NOVEL COMPLEXES OF RUTHENIUM(III) WITH SCHIFF BASES AND INDAZOLE – SYNTHESIS AND CHARACTERIZATION

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ABSTRACT

Two novel cationic Ru(III) complex compounds with Schiff bases, *N*-phenyl-5-*X*-salicylideneimine (where *X* = H or Br) and indazole have been synthesized and characterized by various spectral and electrochemical analysis. The existence of molecular ions M^+ at *m/z* 730.1652 and 887.9818 corresponding to $[C_{40}H_{32}N_6O_2Ru]^+$ and $[C_{40}H_{30}Br_2N_6O_2Ru]^+$, respectively, was obtained by mass spectra analysis. The coordination of the ligands in the Ru(III) octahedral environment occurs through imine nitrogen, deprotonated phenolic oxygen atom from the Schiff bases as well as *via* the free electronic pair on the nitrogen atom in indazole. Furthermore, the effect of the cationic Ru(III) complexes on the Briggs-Rauscher oscillating reaction was preliminary studied and monitored potentiometrically.

Keywords: Ru(III) complex, Schiff base, indazole, Briggs-Rauscher, oscillation

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INTRODUCTION

Schiff bases as a compound with azomethine linkage ($-C=N-$) are versatile and very popular ligands for metal coordination^{1,2}. Since Schiff bases show diverse biological activity, a significant number of metal complexes with various ligands have been synthesized and their activities against different targets have been investigated³⁻⁸. Antibacterial, antifungal, antiviral, antioxidant and cytotoxic activities have been reported^{1,9-12}. Ruthenium(III) complexes are of immense interest regarding their kinetic inertness¹³. Some ruthenium(III) complexes containing ON or ONS donor atoms were synthesized in our laboratory regarding interaction with DNA or genotoxic activity have been previously reported^{4,5,14}. Ru(III) complexes containing indazole, imidazolium *trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)] (KP1019) and sodium *trans*-[tetrachlorobis(1*H*-indazole)ruthenate(III)] (NKP-1339) have proofed an extraordinary antiproliferative properties and entered clinical trials¹⁵. The indazole ring system is a partial component of a huge number of biologically active compounds and most of them exhibit a broad spectrum of bioactivities^{16,17}. Interaction of cationic complex Ru(III) containing indazole and Schiff base derived from 5-chlorosalicylaldehyde and aniline with DNA by spectrophotometric titration according to the calculated binding constant indicated non-covalent binding and was described as a major groove binding¹⁸. In this study, synthesis, characterization and the effect on the Briggs-Rauscher oscillating reaction of new Ru(III) cationic complexes with indazole and Schiff bases derived from salicylaldehyde or 5-bromosalicylaldehyde and aniline were reported. This is a continuation of the research activities of the synthesis and characterization of ruthenium(III) complexes with Schiff bases and *N*-heterocycles.

EXPERIMENTAL

Materials and Methods

All chemicals were of analytical grade, purchased from commercial suppliers. The matrix-assisted laser desorption/ionization (MALDI) mass spectrometer, 4800 Plus TOF/TOF (time-of-flight) (Applied

Biosystems Inc., Foster City, CA, USA) was used for obtaining the mass spectra. A small amount of complex was mixed with 10 μL of 2,6-dihydroxyacetophenone (5 mg/mL) and 1 μL was loaded on MALDI plate. Acquisitions were performed in negative ion reflection mode using thiamine mononitrate, azithromycin and angiotensin or positive mode with riboflavin and trypsin as internal standards. Mass spectra were obtained at mass range m/z 10 to 1000 Da (focus mass 500 Da, delay time 300 ns). Infrared spectra have been obtained at a BX FTIR Perkin Elmer Spectrum System in the range from 4000 to 400 cm^{-1} with samples prepared as potassium bromide (KBr) pellets. Electronic spectra were recorded in CH_2Cl_2 using Perkin Elmer UV/Vis spectrometer model Lambda 35 in the 900 – 200 nm range. Cyclic voltammetry was performed by Autolab potentiostat/galvanostat PGSTAT 12 electrochemical analyzer equipped with three electrodes assembly. Glassy carbon (GC) was used as a working electrode, silver/silver chloride (Ag/AgCl) as a reference while platinum (Pt) wire was an auxiliary electrode. The cyclic voltammograms were recorded in acetonitrile (MeCN) at 0.2 Vs^{-1} scan rate. Tetraethyl ammonium bromide (Et_4NBr) was used as a supporting electrolyte. The Briggs Rauscher reaction mixture contained suitable volumes of an aqueous solution of hydrogen peroxide, potassium iodate, sulphuric acid, malonic acid, manganese(II) sulfate and starch. Oscillations in the Briggs-Rauscher reaction mixture were monitored potentiometrically by recording the potential changes of a Pt electrode versus Ag/AgCl electrode at 25°C.

Synthesis of Cationic Compounds

The preparation of diindazole-bis-[*N*-phenyl-salicylideneiminato-*O,N*)ruthenium(III) chloride, $[\text{Ru}(\text{N-Ph-salim})_2(\text{ind})_2]\text{Cl}$, hereafter **Compound 1** and diindazole-bis-[*N*-phenyl-5-bromosalicylideneiminato-*O,N*)ruthenium(III) chloride, $[\text{Ru}(\text{N-Ph-5-Br-salim})_2(\text{ind})_2]\text{Cl}$, hereafter **Compound 2** was carried out by heating under reflux an ethanol solution of sodium dichlorobis[*N*-phenyl-5-*X*-salicylideneiminato-*N,O*)ruthenate(III) (0.1 mmol) where *X* = H, hereafter Starting compound 1 (58.7 mg) or Br, hereafter Starting compound 2 (74.5 mg) with an ethanol solution of indazole (0.2 mmol; 23.6 mg) (molar ratio of Ru(III) starting compound:indazole = 1:2). The mixtures were refluxed for seven hours at 75°C until the color changed from dark purple to blue-purple and from dark green to petroleum green for Compound 1 and 2, respectively. The final solution volumes were reduced by vacuum distillation to approximately 10 mL and kept in an ice-salt bath for one week. The precipitated complexes were filtered off and washed with water until the negative reaction on chloride ions. The products were vacuum dried in desiccators.

Compound-1: Yield: 53%; MALDI TOF/TOF MS (m/z) calcd for $[\text{C}_{40}\text{H}_{32}\text{N}_6\text{O}_2\text{Ru}]^+$, 730.1625; found, 730.1652; IR (KBr, cm^{-1}) 3434 [$\nu(\text{N-H})$], 1695 [$\nu(\text{C=N})$], 1356 m [$\nu(\text{C-N})$], 1082 [$\nu(\text{N-N})$], 664 w [$\nu(\text{Ru-N})$], 423 w [$\nu(\text{Ru-O})$]; UV-Vis (CH_2Cl_2 , λ/nm) 235, 283, 578.

Compound-2: Yield: 61%; MALDI TOF/TOF MS (m/z) calcd for $[\text{C}_{40}\text{H}_{30}\text{Br}_2\text{N}_6\text{O}_2\text{Ru}]^+$, 887.9828; found, 887.9818; IR (KBr, cm^{-1}) 3435 [$\nu(\text{N-H})$], 1706 [$\nu(\text{C=N})$], 1356 m [$\nu(\text{C-N})$], 1081 [$\nu(\text{N-N})$], 662 w [$\nu(\text{Ru-N})$], 414 w [$\nu(\text{Ru-O})$]; UV-Vis (CH_2Cl_2 , λ/nm) 245, 282, 350, 574.

RESULTS AND DISCUSSION

Synthesis

The starting compounds 1 and 2 were prepared according to the published procedures that involved adding ethanol solution of suitable Schiff base, *N*-phenyl-5-*X*-salicylideneimine where *X* = H or Br (2 mmol) to an ethanol solution of ruthenium(III) chloride (1 mmol) followed by heating under reflux for 3 hours at 65°C. Addition of one millilitre of 2 mmol (0.117 g) NaCl was made in order to precipitate the starting compounds^{14,19}.

Novel cationic Ru(III) complexes, $[\text{Ru}(\text{N-Ph-5-X-salim})_2(\text{ind})_2]\text{Cl}$, where *X* = H or Br and ind = indazole, have been synthesized from ethanol solutions of starting compounds (0.1 mmol) and indazole (0.2 mmol) in molar ratio 1:2 as shown in Fig.-1. In relative moderate reaction conditions indazole replaced two easily outgoing chloride ions in the starting compounds. New cationic Ru(III) complexes were indigo blue

(Compound 1) and green (Compound 2), air and light resistant, soluble in acetonitrile (MeCN), dimethylformamide (DMF), dimethyl sulphoxide (DMSO) and chloroform.

Fig.-1: The Synthesis of $[\text{Ru}(\text{N-Ph-5-X-salim})_2(\text{ind})_2]\text{Cl}$ where $\text{X} = \text{H}$ or Br

Spectral Characterization

The characterization of Ru(III) compounds before and after synthesis with indazole was obtained by MALDI TOF/TOF mass spectrometry (Table-1) and infrared spectroscopy (Table-2). Obtained results confirmed the presence of anionic compounds in starting complexes, as well as cationic compounds in synthesized complexes.

Important proofs regarding functional groups coordinated to ruthenium(III) were obtained. Based on the comparison of infrared spectra of starting complexes, free indazole and synthesized compounds, the coordination of anionic bidentate Schiff bases and monodentate indazole to the ruthenium(III) ion was confirmed.

Table-1: MALDI TOF/TOF Results of the starting and Synthesized Complexes

Compound	Molecular ion	Calc. mass m/z (100%)	Measured Mass m/z (100%)	Mass Error / ppm
Starting compound 1	$[\text{C}_{26}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2\text{Ru}]^-$	563.9952	563.9949	0.53
Starting compound 2	$[\text{C}_{26}\text{H}_{18}\text{Br}_2\text{Cl}_2\text{N}_2\text{O}_2\text{Ru}]^-$	721.8143	721.8130	1.80
Compound 1	$[\text{C}_{40}\text{H}_{32}\text{N}_6\text{O}_2\text{Ru}]^+$	730.1625	730.1652	1.37
Compound 2	$[\text{C}_{40}\text{H}_{30}\text{Br}_2\text{N}_6\text{O}_2\text{Ru}]^+$	887.9828	887.9818	1.13

The main IR vibrations are given in Table-2. Indazole was coordinated to Ru(III) *via* a free electronic pair of nitrogen affecting the C=N, C-N, N-N and N-H stretching vibrations. In Compound 1 and Compound 2, C=N stretching vibrations were shifted for 6 and 5 cm^{-1} toward higher wave numbers, while N-N stretching vibrations were shifted for 6 and 9 cm^{-1} , respectively²⁰. The symmetric stretching vibration of the C-N linkage was obtained at 1356 cm^{-1} in the spectra of free indazole. In the synthesized complexes, a new medium intensity band at 1356 cm^{-1} was observed. Since C-N bond is conjugated to the benzene ring, significant shifts after coordination of indazole to Ru (III) were not expected because there is no change in the bond length. In the spectra of uncoordinated indazole, N-H stretching vibration appeared at 3410 cm^{-1} . This vibration is coupled with vibration in the starting compounds and appears at 3434 cm^{-1} in both synthesized complexes. The weak bands at 664 (662) cm^{-1} and 423 (414) cm^{-1} in Compound 1 (Compound 2) could be assigned to Ru-N and Ru-O, respectively.

In starting compounds, $\text{Na}[\text{RuCl}_2(\text{N-Ph-5-X-salim})_2]$ where $\text{X} = \text{H}$ or Br , characteristic IR vibrations were C=N (azomethine), C-O (phenolic), Ru-N and Ru-O. After the coordination of indazole to Ru(III) these vibrations were not affected. Regarding infrared spectra, as anionic bidentate ligands nitrogen from azomethine group and oxygen from deprotonated phenol group were coordinated to the octahedral environment of ruthenium(III) in Schiff bases, while indazole was coordinated *via* nitrogen atom as a monodentate ligand.

UV/Vis spectra exhibited a few characteristic absorptions given in Table-3. The free indazoles showed two absorption bands attributed to the transitions from π to π^* and n to π^* relating benzene ring. Shifting

of $n \rightarrow \pi^*$ band in synthesized compounds spectra followed the participation of nitrogen from indazole in bonding. The weak broad absorption bands of $\text{Na}[\text{RuCl}_2(\text{N-Ph-5-X-salim})_2]$ centered at 613 nm for X = H or 625 nm for X = Br have been assigned to $^2\text{T}_{2g} \rightarrow ^2\text{A}_{2g}$ transition¹⁴.

Table-2: Characteristic IR Vibrations (cm^{-1}) of starting Compounds, Synthesized Complexes and Free Indazole

	1	2	Compound 1	Compound 2	Ind
$\nu(\text{N-H})_{\text{Ind}}$	-	-	3434	3434	3410
$\nu(\text{C=C})_{\text{Ind}}$	-	-	1626	1624	1621
$\nu(\text{C=N})_{\text{SB}}$	1605	1600	1605	1600	-
$\nu(\text{C=N})_{\text{Ind}}$	-	-	1695	1698	1689
$\nu(\text{C-N})_{\text{Ind}}$	-	-	1356	1356	1356
$\nu(\text{C=O}_{\text{Ph}})_{\text{SB}}$	1295	1289	1295	1289	-
$\nu(\text{N-N})_{\text{Ind}}$	-	-	1082	1081	1076
$\nu(\text{Ru-N})$	664	662	664	662	-
$\nu(\text{Ru-O})$	423	414	423	414	-

Ind – indazole; _{SB} – assigned vibrations in Schiff base; _{Ind} – assigned vibrations in Indazole

This transitions shifted towards higher energies in the spectra of complexes with indazole (578 nm for X = H and 574 nm for X = Br). The substitution of two chloride ions in the starting complexes with indazole resulted in higher separation energies of d-atomic orbitals. The chloride ion is a weaker ligand than indazole in accordance with the spectrochemical series. Indazole splits stronger crystal field and shifts d-d transition to lower wavelengths.

Table-3: The Characteristic Absorptions (nm) in Electronic Spectra of Starting Compounds, Synthesized Complexes and Free Indazole in CH_2Cl_2

	Starting compound 1	Starting compound 2	Compound 1	Compound 2	Ind
$\pi \rightarrow \pi^*$	239	244	235	245	250
$n \rightarrow \pi^*$	sh	sh	283	282	285
IL(SB)	348	351	sh	350	-
d-d	613	625	578	574	-

$\pi \rightarrow \pi^*$ - electronic transition of delocalized electrons of the aromatic system; $n \rightarrow \pi^*$ - electronic transitions of the atoms of azomethine group or free electron pair on the N atom of indazole with aromatic π electrons; IL (SB) – intraligand transition of whole Schiff base molecule; d-d – transition of low spin complex; sh-shoulder.

Compounds 1 and 2 were insoluble in water and therefore the cyclic voltammograms were recorded in acetonitrile solution with the use of glassy carbon working electrode (GCE). In this study, tetraethyl ammonium bromide (Et_4NBr) was used as a supporting electrolyte. Cyclic voltammetry data are given in Table-4. Cyclic voltammograms of the Compounds 1 and 2 showed well-defined anode and cathode peaks. The values of formal potentials ($E_{1/2}$) assigned to Ru(III)/Ru(II) couple indicated that Ru(III) in the complexes was stabilized *via* ON_2 ligands. Quasi-reversible one-electron transfer process was indicated by i_k/i_a ratio and the peak to peak separation (ΔE_p) in cyclic voltammograms²².

Table-4: The Cyclic Voltammetric Data of Compounds 1 and 2 in Acetonitrile Solutions

	E_{pc} / V	E_{pa} / V	$E_{1/2} / \text{V}$	$\Delta E_p / \text{mV}$
Compound 1	-0.918	-0.720	-0.819	198
Compound 2	-0.924	-0.723	-0.824	201

Supporting electrolyte: Et_4NBr ; potential range: (-1.1) – (-0.5) V; scan rate: 0.2 V/s; all data are referred to Ag/AgCl reference electrode; $E_{1/2} = 0.5 (E_{pa} + E_{pk})$ where E_{pa} – anodic potential, E_{pk} – cathodic potential.

The Effect on the Briggs-Rauscher Oscillating Reaction

The pH value of the Briggs-Rauscher reaction mixture was around 2. This value in part mimics the physiological conditions similar to the fluids in the human stomach^{23,24}. Synthesized Ru(III) complexes were dissolved in absolute ethanol after initial dissolving in DMSO and after third oscillation, an appropriate volume was added to the reaction mixture. An immediate effect on quenching of oscillations was caused by an addition of the compound solution. The elapsed time between ending the addition and first regenerated oscillation was defined as inhibition time (t_{inhib}). After t_{inhib} the oscillations were restarted with different amplitude and frequency compared to a non-inhibited Briggs-Rauscher reaction mixture²³. Plotting t_{inhib} vs. concentration of the compounds, linear correlations were found in the range of 5.36 to 21.0 $\mu\text{mol/L}$ (Fig.-2) and obtained parameters are listed in Table-5.

Fig.-2: Inhibition time versus compounds concentration

The path of the immediate quenching of oscillations – inhibition time – resumption of oscillations was similar to antioxidant free radical scavenger²⁴. However, the obtained preliminary results suggested further examination of this effect.

Table-5: Parameters of the Straight Line Equations $t_{\text{inhib}} = m[\text{compound}] + q$

Complex	m (s L/ μmol)	q (s)	R^2
Compound 1	10.3	15.8	0.955
Compound 2	4.82	9.80	0.958

CONCLUSION

Two new cationic complex compounds of Ru(III) with Schiff bases, *N*-phenyl-5-X-salicylideneimine (where X = H or Br) and indazole were synthesized. Based on the experimental results, the complexes were formulated as $[\text{Ru}(\text{N-Ph-5-X-salim})_2(\text{ind})_2]\text{Cl}$ where X = H or Br, ind = indazole. In the obtained Ru(III) octahedral complexes, Schiff bases acted as an anionic bidentate O, N donor ligands, while indazole occurred as a monodentate N ligand. The perturbation path was similar to that stimulated by an antioxidant free radical scavenger.

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