ORIGINAL ARTICLE

Synthesis, spectral studies and electrochemical properties of ruthenium(II) complex with the new bidentate ligand 5-Chloro-2-(phenylazo)pyridine

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Abstract

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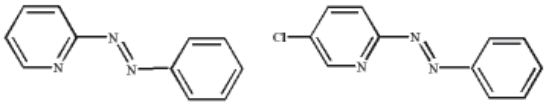
5-Chloro-2-(phenylazo)pyridine (Clazpy) was synthesized as a new bidentate ligand, containing an azo moiety. Its structure was similarly to 2-(phenylazo)pyridine (azpy) but the hydrogen atom on the fifth position on the pyridine ring was replaced by a chlorine atom. The $[Ru(Clazpy)_3](PF_6)$ complex was prepared from the reaction between *ctc*-$[Ru(Clazpy)_2Cl_2]$ with the Clazpy ligand in methanol. The $[Ru(Clazpy)_3](PF_6)_2$ complex was characterized by elemental analysis, IR and ^1H NMR data. Electronic absorption spectra in various solvents exhibit strong metal-to-ligand charge transfer (MLCT) bands at 490-550 nm. Results from cyclic voltammetry show that the bidentate Clazpy ligand is a better π-acceptor than azpy in order to stabilize Ru(II) center.



azpy Clazpy

Key words : ruthenium, azopyridine, π-acceptor

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บทคัดย่อ

ลักษมี สหวิศิษฏ์ และ ขนิษฐา หาญสูงเนิน

การสังเคราะห์ การยืนยันโครงสร้าง และคุณสมบัติทางไฟฟ้าเคมีของสารประกอบเชิงซ้อนของรูทีเนียมกับลิแกนด์ไบเดนเทตชนิดใหม่ 5-Chloro-2-(phenylazo)pyridine

ว. สงขลานครินทร์ วทท. ธ.ค. 2548 27(ฉบับพิเศษ 3) : 751-759

ได้สังเคราะห์ลิแกนด์ไบเดนเทตชนิดใหม่ที่มีหมู่เอโซร่วมด้วยคือ 5-Chloro-2-(phenylazo)pyridine (Clazpy) โครงสร้างของลิแกนด์ Clazpy คล้ายคลึงกับลิแกนด์ 2-(phenylazo)pyridine (azpy) ต่างกันตรงที่อะตอมไฮโดรเจนตำแหน่งที่ห้าบนวงแหวนพิริดีนถูกแทนที่ด้วยอะตอมคลอรีน สารประกอบเชิงซ้อนของรูทีเนียม $[Ru(Clazpy)_3](PF_6)_2$ เตรียมจากปฏิกิริยาระหว่าง *ctc*-$[Ru(Clazpy)_2Cl_2]$ กับลิแกนด์ Clazpy ในตัวทำละลายเมทานอล โครงสร้างของสารประกอบเชิงซ้อน $[Ru(Clazpy)_3](PF_6)_2$ นี้ถูกยืนยันโดยข้อมูลจากเทคนิคการวิเคราะห์หาปริมาณธาตุที่เป็นองค์ประกอบ (elemental analysis) อินฟราเรด และนิวเคลียร์แมกเนติกเรโซแนนซ์สเปกโทรสโกปี ศึกษาแถบการดูดกลืนแสงของสารในตัวทำละลายต่าง ๆ พบแถบการดูดกลืนแบบถ่ายโอนประจุจากโลหะไปยังลิแกนด์ปรากฏที่ความยาวคลื่น 490-550 นาโนเมตร ผลจากข้อมูลไซคลิกโวลแทมเมทรีพบว่าลิแกนด์ Clazpy เป็นตัวรับไพอิเล็กตรอน (π-acceptor) ที่ดีกว่า azpy ในการรักษาเสถียรภาพของรูทีเนียม(II)

ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ อำเภอหาดใหญ่ จังหวัดสงขลา 90112

Since the discovery of antitumor activity of cisplatin (*cis*-diamminedichloro-platinum(II), *cis*-$[PtCl_2(NH_3)_2]$, many other metal complexes have been investigated for their possible applications as antitumor drugs (Zhang and Lippard, 2003). At present several ruthenium complexes are known for their cytotoxic or antitumor activities (Clarke, 2002). For example, the isomers of $[Ru(azpy)_2Cl_2]$, where azpy is 2-(phenylazo)pyridine, were found to be reactive as anticancer agents, especially, the *ctc*-$[Ru(azpy)_2Cl_2]$ complex (*ctc*-indicating the coordinating chlorides, the pyridine nitrogens and the azo nitrogens in mutual cis, trans and cis orientation) or α-$[Ru(azpy)_2Cl_2]$. This isomer has shown a remarkably high in vitro cytotoxicity in many cell lines such as MCF-7 (breast cancer), IGROV (ovarian cancer) and H226 (nonsmall cell lung cancer) (Velder *et al*., 2000). The water-soluble compound α-$[Ru(azpy)_2(NO_3)_2]$ has also been developed. However, its cytotoxicity compared to α-$[Ru(azpy)_2Cl_2]$ was decreased approximately by a factor of 10^9 (Hotze *et al*., 2000). Recently, replacing the chlorine atoms of α-$[Ru(azpy)_2Cl_2]$ by a bidentate ligand gave rise to $[Ru(azpy)_2L](PF_6)_2$ (where L = azpy and bpy (2, 2′-bipyridine) (Hotze *et al*., 2005). These complexes show moderate cytotoxicity in MCF-7 (breast cancer) and M19 MEL (melanoma). Therefore, it is our interest to synthesize a new azo compound, 5-Chloro-2-(phenylazo)pyridine, to form a similar type of ruthenium complex $[Ru(Clazpy)_3](PF_6)_2$. We describe here the synthesis, structural characterization, redox activity and absorption spectroscopic properties of this compound.

Materials and Methods

Materials

Ruthenium trichloride was purchased from Fluka, and was digested three times with concentrated HCl before use. The synthesis of the ligand 5-Chloro-2-(phenylazo)pyridine from reaction between nitrosobenzene and 5-Chloro-2-aminopyridine was performed as modification of the synthesis of 2-(phenylazo)pyridine (Krause and Krause, 1980). The synthesis of α-$[Ru(Clazpy)_2Cl_2]$ complex was done analogously to that of the α-$[Ru(azpy)_2Cl_2]$ complex, as described previously (Hansongnern and Sahavisit, 2004). All other chemicals and solvents were of reagent grade and

were used without further purification. Ferrocene and tetra-*n*-butylammonium hexafluorophosphate (TBAH) for electrochemical work were obtained from Aldrich.

Instrumentation

Microanalytical data (C, H, N) were collected using a Carlo Erbra EA 1108 elemental analyzer. Fast atom bombardment mass spectra were recorded on a VG Autospec instrument. Infrared (IR) spectra were obtained on a Perkin Elmer Spectrum GX FT-IR spectrophotometer. UV/Visible spectra were recorded on a Hewlett Packard 8425A diode array spectrophotometer. 1D and 2D NMR spectra in acetone-d_6 were collected on a Varian UNITY SNOVA 500 MHz FT-NMR spectrometer using tetramethylsilane (SiMe4) as an internal reference.

Electrochemical measurements were performed by using Cyclic voltammetric technique with EChem 1.5.1 program. Cyclic voltammograms were obtained using a glassy carbon as the working electrode, a platinum wire as the auxiliary electrode, and a platinum disc as the reference electrode. The supporting electrolyte was 0.1 M TBAH in acetronitrile. At the end of each experiment, ferrocene was added as an internal standard. All potentials were quoted vs the ferrocene/ferricinium couple.

Procedures

Synthesis of the 5-Chloro-2-(phenylazo) pyridine (Clazpy) ligand

The 5-Chloro-2-(phenylazo)pyridine ligand was prepared by condensation of 5-chloro-2-aminopyridine (378 mg, 2.94 mmol) and nitrosobenzene (318 mg, 2.97 mmol) in benzene solution in the presence of sodium hydroxide. The mixture was refluxed for 12 h which gradually became dark brown. The product was extracted with benzene and purified by column chromatography on a silica gel. The orange band was collected after elution with dichloromethane and hexane (1:9 by volume) and evaporated to dryness. The yield was 354 mg (54%). Anal. Calcd. for $C_{11}H_8N_3Cl$: C, 60.70, N, 19.30: H, 3.70. Found: C, 60.06; N, 19.31; H, 3.49. IR (KBr); ν(N=N), 1364 cm^{-1}, ν(C-Cl), 547 cm^{-1}

Synthesis of *ctc*-[Ru(Clazpy)$_2$Cl$_2$]

ctc-[Ru(Clazpy)$_2$Cl$_2$] was synthesized by reaction of $RuCl_3.3H_2O$ (22 mg, 0.106 mmol) and Clazpy (46 mg, 0.212 mmol). The solution was refluxed in 25 mL of dimethylformamide for 40 min. The solution mixture was filtered and solvent was removed. The crude product was purified by column chromatography on a silica gel with toluene-CH_3CN (9:1 V/V) as eluent. The mainly blue band was collected. The solvent was removed and a blue solid was obtained. The yield was 28 mg (50 %). Anal. Calcd. for $RuCl_4C_{22}H_{16}N_6$: C, 43.51, N, 13.84: H, 2.65. Found: C, 44.14; N, 13.88;H, 2.58. IR (KBr); ν(N=N), 1336 cm^{-1}, ν(C-Cl), 601 cm^{-1}

Synthesis of [Ru(Clazpy)$_3$](PF$_6$)$_2$

[Ru(Clazpy)$_3$](PF6)$_2$ was prepared by reaction of *ctc*-[Ru(Clazpy)$_2$Cl$_2$] (25 mg, 0.04 mmol), Clazpy (13 mg, 0.06 mmol) and $AgNO_3$ (15 mg, 0.09 mmol). The solution was refluxed in 50 mL of methanol for 6 h and filtered while hot. NH_4PF_6 was added to the filtrate, and the mixture was heated further for 1 h. After 4 days, the product was collected as brown solid in 70% yield. Anal. Calcd. for $RuC_{33}H_{24}N_9C_{13}P_2F_{12}$:C, 37.27, N, 12.08: H, 2.32. Found: C, 37.54; N 12.54; H, 2.32. IR (KBr); ν(N=N), 1368 cm^{-1}, ν(C-Cl), 558 cm^{-1}.

Results and Discussion

Synthesis

5-Chloro-2-(phenylazo)pyridine (Clazpy) is an unsymmetric N,N$^/$-chelating bidentate ligand. The nitrogen donor atoms are from pyridine (N_{py}) and azo (N_{azo}) functional groups. The [Ru(Clazpy)$_3$](PF$_6$)$_2$ complex was synthesized by replacing two chloride atoms in α-[Ru(Clazpy)$_2$Cl$_2$] with Clazpy via $AgNO_3$ assisted route. The equation is shown.

$$\alpha - [Ru(Clazpy)_2Cl_2] + Clazpy \xrightarrow[(2)NH_4PF_6]{(1)Ag^+,MeOH} [Ru(Clazpy)_3](PF_6)_2 + 2AgCl$$

After AgCl was filtered off, the product was collected. The composition of the complex was

confirmed by elemental analysis.

Spectral characterization

IR spectra of Clazpy and the $[Ru(Clazpy)_3](PF_6)_2$ complex displayed many characteristic frequencies in the range 4000-400 cm^{-1}. The important functional groups C=N, C=C and N=N stretching mode were observed in this range. From IR data, the Clazpy ligand showed the N=N stretching vibration at 1364 cm^{-1}, whereas the N=N stretching mode of azpy ligand appeared at 1421 cm^{-1} (Krause and Krause, 1980). This indicated that the electron delocalized into the π^* orbital of the azo function in Clazpy was greater than that in azpy due to the effect of substituent chloride at the fifth position on the pyridine ring. In the case of $[Ru(Clazpy)_3](PF_6)_2$ and $[Ru(azpy)_3](PF_6)_2$, the N=N stretching mode occurred at 1368 cm^{-1} and 1360 cm^{-1} (Changsaluk, 2003), respectively. In general, the N=N stretching mode in the complex occurred at lower frequencies than that in the free ligand due to $t_{2g} \rightarrow \pi^*$ (azo) donation (π-back bonding). In addition, $[Ru(bpy)_3]^{2+}$ (Tempiam, 2002) displayed C=N, C=C stretching modes at 1601 cm^{-1} and 1535 cm^{-1}, respectively, whereas in $[Ru(phen)_3]^{2+}$ (Rattanawit, 2002) these were observed at 1599 cm^{-1} and 1424 cm^{-1}, respectively.

Electronic spectra of $[Ru(Clazpy)_3](PF_6)_2$ were recorded in both UV and visible regions in seven different solvents; dichloromethane (CH_2Cl_2), methanol (MeOH), ethanol (EtOH), acetone, acetonitrile (CH_3CN), dimethyl sulfoxide (DMSO) and N, N′-dimethylformamide (DMF) and all data are summarized in Table 1. The Clazpy ligand exhibits two absorption bands in the range 320-350 nm ($\varepsilon \approx 20{,}000\ M^{-1}cm^{-1}$) and 440-460 nm ($\varepsilon \approx 500\ M^{-1}cm^{-1}$). These are assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively (Hansongnern and Sahavisit, 2003). The spectrum of $[Ru(Clazpy)_3](PF_6)_2$ displays two absorption bands in the range 200-390 nm ($\varepsilon \approx 45{,}000\ M^{-1}cm^{-1}$) and 440-550 nm ($\varepsilon \approx 15{,}000\ M^{-1}cm^{-1}$). These are assigned to intraligand and metal-to-ligand charge -transfer (MLCT) transitions. In addition, the lowest energy absorption band of $[Ru(Clazpy)_3](PF_6)_2$ was slightly shifted, when the polarity of solvents was increased.

The ^1H NMR spectrum of $[Ru(Clazpy)_3](PF_6)_2$ (500 MHz) was obtained in acetone-d_6 and tetramethylsilane (TMS, $SiMe_4$) was used as internal reference. The proton numbering pattern of the complex is shown in Figure 1 (these have been denoted as Clazpy ligand A, B and C). The NMR spectroscopic data of $[Ru(Clazpy)_3](PF_6)_2$ and the free ligand are summarized in Table 2. The ^1H NMR spectrum of $[Ru(Clazpy)_3](PF_6)_2$ is shown in Figure 2 where 12 resonances (24 protons) can be observed and some appear to be multiplet signals due to overlap of resonances.

From ^1H-^1H COSY NMR (Figure 3) the three sets of Clazpy pyridine signals have been distinguished. Since two of the three Clazpy pyridine rings (B and C) are trans to each other, the positions of protons are slightly different similar to

Table 1. The electronic absorption spectral data of $[Ru(Clazpy)_3](PF_6)_2$ in different solvents.

solvents	λ_{max}, nm (ε^a x10^{-4}, $M^{-1}cm^{-1}$)
CH_2Cl_2	233(3.38), 392(5.04), 494(1.57)
MeOH	210(4.90), 383(4.30), 493(1.32)
EtOH	207(2.71), 276(2.32), 385(2.32), 492(0.73)
Acetone	383(3.94), 494(1.30)
CH_3CN	203(4.93), 383(4.29), 493(1.34)
DMSO	282(4.16), 383(4.78), 498(1.72)
DMF	278(4.22), 371(4.22), 526(2.46)

[a]**Molar extinction coefficient**

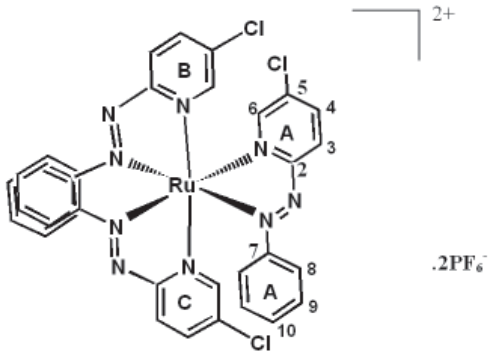

Figure 1. The structure and atom numbering scheme of $[Ru(Clazpy)_3](PF_6)_2$.

Table 2. ^1H and ^{13}C NMR assignments of Clazpy and $[Ru(Clazpy)_3](PF_6)_2$ [500 MHz, in acetone-d_6].

Position (free Clazpy)	δ_H(ppm), Multiplicity, *J* in Hz	Position (complex)	δ_H(ppm), Multiplicity, *J* in Hz	δ_C(ppm)
H3	7.81, 1H, dd, 8.5, 0.5 Hz	H3A	9.29, 1H, d, 9.0 Hz	133.3
H6	8.69, 1H, dd, 2.5, 0.5 Hz	H6A	8.96, 1H, d, 2.0 Hz	152.5
H4	7.87, 1H, dd, 8.5, 2.5 Hz	H4A	8.76, 1H, dd, 9.0, 2.0 Hz	142.5
		H3, 3	8.74, 2H, d, 8.5 Hz	131.5
		H4	8.62, 1H, dd, 8.5, 2.0 Hz	143.0
		H4	8.60, 1H, dd, 8.5, 2.0 Hz	151.5
		H6	8.58, 1H, d, 2.0 Hz	142.0
		H6	8.51, 1H, d, 2.0 Hz	141.5
H10, 9	7.54, 3H, m	H10, 10	7.68, 2H, t, 8.0 Hz	134.5
		H9, 9	7.57, 4H, t, 8.0 Hz	130.5
H8	8.04, 2H, m	H8, H10A	7.53, 3H, m	134.5
		H8	7.48, 2H, d, 8.0 Hz	124.0
		H9A	7.40, 2H, t, 8.0 Hz	130.0
		H8A	7.10, 2H, d, 8.0 Hz	124.0

the situation of the $[Ru(azpy)_3](PF_6)_2$ complex (Hotze *et al*., 2005). In contrast to the protons in the Clazpy pyridine ring (A), the chemical shift appeared at the lowest field due to trans to N=N azo function. These data confirm the configuration of N(py) and N(azo) orientation from the starting material, *ctc*-$[Ru(Clazpy)_2Cl_2]$. In addition, the protons H3, H4 and H6 appear at lower downfield than protons H8, H9 and H10. This may be due to the pyridine protons having less electron density than the phenyl protons.

The ^{13}C NMR signals assignments (Figure 4) were based on the ^1H - ^{13}C HMQC spectrum (Figure 5) which is generally used for studying large and complicated molecules. The ^{13}C NMR spectrum showed 14 signals from 24 methine carbons and three signals of six quaternary carbons. The signals at 162.59, 139.54 and 135.34 ppm were assigned to the quaternary carbons C2, C5 and C7, respectively. Since C2 was located between nitrogen atoms, the chemical shift occurred at the lowest field. It is noted that chemical shifts of the complex move to downfield compared to those of the free ligand.

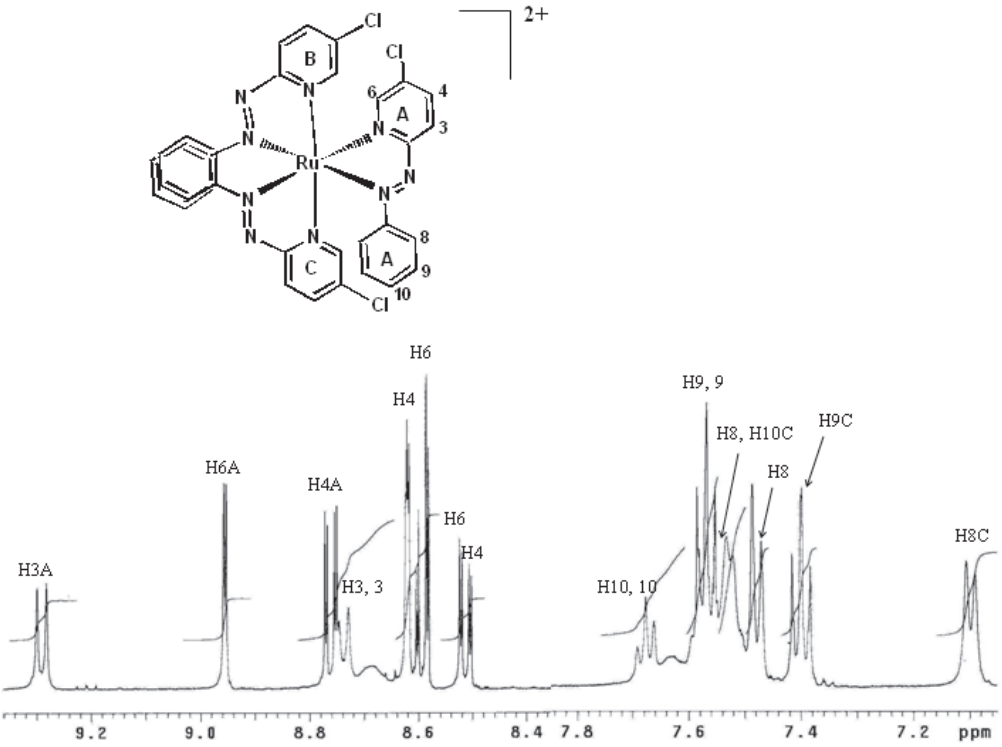

Figure 2. ^{1}H NMR spectrum of [Ru(Clazpy)$_3$](PF$_6$)$_2$ in acetone-d_6.

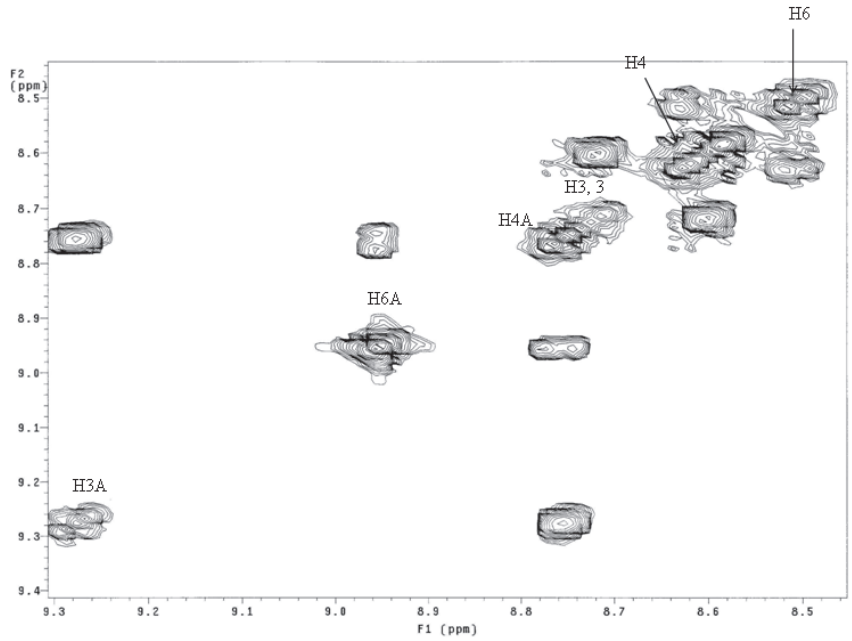

Figure 3. ^{1}H-^{1}H COSY NMR spectrum of [Ru(Clazpy)$_3$](PF$_6$)$_2$ in acetone-d_6.

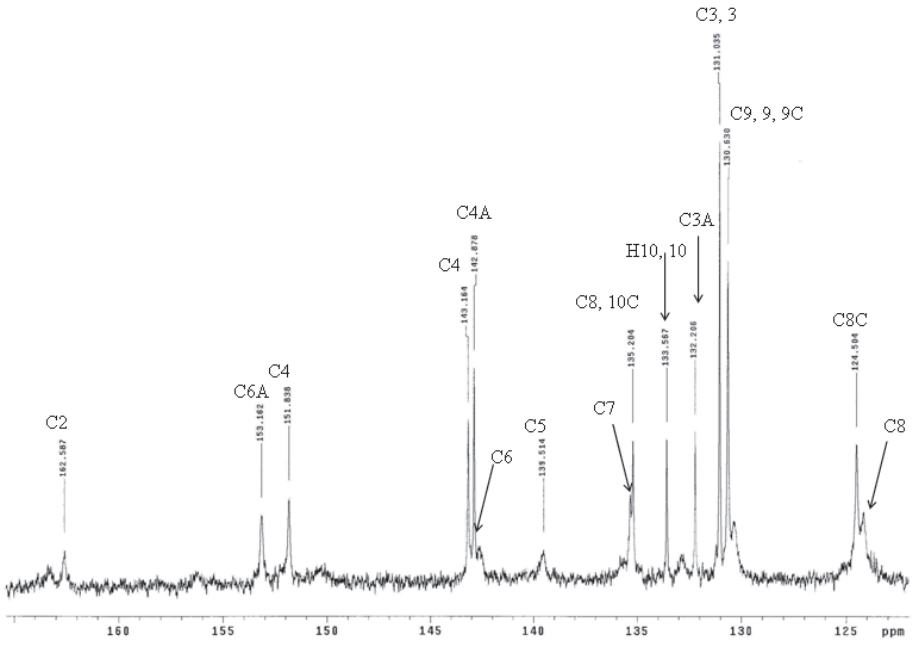

Figure 4 ^{13}**C NMR spectrum of [Ru(Clazpy)$_3$](PF$_6$)$_2$ in acetone-*d*$_6$.**

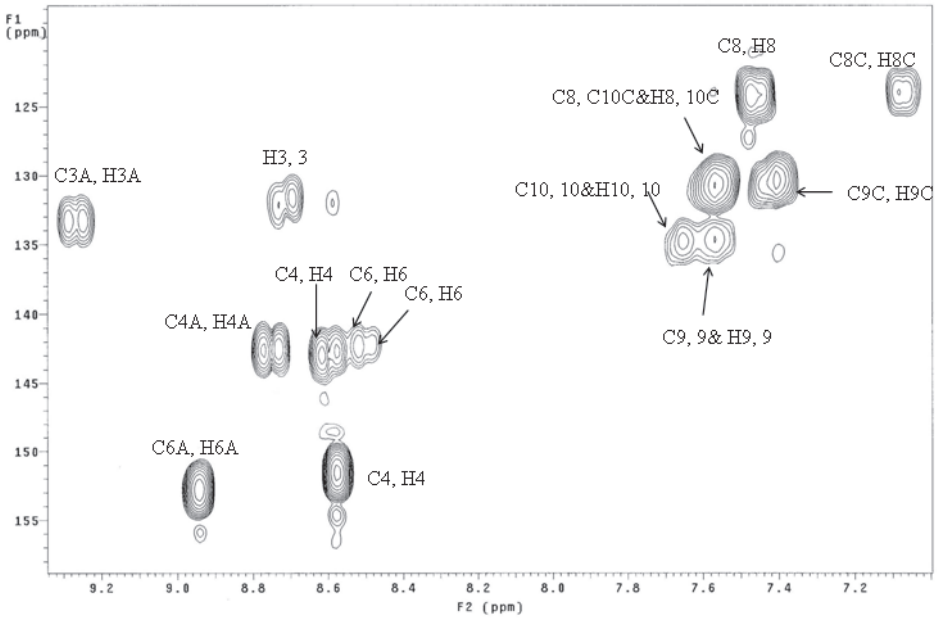

Figure 5. ^{1}**H-**^{13}**C HMQC NMR spectrum of [Ru(Clazpy)$_3$](PF$_6$)$_2$ in acetone-*d*$_6$.**

Electrochemistry

Electrochemical studies were measured in the potential range +2.00 V to -2.60 V in acetonitrile. The cyclic voltammetric data of [Ru(Clazy)$_3$](PF$_6$)$_2$ are summarized in Table 3. The cyclic voltammogram of [Ru(Clazy)$_3$](PF$_6$)$_2$ displayed reduction couples at the negative potential. These were assigned to the reductions of co-

Table 3. Cyclic voltammetric data of $[Ru(Clazpy)_3](PF_6)_2$ and other complexes in 0.1 M TBAH acetronitrile at scan rate 50 mV/s. (ferrocene was used as internal standard).

Compounds	$E_{1/2}$, V						
	Oxidation	Reduction					
		I	II	III	IV	V	VI
$[Ru(Clazpy)_3]^{2+}$	n	-0.32	-0.60	-1.05	-1.70	-2.03[a]	-2.52[b]
[c]$[Ru(azpy)_3]^{2+}$	n	-0.39	-0.70	-1.14	-1.78	-1.98	-
[d]$[Ru(bpy)_3]^{2+}$	+0.91	-1.74	-1.93	-2.17	-	-	-
[e]$[Ru(phen)_3]^{2+}$	+0.89	-1.80	1.89[a]	-	-	-	-

n = cannot be observed
[a] anodic peak (E_{pa}), [b] cathodic peak (E_{pc})
[c] Changsaluk, U. 2003, [d] Tempiam, S. 2002, [e] Rattanawit, N. 2002.

ordinated azo (-N=N-) groups. The N=N function in the azopyridine ligand was known to be a potential electron transfer center and could accept a maximum of two electrons. In addition, it was well documented in literature that the azopyridine ligands were better π-acceptor and underwent easier reduction than those of the pyridine ligands (Krause and Krause, 1980).

Since three of the -N=N- functional groups were present in the $[Ru(Clazpy)_3]^{2+}$ complex and LUMO was primarily dominated by the -N=N- function, five successive one electron azo reduction were expected. In this work, five reductions (near -0.32, -0.60, -1.05, -1.70, -2.03 and the cathodic peak at -2.52 V) have been observed within the specified potential range. In addition, the first reduction potential can be used to determine π-accepting ability of ligand. From previous studies, the first reduction potential appears at -0.39 V for $[Ru(azpy)_3]^{2+}$ (Changsaluk, 2003) and -1.80 V for $[Ru(phen)_3]^{2+}$ (Rattnawit, 2002) and -1.74 V for $[Ru(bpy)_3]^{2+}$ (Tempiam, 2002). To compare this ability we should focus at the first reduction potential, which can be arranged in order as follows:

Clazpy > azpy > bpy > phen

In the oxidation range, the couple of Ru(II)/(III) of $[Ru(Clazpy)_3]^{2+}$ cannot be observed because the redox of Ru(II/III) could occur at positive potential greater than +2.00 V which is out of the solvent window.

Conclusion

In this work, the synthesis and characterization of the new ligand 5-Chloro-2-(phenylazo) pyridine (Clazpy) and the corresponding ruthenium(II) complex have been described. The $[Ru(Clazpy)_3]^{2+}$ was isolated as hexafluorophosphate salt, $[Ru(Clazpy)_3](PF_6)_2$. This complex was characterized by elemental analysis and spectroscopic techniques and its structure was determined by 1D and 2D NMR. The cyclic voltammetric results show that the first reduction couple of the Clazpy complex occurred at higher positive value than that of the polypyridine complexes containing bpy and phen ligands. Therefore, Clazpy is the strongest π-acceptor as compared to bpy and phen. For the furture work, anticancer activity of this complex is planned to be investigated by testing with cell lines.

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