



Synthesis and characterization of Ru(III) complexes with thiosemicarbazide-based ligands

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Article info

Received: 15/11/2016

Accepted: 07/12/2016

Keywords:

Thiosemicarbazones

Thiosemicarbazide

Tridentate ligand

ONS donors

Ruthenium

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Abstract: Three Ru(III) complexes general formula $\text{Na}[\text{RuL}_2]$ (where L = dibasic tridentate thiosemicarbazone ligands) have been synthesized by reacting RuCl_3 with thiosemicarbazide-based ligands with ONS donors. Ligands of general formula $(\text{X})\text{N-NH-C}(\text{S})\text{-NH}_2$ were prepared through the condensation reaction of salicylaldehyde or its derivatives (X = salicylaldehyde, 5-Cl-salicylaldehyde, 5-Br-salicylaldehyde) with thiosemicarbazide. Complexes have been formulated and characterized by mass spectrometry and infrared spectroscopy. The data showed the formation of a complex with a 1:2 metal:ligand stoichiometries. The ligands coordinated as an ONS tridentate dianion through the oxygen atom of the deprotonated phenolic OH-group, the azomethine nitrogen atom and the sulfur atom after deprotonation of the thiosemicarbazide residue in its thiol form.

INTRODUCTION

Thiosemicarbazones have been the subject of many studies because of their variable bonding modes, promising biological implications and structural diversity (Al-Amiery et al., 2011). Among the most examined compounds of this group is certainly salicylaldehyde thiosemicarbazone (Vojinović-Ješić et al., 2011). The synthesis of the transition metal complexes with thiosemicarbazone ligands has been receiving considerable attention due to the potentially chemotherapeutic properties of both ligands and complexes as antitumor and antibacterial agents (Sampath and Jayabalakrishnan, 2016). It was found that their dibasic tridentate thiosemicarbazones with ONS donors

are of immense importance as they possess a wide spectrum of medicinal properties (El-Bahnasawy et al., 2014). Thiosemicarbazone derivatives are of particular chemical and pharmacological importance for the possession of a number of different biological activities: anticancer, antiviral, antibacterial, antifungal activity, etc. (Kumar et al., 2013). Pharmacological potential of thiosemicarbazone as antitumor agent is one of the most promising areas of its research (Chil J. 2013). Salicylaldehyde thiosemicarbazone and its derivatives are a group of flexible tridentate ONS donors capable of stabilizing the upper and lower oxidation state of transition metal ions (Leovac, et al., 1983). Thiosemicarbazone complexes differs from the free ligand with respect to their biological properties (Chandra et al., 2014). Although the thiosemicarbazone, obtained by

the condensation process with *o*-hydroxyl carbonyl compounds, show antibacterial activity, the metal complexes often manifest effect of a larger order of magnitude compared to the corresponding ligand (Ngan et al., 2011). A particularly important feature is the reduction of the cytotoxic action of thiosemicarbazone, which may be reduced by complexing to the metal cation (Rana et al., 2002). Synthesis of transition metal complexes with thiosemicarbazone ligands attracted considerable attention because of the potentially useful chemotherapeutic properties and ligands and complex in terms of anticancer and antibacterial activity (Al-Amiery et al., 2012). Salicylaldehyde thiosemicarbazone is usually expected to bind to a metal center, *via* dissociation of two acidic protons, as a dianionic tridentate ONS donor forming stable chelate (Datta et al., 2011). Platinum group metal complexes with thiosemicarbazones show a wide range of pharmacological activity (Thangadurai et al., 2001). The aim of this work was to study the syntheses, as well as the spectral and structural characteristics of three Ru(III) complex with salicylaldehyde thiosemicarbazone derived from salicylaldehyde and Cl and Br substituted salicylaldehyde and thiosemicarbazide.

EXPERIMENTAL

Materials and methods

Physical measurements

All chemicals used were commercially available with analytical grade of purity and used without further purification. Infrared spectra were recorded as KBr pellets on a Perkin Elmer spectrum BX FTIR System in region 4000 – 400 cm^{-1} . Agilent 6210 Time-of-Flight LC/MS system (Agilent Technologies, Santa Clara, California, USA) equipped with an ESI interface (ESI-ToF-MS) was used for recording of mass spectra and for the confirmation of molecular formulas of compounds. The ESI was operated in a negative mode and nitrogen was used as the drying gas (12 L/min) and nebulizing gas at 350°C (45 psi). The OCT RF voltage was set to 250 V and the capillary voltage was set to 4.0 kV. The voltages applied to the fragmentor and skimmer were 140 V and 60 V, respectively. Scanning was performed from 100 to 2000 m/z (mass-to-charge ratio). The identification of compound was as follows: compound was dissolved in the acetonitrile (concentration of 1 mg/mL), and a direct injection of 5 μL sample was conducted by 1200 Series HPLC (Agilent Technologies, Waldbronn, Germany) without a separation column. The isocratic mobile phase consisted of 50% acetonitrile and 50% of 0.2% formic acid in water (v/v) at a flow rate of 0.2 mL/min. Using these parameters, the anionic part of the compound was detected as the corresponding $[\text{M}]^-$ ion.

Synthesis of ligands

Thiosemicarbazide (0.01 mol; 0.91 g) was dissolved in ethanol (60 mL) by refluxing at 50°C and ethanolic solution (30 mL) of the salicylaldehyde or 5-Cl-salicylaldehyde or 5-Br-salicylaldehyde (0.01 mol; 0.89 mL, 0.157 g, 0.201 g, respectively) was added. The reaction mixture was refluxed for four hours at 60°C. The

volume of reaction mixture was reduced and then cooled on ice water. The crystals of salicylaldehyde thiosemicarbazone, 5-Cl-salicylaldehyde thiosemicarbazone and 5-Br-salicylaldehyde thiosemicarbazone, hereinafter HL1, HL2 and HL3, respectively, were precipitated out. The crystals were recrystallized in ethanol.

Synthesis of complexes

Ethanolic solution (20 mL) of the thiosemicarbazone ligand HL1 or HL2 or HL3 (1 mmol; 0.195 g or 0.229 g or 0.273 g, respectively) was added to the solution of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (0.5 mmol; 0.131 g) in ethanol (20 mL) and the reaction mixture was refluxed for 4-5 hours. Volume of the resulting solution was reduced to 10 mL at rotary vacuum evaporator and the solution was left overnight. The precipitation was performed by adding the equimolar amounts of water solution of NaCl. The resulting crystalline compound was filtered under suction, washed with ethanol and ether, and dried in vacuum. Dark green partly crystalline product is air stable, soluble in most common polar organic solvents and insoluble in apolar organic solvents and water. Yield: 63%

RESULTS AND DISCUSSION

Ligands HL1, HL2, HL3, general formula (X)N-NH-C(S)-NH₂ were prepared by mixing equimolar amounts of thiosemicarbazide and salicylaldehyde or its derivatives (X = salicylaldehyde, 5-Cl-salicylaldehyde, 5-Br-salicylaldehyde) in absolute ethanol under reflux for four hours at 60°C (Pahontu et al., 2013) (Figure 1).

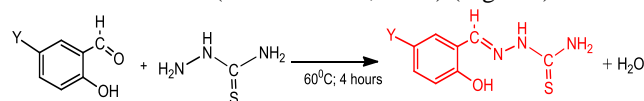


Figure 1. Preparation scheme for ligands L1, L2, L3; Y = H, Cl, Br, respectively

The complexes $\text{Na}[\text{RuL}_2]$ (L = HL1, HL2, HL3) were prepared by the modified synthetic procedure (Kumar et al., 2013) by mixing 1:2 molar ratio of RuCl_3 and the ligands in absolute ethanol (Figure 2).

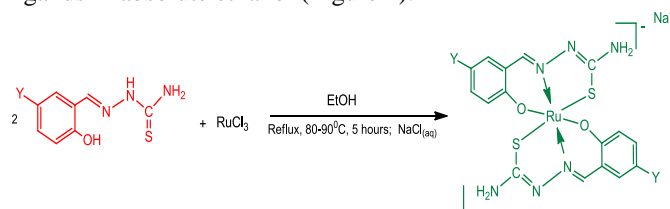


Figure 2. Preparation scheme for complexes $\text{Na}[\text{Ru}(\text{HL}1)_2]$, $\text{Na}[\text{Ru}(\text{HL}2)_2]$, $\text{Na}[\text{Ru}(\text{HL}3)_2]$; Y = H, Cl, Br, respectively

$\text{Na}[\text{Ru}(\text{HL}1)_2]$

ESI-ToF MS m/z : $[\text{C}_{16}\text{H}_{14}\text{N}_6\text{O}_2\text{S}_2\text{Ru}]^-$ 487.96567; FT-IR HL1 (KBr, cm^{-1}): 1616 s $[\nu_s(\text{C}=\text{N})]$, 1269 s $[\nu_s(\text{C}-\text{O}_{\text{phen}})]$; 777 s $[\nu_s(\text{C}=\text{S})]$, FT-IR $\text{Na}[\text{Ru}(\text{HL}1)_2]$ (KBr, cm^{-1}): 1605 s $[\nu_s(\text{C}=\text{N})]$, 1280 s $[\nu_s(\text{C}-\text{O}_{\text{phen}})]$, 723 s $[\nu_s(\text{C}-\text{S})]$, 587 s $[\nu_s(\text{Ru}-\text{N})]$, 509 s $[\nu_s(\text{Ru}-\text{O})]$, 441 s $[\nu_s(\text{Ru}-\text{S})]$

Na[Ru(LH2)₂]

ESI-ToF MS m/z : [C₁₆H₁₂N₆O₂S₂Cl₂Ru]⁻ 555.88615; FT-IR HL2 (KBr, cm⁻¹): 1611 s [ν_s(C=N)], 1280 s [ν_s(C-O_{phen})]; 777 s [ν_s(C=S)], FT-IR Na[Ru(HL2)₂] (KBr, cm⁻¹): 1589 s [ν_s(C=N)], 1266 s [ν_s(C-O_{phen})], 723 s [ν_s(C-S)], 547 s [ν_s(Ru-N), 484 s [ν_s(Ru-O), 438 s [ν_s(Ru-S)]

Na[Ru(LH3)₂]

ESI-ToF MS m/z : [C₁₆H₁₂N₆O₂S₂Br₂Ru]⁻ 643.78526; FT-IR HL3 (KBr, cm⁻¹): 1611 s [ν_s(C=N)], 1261 s [ν_s(C-O_{phen})]; 777 s [ν_s(C=S)], FT-IR Na[Ru(HL3)₂] (KBr, cm⁻¹): 1595 s [ν_s(C=N)], 1278 s [ν_s(C-O_{phen})], 723 s [ν_s(C-S)], 544 s [ν_s(Ru-N), 506 s [ν_s(Ru-O), 438 s [ν_s(Ru-S)]

ESI ToF MS mass spectrometry confirmed existence of [C₁₆H₁₄N₆O₂S₂Ru]⁻, [C₁₆H₁₂N₆O₂S₂Cl₂Ru]⁻ and [C₁₆H₁₂N₆O₂S₂Br₂Ru]⁻ ions with m/z values at 487.96567, 555.88615 and 643.78526, respectively. These ligands are coordinated to ruthenium center as a ONS tridentate dianion through the oxygen atom of the deprotonated phenolic OH-group, the azomethine nitrogen atom and the sulfur atom after deprotonation of the thiosemicarbazide. This was confirmed by IR spectra: shift of azomethine stretching to lower frequencies, shift of C-O(H) vibration to higher frequency and disappearance of the vibration of C=S double bond in the spectra of complexes (El-Bahnasawy et al., 2014).

In order to determine the mode of coordination the most significant infrared spectral frequencies for the metal complexes are compared with the free ligands. A band observed at 1616, 1611 and 1611 cm⁻¹ due to the azomethine C=N stretching frequency of the free ligands

HL1, HL2 and HL3 respectively was shifted to lower frequency in the spectra of the complexes at 1586 – 1605 cm⁻¹ indicating the coordination through N atom. Deprotonated phenolic oxygen – strong absorption band in spectra of ligand positioned at 1261 – 1269 cm⁻¹ after coordination is shifted to 1278 – 1280 cm⁻¹ (Baiu et al., 2009), which corresponds to forming of weaker C-O(Ru) bond comparing to C-O(H) and confirms coordination of ligands to Ru(III) *via* deprotonated phenolic oxygen.

Also, in the IR spectra of ligands, HL1, HL2 and HL3, the characteristic vibration of the (OH) band is observed at 3444, 3410, 3454 cm⁻¹, respectively. The absence of this band in the IR spectra of the complexes indicates the coordination through the phenolic oxygen (Vojinović-Ješić et al., 2011). The ligands showed band at 777 cm⁻¹ for HL1, HL2 and HL2 for the vibration of the C=S double bond (Wiles et al., 1967; Thangadurai et al., 2001). The C=S band was disappeared in the complexes (Al-Amiery et al., 2011) and a new band, C-S appeared at 723–743 cm⁻¹. This confirms that the other coordination site to ruthenium is through thiolate sulphur (Sampath et al., 2016). The appearance of bands in the spectra complexes, Na[Ru(LH1)₂], Na[Ru(LH2)₂] and Na[Ru(LH3)₂] at 1636, 1634, 1629 and 1616, 1588, 1599 cm⁻¹ due to C=N-N=C (Bharti et al., 2013) and new C=N bond, respectively, also indicates that Ru is bonded through thiol sulphur (El Bahnasawy et al., 2014). The medium intensity band in the region 544 – 587 cm⁻¹ is attributed to Ru-N, in the region 484 – 509 cm⁻¹ is attributed to Ru-O, and in the region 438 – 448 cm⁻¹ is attributed to Ru-S bonds (Bahnasawy et al., 2014).

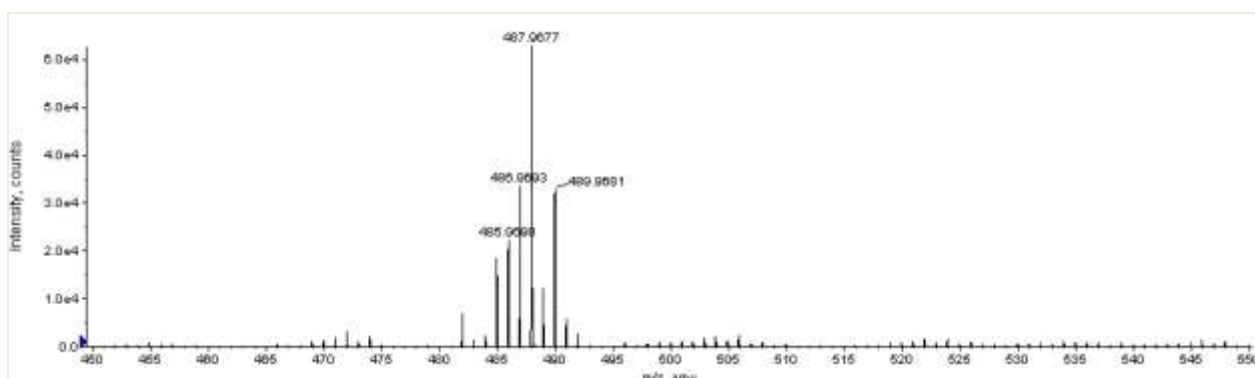
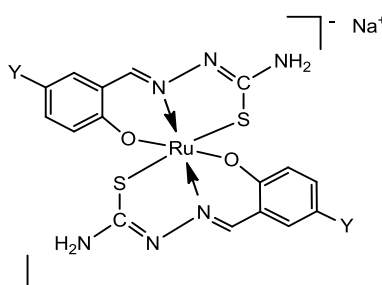
Figure 3. Mass spectrum of Na[Ru(HL1)₂]

Figure 4. Proposed structure for the complexes

Table 1: ESI ToF MS data for molecular ions of compounds

Complex	Molecular ion	Ion Mass	Measured Mass	Error (mDa)	Error (ppm)
Na[Ru(HL1) ₂]	[C ₁₆ H ₁₄ N ₆ O ₂ S ₂ Ru] ⁻	487.96686	487.96770	-1.18976	-2.44
Na[Ru(HL2) ₂]	[C ₁₆ H ₁₂ N ₆ O ₂ S ₂ Cl ₂ Ru] ⁻	555.88892	555.88615	-2.76566	-4.98
Na[Ru(HL3) ₂]	[C ₁₆ H ₁₂ N ₆ O ₂ S ₂ Br ₂ Ru] ⁻	643.78789	643.78526	-2.63104	-4.09

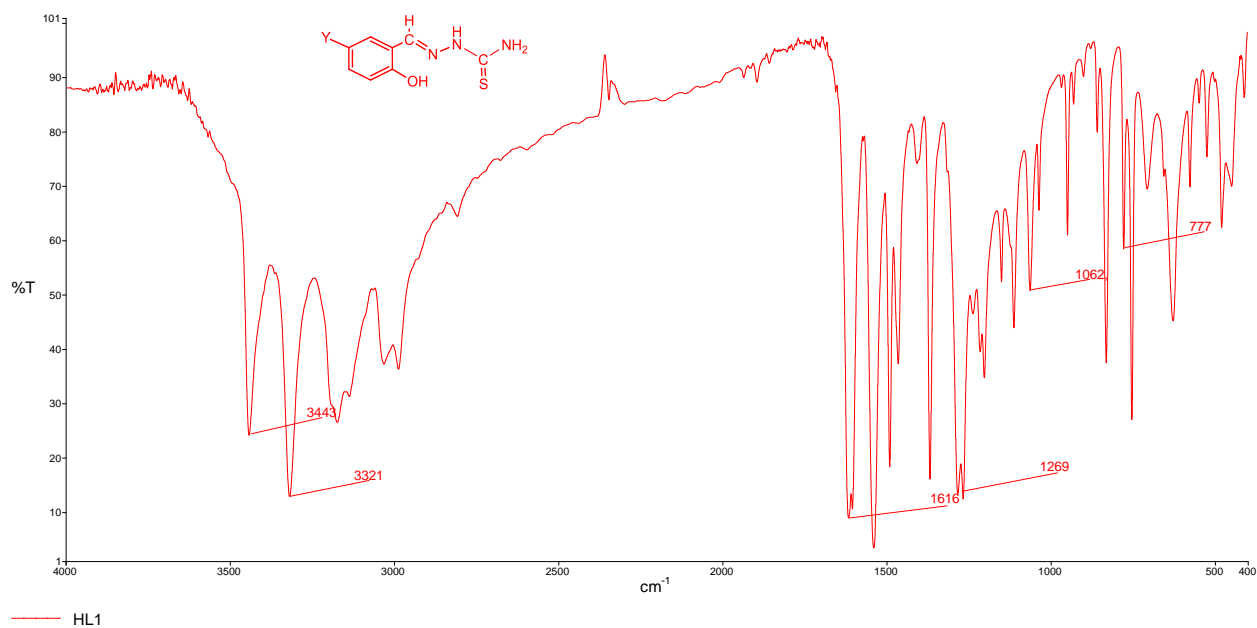


Figure 5. FT IR spectrum of ligand HL1

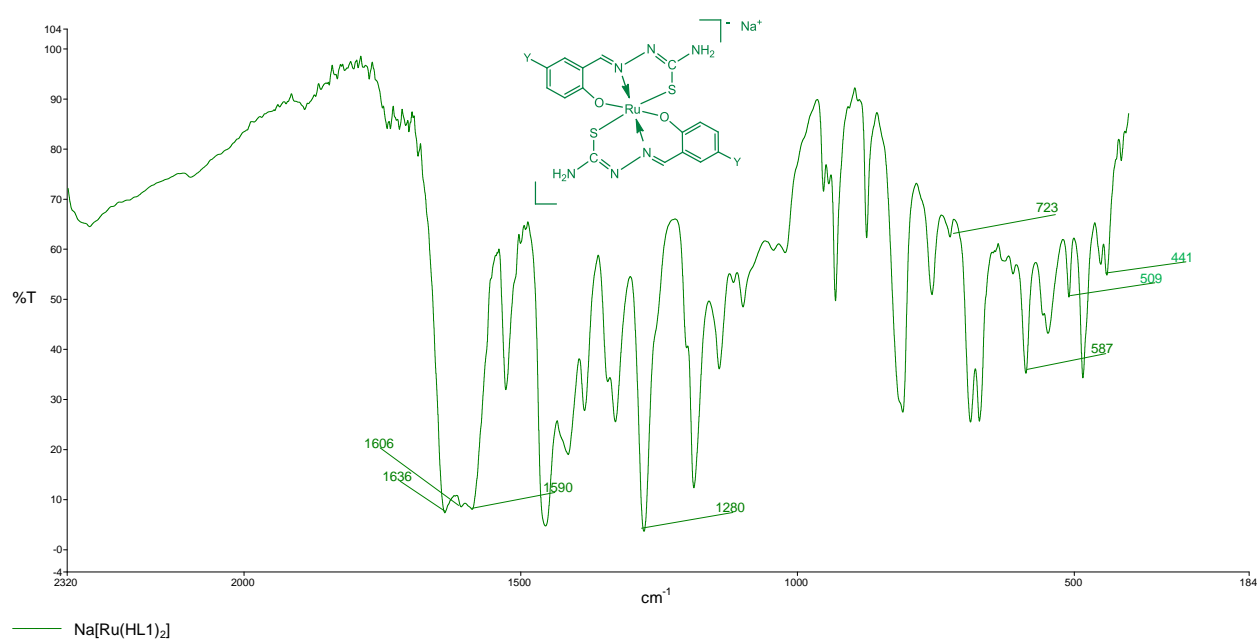
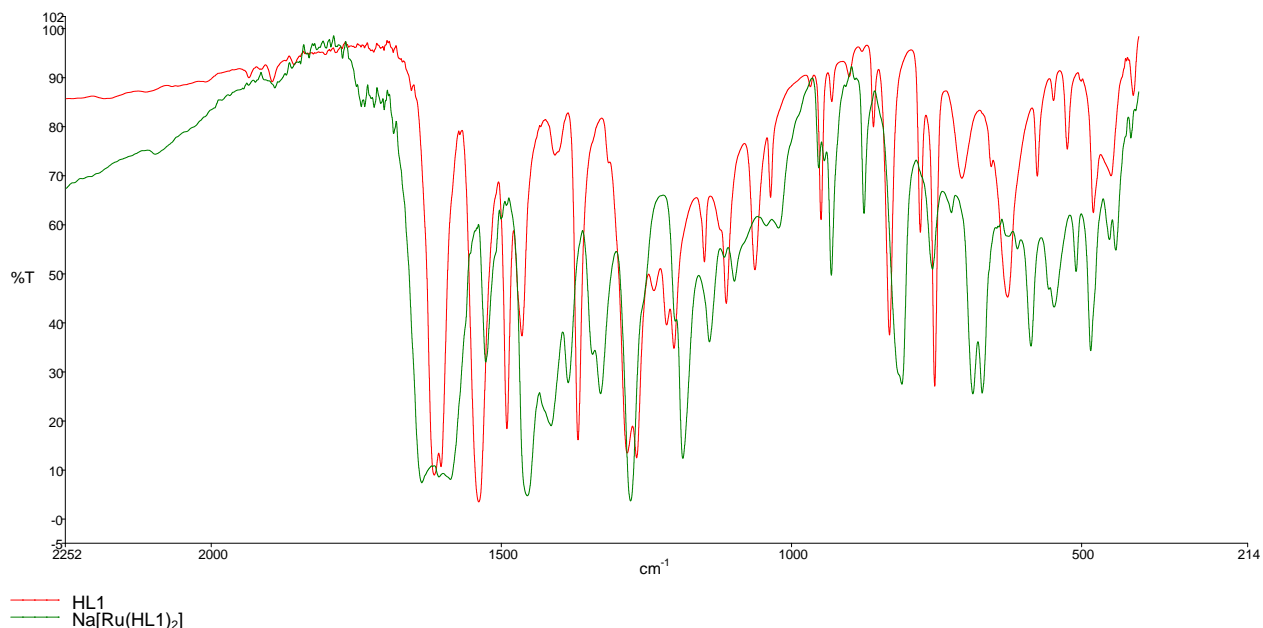
Figure 6. FT IR spectrum of complex Na[Ru(HL1)₂]

Table 2: Characteristic vibrations of ligands and complexes

Ligand/complex	$\nu(\text{C}=\text{N})$, cm^{-1}	$\nu(\text{C}-\text{O})$, cm^{-1}	$\nu(\text{C}=\text{S})$, cm^{-1}	$\nu(\text{C}-\text{S})$, cm^{-1}	$\nu(\text{Ru}-\text{N})$, cm^{-1}	$\nu(\text{Ru}-\text{O})$, cm^{-1}	$\nu(\text{Ru}-\text{S})$, cm^{-1}
HL1	1616	1269	777	-	-	-	-
Na[Ru(HL1) ₂]	1606	1280	-	723	587	509	441
HL2	1611	1266	777	-	-	-	-
Na[Ru(HL2) ₂]	1589	1280	-	723	547	484	438
HL3	1611	1261	777	-	-	-	-
Na[Ru(HL3) ₂]	1595	1278	-	743	544	506	438

Figure 7. Comparative FT IR spectra of ligands HL1 and complex Na[Ru(HL1)₂]

CONCLUSION

Three ruthenium(III) complexes of the type Na[RuL₂] (where L = dibasic tridentate thiosemicarbazone ligand), have been synthesized. Complexes have been synthesized and characterized by mass spectrometry and infrared spectroscopy. The data showed the formation of a complex with a 1:2 metal:ligand stoichiometries. The ligands coordinated as an ONS tridentate dianion through the oxygen atom of the deprotonated phenolic OH-group, the azomethine nitrogen atom and the thiolate sulfur atom after deprotonation of the thiosemicarbazide. ESI ToF mass spectrometry confirmed existence of [C₁₆H₁₄N₆O₂S₂Ru]⁻, [C₁₆H₁₂N₆O₂S₂Cl₂Ru]⁻ and [C₁₆H₁₂N₆O₂S₂Br₂Ru]⁻ ions with *m/z* values at 487.96567, 555.88615 and 643.78526, respectively.

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Summary/Sažetak

Sintetizirana su tri Ru(III) kompleksa opšte formule $\text{Na}[\text{RuL}_2]$ (L = dibazni tridentatni tiosemikarbazon ligand), reakcijom RuCl_3 sa ONS donorskim ligandima na bazi tiosemikarbazona. Ligandi opšte formule (X)N-NH-C(S)-NH₂ pripremljeni su reakcijom kondenzacije salicilaldehida i njegovih derivata (X = salicilaldehid, 5-Cl-salicilaldehid, 5-Br-salicilaldehid) sa tiosemikarbazidom. Kompleksi su formulisani i karakterizirani ESI ToF masenom spektrometrijom i infracrvenom spektroskopijom. Podaci pokazuju formiranje kompleksa sa 1:2 metal:ligand stehiometrijom. Ligandi su koordinirani kao ONS tridentatni dianioni preko atoma kisika deprotonizirane OH-grupe, azometinskog atoma azota i atoma sumpora nakon deprotonizacije ostatka tiosemikarbazida u njegovom tiolnom obliku.