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Original Scientific Article

Bis(iminato)ruthenates(III): Correlation of Half-wave Potential and Hydrolysis Constant with Electronic Effects of Substituent

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Abstract: Influence of electronic effects of substituent on Schiff base ligands, derived from salicylaldehyde and 5-substituted salicylaldehydes with 2-aminophenole, on half-wave potential and hydrolysis constants of Sodium bis(iminato)ruthenates(III) hemitriethylamine solvate was investigated by cyclic voltammetry and electronic spectroscopy. New complex, Sodium bis[*N*-(2-oxy-κO-phenyl)salicylideneimine-$\kappa^2 N,O$(1-)]ruthenate(III) hemitriethylamine solvate was prepared and characterized on the basis of infrared and electron spectroscopy, MALDI-TOF/TOF mass spectrometry and ruthenium content. Cyclic voltammograms of complexes in organic solvents demonstrate quasi-reversible one-electron process with pronounced reducing power of Ru(II). Appling Hammet equation for half-wave potential of complexes we found that substituents conduct electronic density *via* X-C_6H_3-O-Ru-O-C_6H_3-X bonds. Electron spectroscopy was used to investigate behavior of complexes under physiological conditions and showed that hydrolysis occur. Constants of hydrolysis were determined spectrophotometrically using kinetics of pseudo-first order.

INTRODUCTION

During the last fifty years chemistry of ruthenium complexes is in focus of research in at least two fields: (i) bioinorganic chemistry, due to biological activity of compounds which exhibit antitumor (Rademaker-Lakhai *et al.*, 2004; Kahrović, 2011) and antibacterial properties (Jayabalakrishnan *et al.*, 2002), (ii) material science, due to potential usage as catalysts (Scholl *et al.*, 1999), (bio)sensors (Zhang *et al.*, 2008) and solar cells based materials (Wang *et al.*, 2003). Concerning the biological activity of ruthenium based compounds there are two important factors that strongly control their activity, reduction potential and hydrolysis ability. It is found that well-known antimetastatic drug, NAMI-A named Imidazolium *trans*-[tetrachloro(dimethyl--sulfoxide-κS)(imidazole-κN)ruthenate(III)] reaches its maximum activity after reduction *in situ*, which indicates significance of reduction potential on activity of Ru compounds (Sava *et al.*, 2002). On the other hand, activity of another clinically important compound ICR, indazole analog of NAMI-A, is dependent on hydrolysis of acido-ligand, demonstrating that kinetics of ligand substitution is also essential factor for biological activity of these metallofaramaceutics (Vargiu *et al.*, 2008). In the frame of our investigation on ruthenium compounds we report here on the effect of the substituent on Scfiff bases in bis(iminato)ruthenium(III) complexes on redox potentials and constants of hydrolysis, as essential in design and development of new potential anticancer drugs.

EXPERIMENTAL

Materials and methods

All chemicals were commercially available, analytical grade of purity, and used without further purification. Tetraethylammonium perchlorate was prepared from bromide salt as previously described (Kolthoff *et al.*, 1957). Complexes Sodium bis[*N*-(2-oxy-*κO*-phenyl)-5-substituted-salicylideneimine-κ^2*N*,*O*(1-)]ruthenate(III) hemitriethylamine solvate, hereinafter Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et_3N, where Et_3N= triethylamine, R = C_6H_4O and X = Cl, Br or NO_2 were prepared by published procedure (Kahrović *et al.*, 2014). Purity was checked by FTIR and electronic spectra. Complex in which X = H was prepared on the basis of the same general procedure and was characterized by infrared and electron spectroscopy, MALDI/TOF-TOF (matrix assisted laser desorption / ionization – time of flight) mass spectrometry, FA AAS (flame atomization atomic absorption spectroscopy) and cyclic voltammetry.

Synthesis of N-(2-hydroxyphenyl)salicylideneimine

Ligand *N*-(2-hydroxyphenyl)salicylideneimine, here in after *N*-RH-5-H-salimH (R = C_6H_4O) was prepared according to published procedure (Ligtenbarg *et al.*, 1999). *Yield*: 0.33 g (80 %).

Synthesis of Na[Ru(N-R-5-H-salim)$_2$] × ½ Et_3N

Ruthenium trichloride hydrate (Ru content 40 – 42%) (0.5 mmol, 0.13 g) was dissolved in absolute ethanol (5 mL) and ethanol mixture (40 mL) of *N*-(2-hydroxyphenyl)salicylideneimine (1 mmol, 0.21 g) and triethylamine (1 mmol, 0.13 mL) was added dropwise. Brownish solution was heated in rotary evaporator with constant stirring during 4 hours at 70°C changing its color to dark green. After the mixture was cooled to room temperature aqueous solution (0.5 mL) of NaCl (0.5 mmol, 0.03 g) was added to precipitate anionic complex. Weakly crystalline dark green powder of compound was obtained after reducing volume of solvent to half and cooling the mixture in ice. Product was filtered off, washed with ethanol (2 × 5 mL), water (2 × 5 mL) and petrol ether (2 × 5 mL). Recrystallization was made from mixed solvent ethanol:dichloromethane 1:1 v/v and complex was dried in vacuum desiccator. *Yield*: 0.12 g (78%).

Anal. Calc. for $NaRuC_{26}H_{18}N_2O_4 \times ½\ C_6H_{15}N$: Ru 16.93. *Found*: Ru: 16.55. MALDI-TOF/TOF MS *m / z* 100 %: 524.0306 $[C_{26}H_{18}N_2O_4Ru]^-$. IR (KBr) ν_{max}/ cm^{-1}: 1597 vs (C=N), 1288 m (C-O). IR (CsI) ν_{max}/ cm^{-1}: 393 w (Ru-O), 460 w (Ru-N). UV / Vis [CH_2Cl_2, λ_{max} / nm]: 334, 395 and 578 (ε / M^{-1} cm^{-1}): 9982, 13109 and 5397, respectively.

Physical measurements

Determination of ruthenium content was performed by flame atomization atomic absorption spectroscopy (FA AAS) on Varian AA 240 Z atomic absorption spectrophotometer by already reported procedure using standard curve method from DMSO solution (Rowston *et al.*, 1970).

Electron spectra measurements were performed on Perkin Elmer spectrophotometer Lambda 35. Electron spectrum of complex Na[Ru(*N*-R-5-H-salim)$_2$] × ½ Et_3N was recorded in dichloromethane in range from 200 to 700 nm. Hydrolysis of complexes of general formula Na[Ru(N-R-5-X-salim)$_2$] × ½ Et_3N were monitored spectrophotometrically for one hour recording spectra in three minute-intervals under physiological conditions, in Tris-HCl (Tris(hydroxymethyl)aminomethane) buffer pH 7.40 and in the presence of 150 mM NaCl. Complexes were initially dissolved in small volume of DMSO (dimethylsulfoxide) and then diluted to required concentration. Constants of hydrolysis were determined graphically by kinetics of pseudo-first order.

IR spectra were obtained on Perkin Elmer BX FTIR using KBr pallets technique in range 4000 – 400 cm^{-1}.

Electrochemical measurements were performed on Potentiostat /galvanostat Autolab 12 in 2.00 mL self-made three electrode electrochemical cell using glassy carbon electrode as working electrode, platinum wire as counter electrode and Ag/AgCl as reference electrode. Salt bridge with saturated KCl was used to minimize liquid junction potential. Cyclic voltammograms were recorded in DMF/$NaClO_4$ (dimethylformamide) in potential range -1.1 to 0.0 V and in MeCN/Et_4NClO_4 (acetonitrile) in range -1.1 to -0.5 V, both with scan rate of 0.3 Vs^{-1}. Working electrode was polished prior to measurements with 1 μm diamond paste.

Mass spectrum was obtained on a matrix–assisted laser desorption / ionization – Time – of – flight MALDI-TOF/TOF mass spectrometer (4800 Plus MALDI TOF/TOF analyzer, Applied Biosystems Inc., Foster City, CA, USA) equipped with Nd:YAG laser operating at 355 nm with firing rate 200 Hz in the negative ion reflector mode. 1600 shots per spectrum was taken with mass range 10−1500 Da, focus mass 500 Da and delay time 100 ns. Small amount of sample (on pipette tip) was resuspended in 10 μl of DHB (2,5-dihydroxybenzoic acid) MALDI matrix (5 mg/mL; dissolved in 50/50 acetonitrile/water, *v*/*v*) and 1 μl was spotted on MALDI plate. The spectrum was internally calibrated providing measured mass accuracy within 5 ppm of theoretical mass. Riboflavin and 3-aminosalicylic acid were used as internal calibrants in negative ion mode.

RESULTS AND DISCUSSION

Synthesis and spectroscopic characterization

Na[Ru(*N*-R-5-H-salim)$_2$] × ½ Et_3N was prepared as a part of homologous series of Na[Ru(*N*-R-5-H-salim)$_2$] × ½ Et_3N, where X = H, Cl, Br, NO_2 using procedure previously published by our team. Ruthenium(III) chloride and ligand were mixed in molar ratio 1:2 to

ensure replacement of all six positions on octahedrally coordinated Ru(III) with two tridentate dibasic Schiff base ligands. Anionic complex was precipitated by adding concentrated aqueous solution of sodium chloride. Air stable weakly crystalline dark green compound is insoluble in water and soluble in common polar organic solvents such as CH_2Cl_2, DMSO, DMF, MeCN, acetone etc.

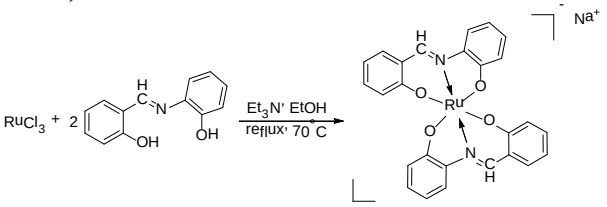

Figure 1. Synthesis of complex

The characterization is based on FA AAS, MALDI-TOF/TOF mass spectrometry, infrared and electron spectroscopy. Mass spectrum showed molecular ion (M^-) at *m/z* (100%) = 524.0306 confirming existence of $[C_{26}H_{18}N_2O_4Ru]^-$. Formulation of complex as Na[Ru(*N*-R-5-H-salim)$_2$] × ½ Et_3N was supported by FA AAS determination of ruthenium content.

Strong sharp absorption band positioned at 1632 cm^{-1} in IR spectrum of free ligand is attributed to CH=N stretching vibrations. After coordination the frequency was moved to lower wavenumber, and appears in spectrum of complex at 1597 cm^{-1} confirming coordination of ligand *via* azomethine nitrogen. On the other hand, phenolic C-O stretching vibration after coordination is shifted from 1276 cm^{-1} in ligand to 1288 cm^{-1} in spectrum of complex. Hypsochromic shift of 12 cm^{-1} is a result of the fact that C-O(Ru) bond is stronger than C-O(H) bond and confirms coordination *via* deprotonated oxygen atom. If a shift of CH=N and C-O bonds vibrations is taken as a rough measure of bond strength then new weak absorption bands in spectrum of complex positioned at 460 and 393 cm^{-1} can be ascribed to Ru-N and Ru-O bonds, respectively.

Absorption bands located in electronic spectrum of ligand and complex around 230 nm belong to intraligand aromat $\pi\rightarrow\pi^*$ transitions. Weakly defined absorption band at 270 nm is spectrum of ligand is attributed to $n\rightarrow\pi^*$ transition on phenolic oxygen and after coordination is shifted to 293 nm. Bathochromic shift of 23 nm is consequence of weaker localization of electron density (less covalent bond) in O-Ru compared to O-H bond and is in good correlation with infrared spectrum and coordination of ligand *via* deprotonated oxygen atom. Significant localization of electron pair of azomethine nitrogen after coordination is in correlation with 20 nm hypsochromic shift of the band located in spectrum of ligand at 354 nm. Broad absorption at 395 nm in spectrum of complex, which is not found in spectrum of ligand is ascribed to ligand metal charge transfer (LMCT). Weak absorption at 578 nm in spectrum of complex is assigned to *Lapport* forbidden spin allowed $t_{2g}^5\rightarrow t_{2g}^4e_g^1$ transition of low spin Ru(III).

Electrochemical behavior: Cyclic voltammetry studies

Cyclic voltammetry was used to investigate and correlate electrochemical properties of complexes with electronic effect of substituent on Schiff base ligand. Since the possibility of reduction *in vivo* is one of the most important parameters in design of new ruthenium based anticancer compounds due possibility to be activated through mechanism known as reduction *in situ*, determination of redox potentials is ultimate. Cyclic voltammograms of complexes in DMF/$NaClO_4$ and MeCN/Et_4NClO_4 showed quasi-reversible redox reaction and pronounced reduction character of Ru(II) in Ru(III)/Ru(II) pair. Although the ratio of cathodic and anodic current is nearly 1, separation of peaks is significantly higher than theoretically expected 59 mV for one-electron processes, 0.141 to 0.183 V in MeCN and 0.537 to 0.683 V in DMF. Reversibility in MeCN is improved compared to DMF, which can be ascribed to better coordinating properties of DMF. Quite negative values of half-wave electrode potential, -0.804 to -0.824 V in MeCN and -0.482 to -0.560 V in DMF correlate with O_4N_2 coordination environment of Ru(III). Small electronegative oxygen atom is hard in character and prefers binding with harder Ru(III) compared to Ru(II). On contrary, azomethine nitrogen is softer in character and stabilizes lower oxidation state. Since there are four atoms of oxygen in primary coordination sphere, Ru(III) is significantly stabilized making reduction significantly harder, which results with very negative $E_{1/2}$ values. Cyclic voltammograms are shown in Fig. 2. and data obtained from them are collected in Table 1.

Table 1. Data from cyclic voltammograms of Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et_3N in DMF / $NaClO_4$ and MeCN / Et_4NClO_4

	MeCN / Et_4NClO_4				DMF / $NaClO_4$			
X	E_c / V	E_a / V	$E_{1/2}$ / V	ΔE_p / V	E_c / V	E_a / V	$E_{1/2}$ / V	ΔE_p / V
H	-0.900	-0.725	-0.812	0.175	-0.828	-0.291	-0.560	0.537
Cl	-0.895	-0.712	-0.804	0.183	-0.814	-0.250	-0.532	0.564
Br	-0.883	-0.742	-0.812	0.141	-0.826	-0.240	-0.533	0.586
NO_2	-0.915	-0.734	-0.824	0.181	-0.823	-0.140	-0.482	0.683

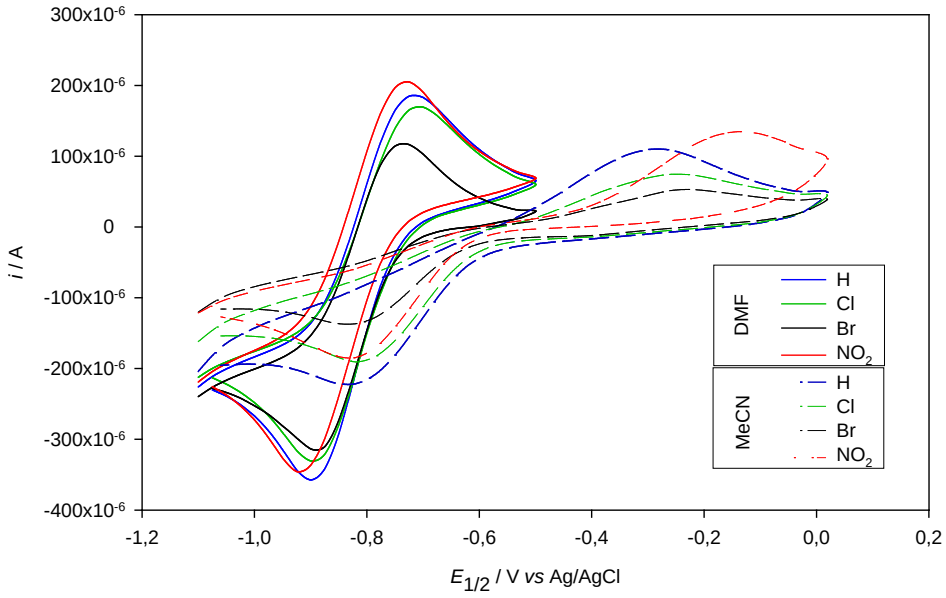

Figure 2. Cyclic voltammograms of Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N in DMF / NaClO$_4$ and MeCN / Et$_4$NClO$_4$

Half-wave potential of a system involving metal complex is determined by many factors such as electronic effects of ligand, stereochemical characteristics of redox couples, degree of solvation, temperature and metal oxidation state.

If we consider electronic effects of ligand as a factor determining redox potential of a metal complex we can discuss about two ways that substituents affect electronic density. Electron withdrawing substituents on ligand system decrease electron density making reduction easier over oxidation and electron donating substituents facilitate oxidation over reduction. Changes in electron density are the result of two opposite ways of electron transport through σ bonds (inductive effect) and π bonds (resonance effect) of an aromatic system.

In the case of complex containing *N*-(2-hydroxyphenyl)5-nitrosalicylideneimine in MeCN, the most negative value, $E_{1/2}$ = -0.915 V, corresponds with strong electron withdrawing properties of nitro group, as a consequence of negative resonance effect and decrease of electron density on aromatic ring.

Character of halogen substituents is determined by two opposite effects: negative inductive effect due to their electronegativity and positive resonance effect due to three lone electron pairs. Since resonance effect is stronger than inductive, overall result is partial including of lone pair electrons in delocalization through aromatic ring resulting in more positive values of half wave potentials of halogen derivatives compared to hydrogen- and nitro-homologues. Bromo substituent has more diffused and weakly bonded lone pair electrons then chloro-derivate which results in more positive value of $E_{1/2}$.

Correlation of electronic effects of substituent on ligand system and half-wave potential was made on the basis of *Hammet* equation:

$$\Delta E = \rho \times \sigma \quad (\mathbf{1})$$

where ΔE is difference between the redox potential of the complex containing substituted and unsubstituted ligand respectively, ρ is constant which measures the sensitivity of the redox potential to the electronic effects of the substituents and σ is *Hammett* parameter which assigns a numerical value to the electronic effects of the substituents and normally refer to the inductive electronic effects of the substituents in *metha* or *para* positions of aromatic rings. Our model consider that substituent is in *metha* position to azomethine and in *para* position to phenol oxygen, as it is shown in Fig. 3.

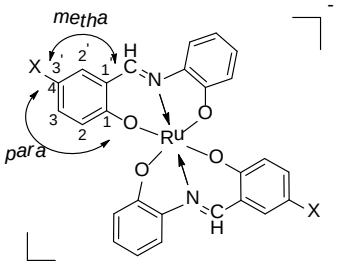

Figure 3. Position of substituent X according to azomethine group (*metha* position) and phenolic oxygen (*para* position) in complex anion [Ru(*N*-R-5-X-salim)$_2$]$^-$.

Table 2. *Hammet* values of constant in *metha* and *para* position of substituent X and half-potential values for Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N in DMF/NaClO$_4$

X	σ_{metha}	σ_{para}	$E_{1/2}$ / V
H	0.00	0.00	-0.560
Cl	+ 0.37	+ 0.23	-0.532
Br	+ 0.39	+ 0.23	-0.533
NO_2	+ 0.78	+ 0.71	-0.482

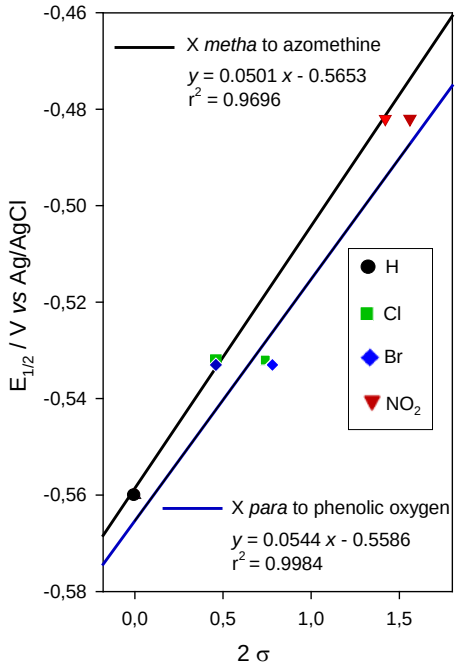

Figure 4. Dependence of half-wave potential for Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N in DMF/NaClO$_4$ on electronic effects of substituent X: Substituent is in *para* position according to phenolic oxygen (blue line) and *metha* position according to azomethine group (black line).

Diagram shown in Fig. 4. demonstrates linear correlation between $E_{1/2}$ and substituent in position 5- on salicylaldehyde part of Schiff base. Correlation coefficient of linear regression (Zanello, 2003) suggests that substituents conduct electronic density *via* X-C$_6$H$_3$-O-Ru-O-C$_6$H$_3$-X bonds (r^2 = 0.9984), but conduction *via* X-C$_6$H$_3$-CH=N-C$_6$H$_3$-X bonds (r^2 = 0.9639) is also not *a priori* excluded. Linearity is not found in the case of less solvating MeCN.

Behavior in solution: Hydrolysis by electronic spectroscopy studies

Taking into account that substituents affect electron density of aromatic system we investigated correlation between rate of hydrolysis of bis(iminato)ruthenates(III) under physiological solution with substituent X in [Ru(*N*-R-5-X-salim)$_2$]$^-$. Since Ru(III) is an inert low spin t_{2g}^5 system and complexes Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N absorb in UV/Vis region of electromagnetic spectrum, electron spectroscopy was used for hydrolysis studies. Study of hydrolysis in physiological solution is essential since ligand-water exchange reaction is of great importance for potential biological properties of the drugs.

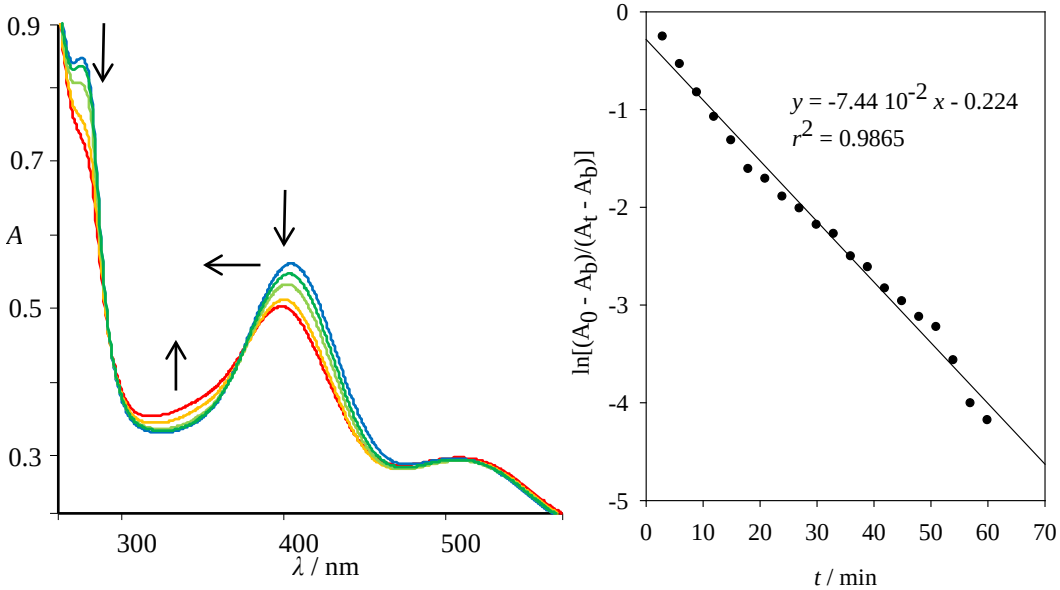

Figure 5. Left: Hydrolysis of Na[Ru(*N*-R-5-Cl-salim)$_2$] × ½ Et$_3$N during an hour. Right: Graphical determination of hydrolysis constant of Na[Ru(*N*-R-5-Cl-salim)$_2$] × ½ Et$_3$N by kinetics of pseudo-first order.

Isosbestic points in hydrolytic profile of complex compounds undoubtedly confirm simultaneous existence of two species in solution as a result of hydrolysis. Ligand to metal charge transfer bands centered near 400 nm are characterized with moderate hypochromism and hypsochromic shift, which correlates with entrance of hydroxyl ion (pH 7.40) in primary coordination sphere. Since the hydrolysis of 10^{-5} M complex compounds was performed in 0.1 M buffered system, keeping concentration of hydroxyl ions constant, rate of hydrolysis is only dependent on complex making this reaction of pseudo-first order. Hydrolysis constants were determined graphically using equation:

$$k = 1/t \times \ln[(A_0 - A_\infty)/(A_t - A_\infty)] \quad (2)$$

where A_0 is the absorbance at the beginning, A_t absorbance in time t and A_∞ is absorbance after $10t_{1/2}$.

Table 3. Hydrolysis constants of complexes Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N under physiological conditions at 294 K measured at LMCT

X	λ / nm	10^{-2} k_H / min^{-1}
H	395	8.31
Cl	416	7.44
Br	404	4.99
NO_2	377	4.60

Hydrolysis constants of complexes have 10^{-2} min^{-1} magnitude. Measured values of k_H suggest that 5-X-substituent on Schiff bases has impact on hydrolysis constant of complexes, which decrease in order H > Cl > Br > NO_2. There are few theoretically possible pathways for hydrolysis of Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N (Fig. 6.)

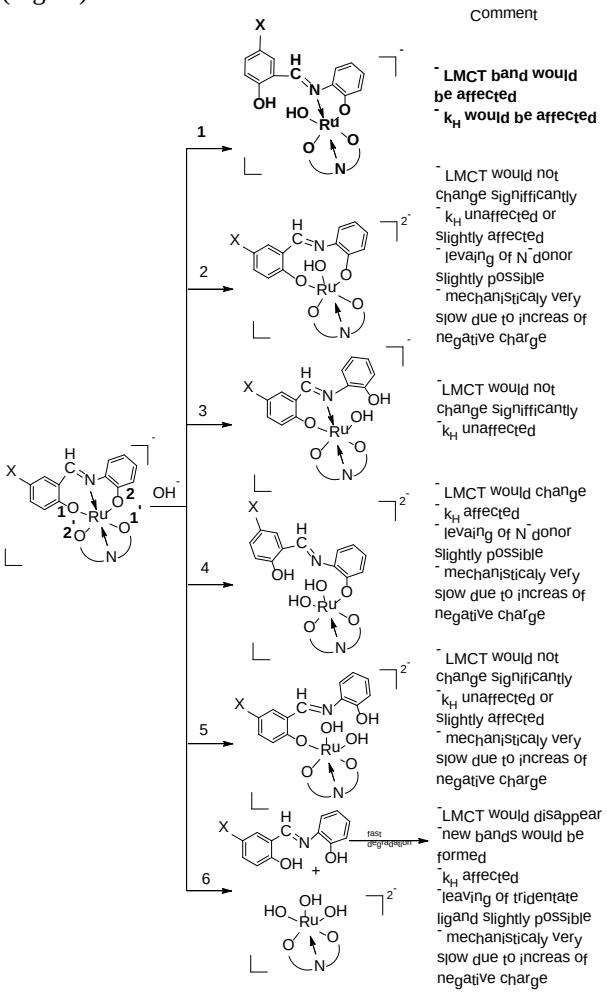

Figure 6. Possible pathways for hydrolysis of complex with short comments. Second ligand molecule was omitted for clarity.

Regarding comments from Fig. 6 hydrolysis occur most probably by pathway 1. Few factors might be determining for k_H values in the case of studied complexes: (i) strength of Ru-O bond, (ii) size of ligand, (iii) electronic effect of substituent. All other parameters that can affect k_H were kept constant (ionic strength, temperature, charge or basic octahedral geometry of complex etc.). The change in vibration frequency of C-O bond in free and bound ligand is rough measure of Ru-O bond strength. Significant change in vibration frequency of C-O bond means weak Ru-O bond and *vice versa*. Change in stretching vibrations of C-O bond for H, Cl, Br and NO_2 are 12, 15, 16 and 19 cm^{-1}, respectively (Kahrović *et al.*, 2014), meaning that strength of Ru-O(1) bond increases in order H < Cl < Br < NO_2. This is in excellent correlation with the fact that strengthening of Ru-O(1) bond leads to decrease of k_H value. Size of ligand increases in order H < Cl < Br ~ NO_2 while constant of hydrolysis decrease. This can be interpreted in the light of solvatation theory, meaning that the degree of solvation decreases with increasing of particle size. Moving from H- to NO_2 derivative of [Ru(*N*-R-5-X-salim)$_2$]$^-$, the number of nucleophile species (OH^-) available in second coordination sphere for binding to the metal atom decreases resulting in decrease of k_H value.

Variation of hydrolysis constants for different 5-X-substituents shows that the entry of OH^- nucleophile into the first coordination sphere of metal center occurs on account of breaking of Ru-O bond that comes from salicylaldehyde part of Schiff bases thus supporting pathway 1(Fig. 6.) for hydrolysis.

Obviously not only effects of substituents are responsible for k_H values of complexes, rather overall effect concerning Ru-O bond strength, size of ligand and electronic effects of substituents are determining for k_H.

The constant of hydrolysis and half wave potentials confirm that Ru(III) complexes Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N are sufficiently inert toward hydrolysis at physiological condition, also might be stable toward different reducing agents, e.g. ascorbic acid or glutathione in biological environment, which recommend these complexes for further studies.

CONCLUSION

A new complex of ruthenium(III) with Schiff base derived from salicylaldehyde and 2-aminophenole was prepared as a homologue of Na[Ru(*N*-R-5-X-salim)$_2$] × ½ Et$_3$N, where X = Cl, Br, NO_2, published by our team recently. The compound is characterized using different spectroscopic and spectrometric techniques. Low spin ruthenium(III) is octahedrally chelated with two dibasic tridentate Schiff base ligands. Four complexes named Sodium bis[*N*-(2-oxy-κO-phenyl)-5-substituted salicylideneimine-$\kappa^2 N,O$(1-)]ruthenate(III) hemitriethylamine solvate were investigated using electron spectroscopy and cyclic voltammetry to study correlation between electronic effects of substituent on Schiff base ligand of complexes and half-wave potential and rate of hydrolysis. We found that ability of hydrolysis and reduction potential can be tuned up by manipulations of substituent on ligand system, which can be very useful in design of new anticancer drugs with required well defined properties.

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Summary/Sažetak

Uticaj elektronskih efekata supstituenata na Šifovim bazama kao ligandima, izvedenim iz salicilaldehida i 5-supstituiranih saliciladehida i 2-aminofenola, na polutalasni potencijal i konstante hidrolize odgovarajućih Natrij bis(iminato)rutenata(III) hemitrietilamin solvata je ispitan cikličkom voltametrijom i elektronskom spektroskopijom. Novi kompleks Natrij bis[*N*-(2-oksi-κO-fenil)salicilidenimin-$\kappa^2 N,O$(1-)]rutenat(III) hemitrietilamin je pripremljen i okarakterisan na bazi infracrvene i elektronske spektroskopije, MALDI-TOF/TOF masene spektrometrije i sadržaja rutenija. Ciklički voltamogrami kompleksa u organskim rastvaračima demonstitraju kvazi-reverzibilan jednoelektronski proces sa izraženom reducirajućom sposobnosti Ru(II). Primjenom Hametove jednačine na polutalsne potencijale kompleksa našli smo da supstituenti utiču na pomijeranje elektronske gustoće preko X-C_6H_3-O-Ru-O-C_6H_3-X veza. Elektronska spektroskopija je korištena za ispitivanje ponašanja kompleksa u fiziološkim uslovima i pokazala je da se dešava hidroliza. Konstante hidrolize su određene spektrofotometrijski na osnovu kinetike pseudo-prvog reda.