protons are also observed which are consistent with the two CH_3 substituents of the 4,5-dimethyl-o-benzoquinonediimine ligand. In the IR spectra of the complexes, the signals at around 3400 and 3300 cm^{-1} are indicative of NHs of benzoquinonediimine ligands and the peak at around 840 cm^{-1} is due to uncoordinated PF_6. The absorption spectra of these complexes are typical of the ruthenium polypyridyl complexes. The intense UV bands at 310, 284.5 nm for complex **(1)** and 237.7, 284 nm for complex **(2)** are assignable to $\pi \rightarrow \pi^*$ transition of the ligands. Metal to ligand charge transfer (MLCT) transitions are observed as slightly broad bands in the visible region at 490 and 529.7 nm for complexes **(1)** and **(2)**, respectively. The presence of two-electron donating methyl substituents on the o-benzoquinonediimine ligand of complex **(2)** has resulted in considerable red shift in the MLCT transition. As it could be seen from Figure 2, the coordination mode of o-phenylenediamine ligand could be one of three forms. Since the electronic spectra of these complexes do not present absorptions at wavelengths higher than 600 nm, it could be rationalized that o-phenylenediamine ligands are not in their semiquinonoid forms (Figures 1 and 2) [44]. Comparison of our data with those of the literature reports [45–48], especially [49, 50], shows that o-phenylenediamine ligands are coordinated in the form of their benzoquinonediimine coordination mode.

Electrochemical studies also support this conclusion. The electrochemical behavior of the complexes was studied by means of cyclic voltammetry in acetonitrile solution. Voltammograms were obtained at room temperature (25°C) using 0.1 M tetra-n-butylammonium hexafluorophosphate (TBAHFP) solution as supporting electrolyte. A platinum electrode was used as the auxiliary electrode and Ag/AgCl electrode as working electrode. Figure 3 shows the CV of complex **(1)**. The results for both complexes are collected in Table 1. As it could be seen from Figure 3, the peak observed in the oxidation region at 1.55 V versus NHE could be attributed to the process of Ru^{II} (bqdi)/Ru^{III} (bqdi). Two peaks are also observed in the reduction region, −0.92 and −1.92 V versus NHE, respectively. The first peak is assigned to the process of Ru^{II} (bqdi)/Ru^{II} (s-bqdi) reduction in which

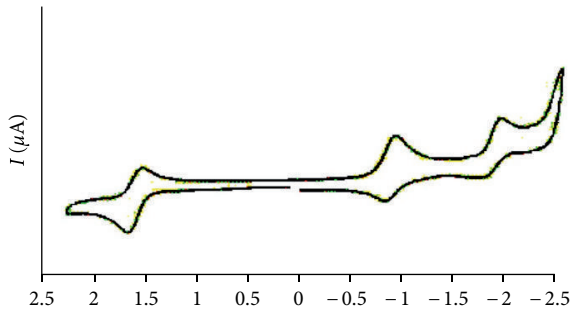


Figure 3: Cyclic voltammogram of 10^{-3} M solution of complex **(1)** in acetonitrile in the presence of 0.1 M of TBAHFP as supporting electrolyte.

bqdi (benzoquinonediimine) NIL ligand is reduced to its s-bqdi (semi-benzoquinonediimine) $NIL^{\bullet}$. The second peak is also a ligand centered reduction in which s-bqdi is reduced to NIL^{Red}. For complex **(2)**, the oxidation peak is observed at 1.44 V versus NHE which is shifted to less positive values compared to complex **(1)**. This is also assignable to the metal-centered oxidation, Ru^{II} (4,5-diMebqdi)/Ru^{III} (4,5-diMebqdi) [50]. This shift in the redox potential is due to the presence of two-electron donating methyl groups on the ancillary ligand. In the reduction region, the anodic peak of the first reduction process is not observed which shows an irreversible process. But the second reduction is reversible and is observed at −1.54 V versus NHE. Since these two peaks are NIL ligand centered reductions, they are more sensitive to the presence of two methyl groups on this ligand. The two signals are shifted to more positive values which is the direct consequence of the presence of the electron donating methyl substituents.

3.3. Biological Studies

3.3.1. T_m Analysis. The melting curves of DNA alone and DNA-Ru complex mixtures are shown in Figure 4. T_m experiments for the DNA alones showed a T_m value of 73 ± 0.2°C which has increased upon the interaction with Ru complexes. The T_m of the DNA increased 1°C by the interaction with complex **(1)** and 4°C with complex **(2)**. It is shown that the groove binders have ΔT_m values similar to our observed values, and hence it could be concluded that the groove binding is the major interaction by these Ru complexes [22, 44]. It is also shown that the presence of electron donating substituents on the coordinated ligands increases the DNA-binding ability of Ru complexes [47]. Similar results are observed for our complex **(2)**. The higher ΔT_m for **(2)** is probably caused by the more positive surface charge of the complex which increases the binding ability of the complex with donor groups of the DNA.

Similar experiments, with other dosages of the complexes, were also performed. Figure 5 shows the results for 20 and 50 dosages of **(2)** (total volume of 2 mL and constant dosage of DNA; 10 μL).

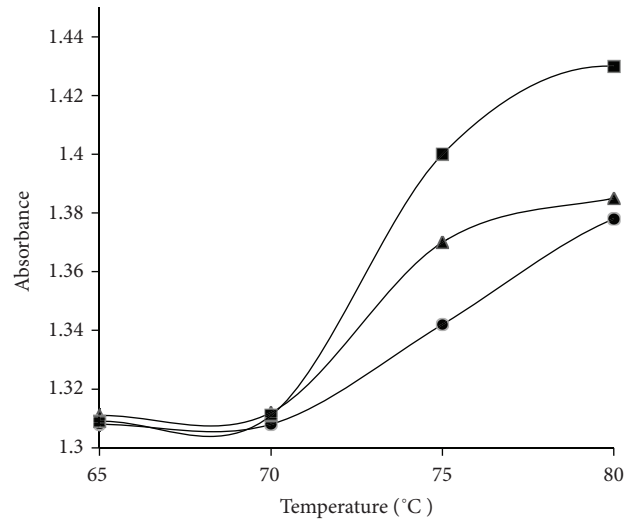


Figure 4: The melting curves of *E. coli* GM109 DNA at 260 nm in the absence and presence of complexes. DNA alone (■), with 10 μL of 3 μM complex **(1)** (▲), and complex **(2)** (●).

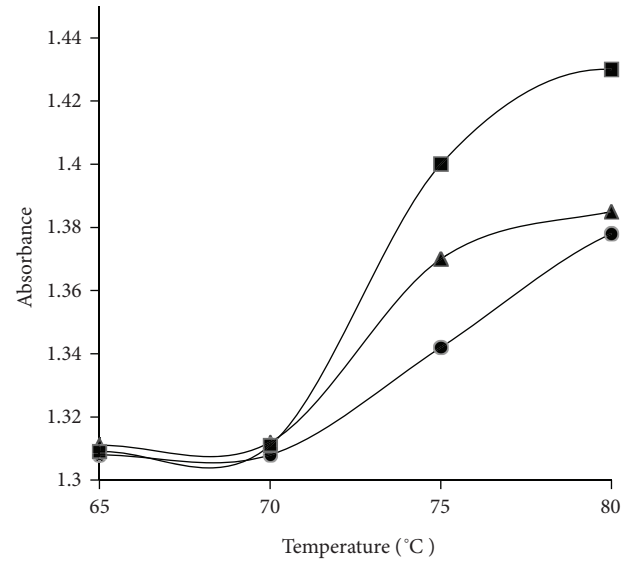


Figure 5: The melting curves of *E. coli* GM109 DNA at 260 nm in the absence and presence of different dosages of complex **(2)**. DNA alone (♦), 20 μL (▲), and 50 μL (●) of 3 μM of **(2)**.

As it could be seen from Figure 5, no significant change was observed for the ΔT_m of the DNA by increasing the dosage of the complexes, and 10 μL of the complexes was chosen as the optimized dosage.

3.3.2. Antibacterial Studies. The antimicrobial activity of the two complexes was studied by microdilution method, and our results show that both complexes inhibited the growth of the *E. coli* bacteria very effectively [51–55]. The MIC values for both complexes were determined to be 12.5 $\mu g\,mL^{-1}$. These values are comparable with standard compounds such as Ampicillin in our conditions.

4. Conclusion

Two new ruthenium polypyridine complexes with noninnocent orthobenzoquinonediimine type ligands were synthesized and characterized. Electrochemical and spectroscopic properties of the complexes were also investigated. The Ru^{II} (4,5-diMebqdi)/Ru^{III} (4,5-diMebqdi) oxidation peak of complex **(2)** was shifted to less positive values compared to complex **(1)** which was attributed to the presence of the electron donating methyl groups on the non-innocent ligand. The interaction of the complexes with *E. coli* GM109 DNA was investigated by means of T_m analysis. The results show that complex **(2)** increases the T_m more than (**1**) which means that it has greater interaction with the DNA. Antibacterial studies also show that these complexes are effective against the studied microorganism.

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