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INVITRO ANTIOXIDANT ACTIVITY OF A MONONUCLEAR RUTHENIUM (II) COMPLEX OF 2-{4, 5-BIS [(*E*)-2-(4-CHLOROPHENYL) ETHENYL]-1*H*-IMIDAZOL-2-YL}-1*H*-BENZIMIDAZOLE

M. Kiruthika*, R. Sivasankari*, K. N. Gita, R. Elayaperumal***, P. Bhavani* & P. Dharmalingam******
* Department of Chemistry, Arignar Anna Government Arts College, Musiri, Tamilnadu
** Department of Chemistry, Government Arts College for Women, Salem, Tamilnadu
*** Department of Chemistry, J.J College of Engineering and Technology, Tiruchirappalli, Tamilnadu
**** Department of Chemistry, Urumu Dhanalakshmi College, Tiruchirappalli, Tamilnadu

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Abstract:

2-{4,5-bis[(*E*)-2-(4-chlorophenyl)ethenyl]-1*H*-imidazol-2-yl}-1*H*-benzimidazole (L) and its ruthenium (II) complex has been synthesized. Structural features were determined by various physicochemical and spectral techniques. Investigation of antioxidative property showed that the ruthenium (II) complex have significant radical scavenging ability compared to that of the ligand.

Key Words: Benzimidazole, Ruthenium (II) & Antioxidant

1. Introduction:

Ruthenium has numerous properties that qualify it as an antineoplastic drug contender. While platinum-based compounds have served as very successful anti-cancer drugs, they have several limitations including their side effects, as well as ineffectiveness against certain types of cancer. Researchers speculated that some of these issues might be resolved with the use of a ruthenium substitute.[1] Though most ruthenium complexes are only in the beginning stages of the approval process for anti-cancer drugs, many of their properties may give them advantages over many platinum-based drugs now in use.[2,3] Ruthenium complexes are very promising, especially from the point of view of overcoming cisplatin resistance with a low general toxicity. Ruthenium has found its way into the clinic, where its properties are exploited for very miscellaneous uses. Other ruthenium compounds have potential as immunosuppressants (*cis*-$[Ru^{(III)}(NH_3)_4(HIm)_2]^{3+}$),antimicrobials ($[Ru^{(II)}Cl_2(chloroquine)_2]$), antioxidants, vasodilator/vasoconstrictor agents and, as above mentioned, as drugs for cancer chemotherapy.[4-6] The chemistry and pharmacology of benzimidazoles have been of enormous interest to medicinal chemistry because its derivatives possessed various biological activities such as antioxidant,[7] antimicrobial,[8] anticancer[9] and anti-inflammatory[10] activity. Here we report the synthesis of benzimidazole group containing ligand L1 and its ruthenium complex and also the antioxidant properties of the synthesized compound have been explored.

2. Experimental:

2.1 Materials and Methods:

Ruthenium chloride trihydrate, ammonium hexafluoro phosphate and 4-chlorobenzaldehyde were purchased from Sigma-Aldrich. Benzimidazole-2-carboxaldehyde was prepared by following a reported procedure.[11] Acetic acid, ammonium acetate, methanol, acetonitrile and ethanol were purchased from SD Fine chemicals. Absorption spectra were recorded on Shimadzu UV-160A UV-Visible spectrophotometer. Cyclic (CV) and differential pulse voltammetries (DPV) were performed by using CH instrument (USA) model CH-620 B electrochemical analyzer. A conventional three electrode system consisting of platinum disc as a working electrode, platinum wire as an auxiliary electrode and saturated calomel (SCE) as a reference electrode was used for the electrochemical measurements. 0.1 M tetrabutyl ammonium perchlorate (TBAP) was used as the supporting electrolyte for all the experiments. Positive ion electrospray ionization mass spectra of the complexes were obtained by using Thermo Finnigan LCQ 6000 advantage max ion trap mass spectrometer. Elemental analyses were performed using Carlo Erba 1108 analyzer at Cochin University. IR spectra were recorded as KBr pellets in the 400 - 4000 cm^{-1} region using a Shimadzu FT–IR 8000 spectrophotometer.

2.2 Synthesis of 2-{4,5-bis[(*E*)-2-(4-chlorophenyl)ethenyl]-1*H*-imidazol-2-yl}-1*H*-benzimidazole (L)

(1*E*,5*E*)-1,6-bis(4-chlorophenyl)hexa-1,5-diene-3,4-dione (0.5 g, 1.51 mmol), benzimidazole-2-carboxaldehyde (0.29 g, 2.00 mmol) and ammonium acetate (4 g, 50 mmol) were dissolved in 30 mL acetic acid and heated to reflux for 3 h. After cooling, cold water (20 mL) was added to the solution, during which reddish brown precipitate appeared. It was filtered and purified by column chromatography on silica gel using ethyl acetate:hexane (1:4) as an eluent (Yield: 0.438 g, 61 %). ESI-MS: m/z (relative intensity): 458.1 $(M+1)^+$. δ_H (400 MHz; DMSO-d6; Me_4Si) 7.32(4H, d, J=2.8 Hz), 7.34(4H, d, J=3.2 Hz), 7.29(4H, d, J=2.8 Hz), 7.71(2H, d, J=2.4 Hz), 7.30(2H, t, J=1.6 Hz), 12.42(2H, s); Anal. Calc. for $C_{26}H_{18}Cl_2N_4$: C, 68.28; H, 3.97; N, 12.25. Found:

C, 68.25; H, 3.95; N, 12.22; IR, cm^{-1}(KBr pellet) 3417, 2312, 1606, 1489, 743, 419; UV-Visible λ_{max}, nm (ε, $M^{-1}cm^{-1}$) 339(15145), 285(49430).

2.3 Synthesis of Ruthenium (II) Complex $[Ru(bpy)_2(L)](PF_6)_2$ (1)

A mixture of [*cis*-$Ru(bpy)_2Cl_2]\cdot 2H_2O$[17] (0.2 g, 0.38 mmol) and L (0.17 g, 0.38 mmol) was suspended in an ethanol/water solvent mixture (3/1, v/v). The mixture was refluxed under an inert atmosphere for 4 h while vigorous stirring was maintained. The reaction mixture was cooled to room temperature; the solvent was reduced under vacuum to one-third of its initial volume. A saturated aqueous solution of NH_4PF_6 was added to precipitate $[Ru(bpy)_2(L1)]^{2+}$ as its hexafluorophosphate salt. The product was filtered and washed with water (3 × 10 mL) and dried. Yield: 0.366 g, 83 %, Anal. Calc. for $C_{46}H_{34}Cl_2F_{12}N_8P_2Ru$: C, 47.60; H, 2.95; N, 9.65. Found: C, 47.57; H, 2.93; N, 9.62; ESI-MS: m/z 435.4 $(M - 2PF_6)^{2+}$; IR, cm^{-1} (KBr pellet) 3717, 3047, 2363, 1516, 844; UV-Visible λ_{max}, nm (ε, $M^{-1}cm^{-1}$) 462(7400), 346(19350), 292(52350), 244(43400).

2.4 DPPH Free Radical Scavenging Activity

1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical having maximum optical absorbance at 517 nm. A stock solution (1 mg/mL) was diluted to final concentrations of 20-100 µg/mL. An ethanolic DPPH solution was added to sample solutions in DMSO at various concentrations (20-100 µg/mL). The test tubes were kept at an ambient temperature for 30 minutes. The absorbance of the sample solutions containing ligands and their ruthenium complexes were measured at 517 nm using UV-Visible spectrophotometer. These measurements were run in triplicate. The percentage of scavenging activity was calculated as follows:

$$\text{Scavenging activity (\%)} = [(A_{DPPH} - A_{TEST})/A_{DPPH}] \times 100$$

Where, A_{DPPH} is the absorbance of DPPH without test sample (control) and A_{TEST} is the absorbance of DPPH in the presence of test sample.

3. Results and Discussion:

3.1 Synthesis and Characterization:

The complex (Figure 1) has been isolated as its hexafluorophosphate salt and characterized by various techniques such as FT-IR, UV-Visible, ESI-MS, elemental analyses, cyclic and differential pulse voltammetries. The analytical data (Table 1) obtained are in good agreement with the proposed molecular formulae. The mass spectra of the complexes $[Ru(bpy)_2(L2)](PF_6)_2$ displayed base peaks at 435.39 respectively. These peaks are reliable with the proposed molecular formulae of the corresponding ruthenium (II) complexes. The electronic spectra of all the complexes were recorded in acetonitrile and the results are listed in Table 1.

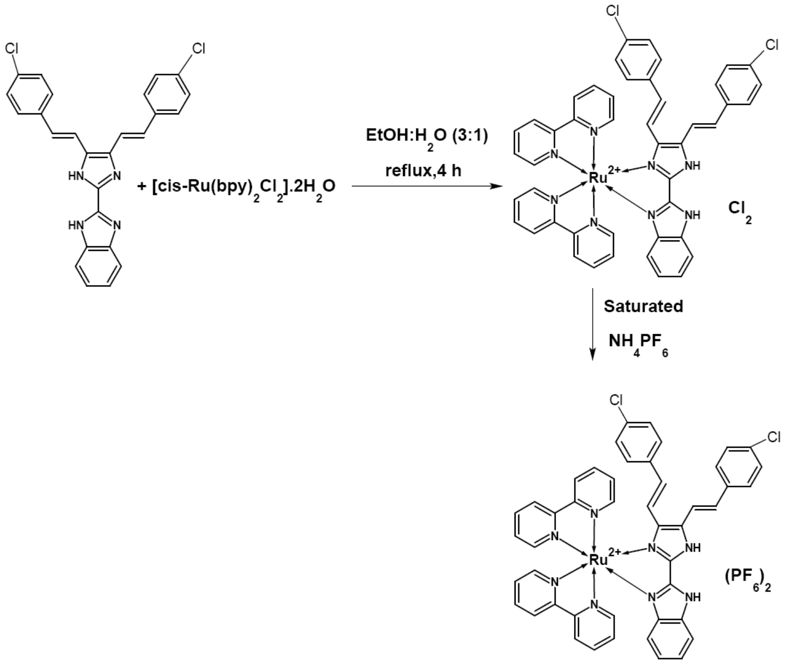

Figure 1: Synthetic route of ruthenium (II) complex

In the IR spectra of all the ligand, sharp band observed in the region of 1524 cm^{-1} has been assigned to $\nu_{C=C}$ stretching frequency. Upon coordination these bands have been shifted around 1516 cm^{-1} thereby indicating the coordination of the ligand with the ruthenium metal. The electrochemical features of the mononuclear ruthenium(II) complex 1 was investigated in acetonitrile by employing cyclic voltammetry(CV) and differential pulse voltammetry(DPV) on a glassy carbon working electrode. The redox parameters of these complexes are listed in Table 1.

Table 1: Electronic and electrochemical data of mononuclear ruthenium (II) complexes in acetonitrile solution at 25 ± 0.2 °C

Complex	λ_{max}, nm (ε, $M^{-1}cm^{-1}$)	$E_{p,a}$(V)	$E_{p,c}$(V)	ΔE_p(mV)	$E_{1/2}$ Ru^{II}/Ru^{III} *vs* SCE	
					CV (V)	DPV (V)
$[Ru(bpy)_2(L2)](PF_6)_2$	462 (7400) 346(19350) 292(52350) 244(43400)	1.1092	0.9964	112	1.0528	1.0489

The present complex exhibits a quasi-reversible metal-based oxidative response with $E_{1/2}$ value of +1.0528 V with the peak separation of 112 mV. Further, the $E_{1/2}$ value of the present complex has been found to be lower than the analogous imidazole based complexes, which may be attributed to the electron withdrawing benzimidazole moiety present in the synthesized complex.

3.2 Investigation of Antioxidant Activity:

The free radical scavenging ability of the metal complexes was determined by their interaction with the stable free radical 2, 2'-diphenyl-1-picryl hydrazyl.

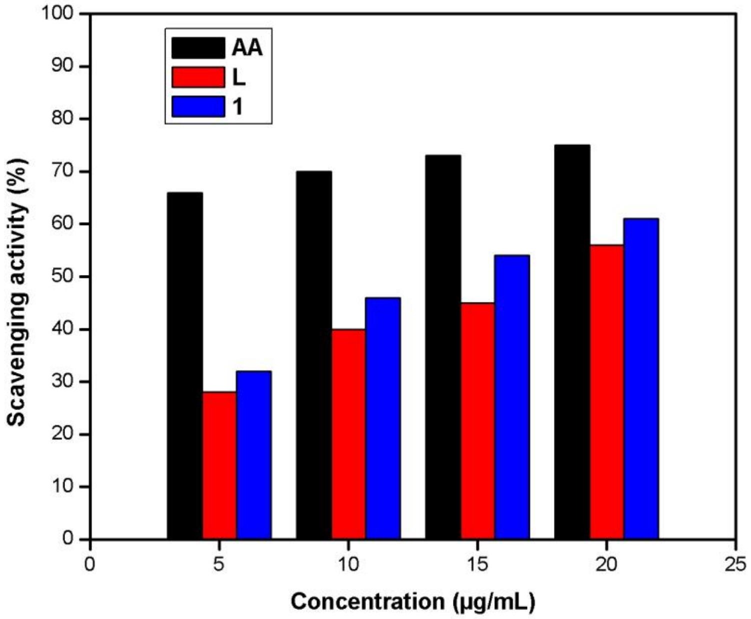

Figure 3: Antioxidant activity of ligand and its ruthenium(II) complex

The ligand and its metal complex were screened for the reduction of DPPH at the concentrations of 5-20 μg/mL. The antioxidant activity results are shown at Figure 3 and compared with the control standard AA. A graph may be plotted with % scavenging effects on the y- axis and concentration (μg/mL) on the x- axis. The synthesized ruthenium complex exhibit better antioxidant activity compared to that of its ligand. When compared to standard ascorbic acid, the antioxidant activity of the newly synthesized complex shows the least activity.

4. Conclusions:

A new mixed ligand ruthenium (II) complex has been derived from ligand containing benzimidazole moiety and the new compounds have been characterized by various spectral techniques and the redox property of the complex has been studied using cyclic and differential pulse voltammetry techniques. DPPH assay mentioned the complex showed better antioxidant activity against the corresponding ligand.

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