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Ru(II) CATALYSTS DERIVED FROM $RuCl_3(NO)(PPh_3)_2$ AND THEIR USE IN THE HYDROLYSIS OF RIVASTIGMINE TARTRATE AND NEOSTIGMINE BROMIDE

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ABSTRACT

New ruthenium (II) organometallics have been synthesized by using the precursor $RuCl_3(NO)(PPh_3)_2$ with amide ligands. The tentative structures are proposed on the basis of elemental analysis, IR, ^1H, ^{13}C and ^{31}P NMR spectral data. These organometallics were used as catalysts for the hydrolysis of rivastigmine tartrate and neostigmine bromide. The percent yields of hydrolyzed products of these drugs were determined spectrophotometrically.

Key words : Hydrolysis, Ruthenium, Catalyst

INTRODUCTION

Extensive work has been reported and comprehensive reviews were written on ruthenium organometallics[1, 2] and their catalytic applications[3, 4]. The transition metal complexes with nitrosyl (NO) ligands have recently shown their potentiality in performing selective catalytic transformations of molecules[5, 6]. As a part of our interest to synthesize ruthenium complexes using inexpensive amide ligands[7-9], in the present investigations, we have described the preparation and characterization of three stable Ru (II) complexes with PPh_3, nitrosyl and amide ligands from the precursor, $RuCl_3(NO)(PPh_3)_2$. To develop the catalytic activity of ruthenium organometallics in the hydrolysis reactions, a detailed study on the drugs viz. rivastigmine tartrate (RS) and neostigmine bromide (NS) was carried out. In the literature, very few methods for the hydrolysis of rivastigmine tartrate to give its hydrolyzed product (HRS)[10] and neostigmine bromide to give its hydrolyzed product (HNS)[11] have been reported. The lack of reports on the ruthenium catalyzed hydrolysis methods led to the development of the present method in basic medium with lesser

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hydrolysis times. The percent yields of HRS and HNS were determined spectrophotometrically by coupling them with 3-methylbenzothiazolinone hydrazone (MBTH) reagent in the presence of sodium metaperiodate[12, 13].

EXPERIMENTAL

Instruments

The percentages of carbon, hydrogen, nitrogen in ruthenium complexes were determined at the Technical University of Berlin; Berlin, using a Perkin-Elmer CHN analyzer at 24ºC. The melting points of all the ligands and complexes were obtained on a Buchi- 510 melting point apparatus. UV-Visible spectra were recorded with Shimadzu UV-160A, a UV-Visible double beam spectrophotometer with matched quartz cells of path length 1 cm. The IR spectra were recorded in KBr pellets on Perkin Elmer-283 spectrophotometer and the scanning rate was 6 minutes in the 4000-200 cm^{-1} range. A Jeol 100 MHz FT NMR spectrometer was used for ^{1}H NMR spectra. Brucker WH 270 (67.93 MHz) and Brucker WH 270 (109-29 MHz) spectrometers were used for ^{13}C NMR and ^{31}P NMR spectra, respectively. A Gouy balance, calibrated with $Hg[Co(NCS)_4]$, was used to determine the magnetic susceptibilities of complexes in the solid state at room temperature. Conductance measurements were done on 10^{-3} M solutions of compounds in dichloromethane at room temperature using a Digison Digital conductivity meter model DL-909.

Materials

$RuCl_3.3H_2O$ (Johnson Matthey and Co. Ltd), Me_2CO (Qualigens) and Et_2O (Qualigens) were used as supplied. The precursor, $RuCl_3(NO)(PPh_3)_2$, was prepared as previously reported[14, 15]. Three amide ligands, viz. N-(3-Methyl-pyridin-2-yl)-phthalamic acid (MPYPA); 3-(3-Methyl-pyridin-2-ylcarbamoyl)-acrylic acid (MPYAA); N-(3-Methyl-pyridin-2-yl)-succinamic acid (MPYSA) were newly prepared.

A 10 % NaOH solution (Merck) was prepared by dissolving NaOH (25 g) in 250 mL of double distilled water. Sodium metaperiodate (0.1 M) solution (Merck) was prepared by dissolving 2.138 g in 100 mL of double distilled water. 0.2 M MBTH solution (Merck) was prepared by dissolving 4.314 g in 100 mL of double distilled water.

Pure drug solutions

Pure rivastigmine tartrate (100 mg) was treated with 20 mL of 0.2 N NaOH and transferred into a 250 mL separator. The free base of the drug viz. rivastigmine was

extracted with $CHCl_3$ (4 x 20 mL) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in 100 mL of double distilled water to obtain a 1 mg/mL solution. This solution was diluted with the same solvent to get the working rivastigmine (as free base) solution of 100 μg/mL. Pure neostigmine bromide (100 mg) was treated with 20 mL of 0.2 N NaOH solution and transferred into a 250 mL separator. Now, neostigmine was extracted with $CHCl_3$ (4 x 20 mL) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in 100 mL of 0.2 N HCl to obtain a 1 mg/mL solution. This solution was then diluted with the same solvent to obtain the working neostigmine (as bromide) solution of 100 μg/mL.

Pharmaceutical solutions

An accurately weighed amount of capsule powder equivalent to 100 mg of rivastigmine tartrate or tablet powder equivalent to 100 mg of neostigmine bromide was treated with 20 mL of 0.2 N NaOH solution and the pharmaceuticals solutions were prepared as described above.

Procedure for the synthesis of ruthenium catalysts

20 mL of acetonic solution containing amide ligand (0.4 mmol) was added to the 20 mL acetonic solution of precursor $RuCl_3(NO)(PPh_3)_3$ (0.304 g, 0.4 mmol) with constant stirring. The reaction mixture was taken in a 100 mL round bottom flask and stirred magnetically for 2 h. The resulting solution was concentrated to 5 mL under reduced pressure and a few mL of diethyl ether was added to initiate the crystallization. The resulting product was separated by suction filtration, washed with diethyl ether, vacuum dried to get a crystalline compound and was recrystallized using CH_2Cl_2 and Et_2O solvent mixture.

Ruthenium catalyzed hydrolysis and spectrophotometric determination method

In a 100 mL round bottom flask, rivastigmine (4 mL) as free base or neostigmine as bromide, 4 mL of sodium hydroxide and $RuCl(CO)(PPh_3)_2$(MPYPA) (0.01 mmol) were taken. The contents of the flask were refluxed for 15 min. at 70 ^{0}C. The contents of the flask were cooled, neutralized with a little excess of hydrochloric acid and transferred into 20 mL calibrated tube. Now, 3 mL each of MBTH solution and sodium metaperiodate solution were added and the tubes are kept aside for 5 min. The total volumes were made up to 20 mL with double distilled water. The absorbances of the colored solutions were measured at 520 nm against their reagent blanks. The amounts of HRS and HNS formed during the hydrolysis process were estimated from their respective calibrated curves. The

procedure is repeated by changing amide complexes of Ru (II) one by one (Complex : 1-3). This procedure was also applied for pharmaceutical solutions.

RESULTS AND DISCUSSION

Characterization of Ru (II) organometallics

All the ruthenium (II) organometallics are crystalline, non-hygroscopic and stable at room temperature. The organometallics are freely soluble in DMSO, DMF and methanol but sparingly soluble in water. The physical and analytical data of all the new Ru (II) organometallics is in good agreement with the proposed molecular formulae viz. $RuCl_2(NO)(PPh_3)(L_2)$.

IR Spectral data

The infrared spectra of free amide ligands and precursor with the spectra of new ruthenium organometallics were compared to study the binding mode of the ligands to ruthenium in new organometallics. In the ligand spectra, strong absorption bands are observed in free ligands around 1705 and 1340 cm^{-1} due to $\upsilon_{C=O}$ stretching and δ_{O-H} deformations of carboxylic acid, respectively. The disappearance of these bands and appearance of new bands in the 1560-1540 and 1390-1375 cm^{-1} ranges in complex spectra corresponding to υ_{COO^-} (asymmetric) and υ_{COO^-} (symmetric) vibrations indicates the participation of oxygen atom of carboxylic group in chelation[16]. The stretching frequencies of amide nitrogen are observed in the range of 3300-3250 cm^{-1} in free ligands. In the complexes spectra, appreciable shifts are not observed in this region confirming the non involvement of amide nitrogen in coordination. The stretching frequencies of amide oxygen are observed at 1685 cm^{-1} in free amide ligands. In all the complexes spectra, a negative shift by 25-35 cm^{-1} is observed in the 1665-1655 cm^{-1} range indicating the coordination of amide oxygen to ruthenium[17]. In the precursor spectrum, a strong absorption band is found at 1880 cm^{-1} due to the presence of a nitrosyl group[18]. The same bands are also observed in complexes spectra indicating the presence of nitrosyl ligands in them. Strong absorption band is present in precursor spectrum at 520 cm^{-1}. In complexes spectra, these bands are found in the range of 540-520 confirming the presence of Ru-P bond[19]. The coordination of oxygen atom of ligand with ruthenium is also indicated by the presence of a band in the range of 450-410 cm^{-1}. Two bands appear in the ranges of 330-320 and 325-300 cm^{-1} in complexes spectra indicating the presence of two chloride ligands in the cis-position around the ruthenium centre. All other characteristic bands of PPh_3 are observed in the expected regions in precursor spectrum and complexes spectra[20].

^{1}H NMR spectral analysis

The integral intensities of each signal in the ^{1}H NMR spectra of precursor, ligands and organometallics are found to agree with the number of different types of protons present. The binding modes of amide ligands are conformed by comparing the ^{1}H NMR spectra of the precursor, free ligands with Ru (II) organometallics. The carboxylic proton signals in the 10.05-12.10 δ range which are present in ligand spectra are not observed in organometallics spectra indicating the deprotonation of carboxylic acid followed by the chelation through oxygen atom. The broad signal of amide proton is observed in the 5.10-9.90 δ and 5.05-8.95 δ range in ligands spectra and complexes spectra, respectively, confirming the non-participation of this group in chelation. The spectrum of MPYAA contains doublet of doublet at 6.25 δ indicating the presence of CH=CH unit and the spectrum of MPYSA contains triplet of triplet at 2.30 δ indicating the presence of CH_2-CH_2 unit[21]. These signals almost remain unchanged in the spectra of respective organometallics. Multiplets observed in the organometallics spectra around 6.50-7.90 δ have been assigned to the aromatic protons of ligands and triphenylphosphines[22].

^{13}C NMR spectral analysis

In the spectra of organometallics, ^{13}C signals are observed in the downfield regions of 180.2-185.4 δ and 179.1-182.4 δ indicating the coordinated carboxylic carbon and carbonyl carbon of amide group, respectively. The spectrum of $RuCl_2(NO)(PPh_3)$(MPYAA) exhibits a signal around 115.5 δ confirming the presence of doubly bonded carbon[23] and the spectrum of $RuCl_2(NO)(PPh_3)$(MPYSA) exhibits a signal around 31.8 δ confirming the presence of singly bonded carbon. The aryl carbons are found to resonate in the 118.5-134.5 δ range.

^{31}P NMR spectral analysis

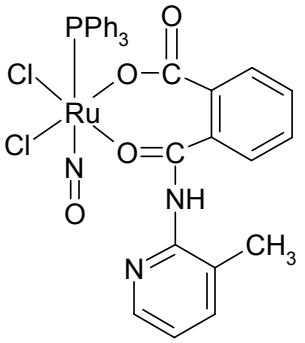
A singlet is observed around 33.45 δ in the ^{31}P NMR spectra of these organometallics due to the presence of a single PPh_3 ligand[24].

Electronic spectral analysis

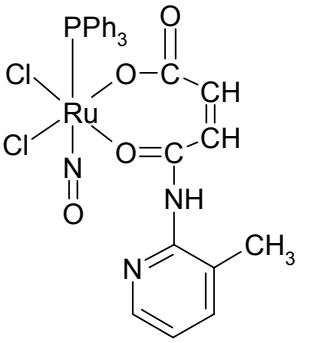
The ground state of Ru (II) (t^6_{2g} configuration) is $^{1}A_{1g}$. The excited states, corresponding to the $t^5_{2g}e_{1g}$ configuration, are $^{3}T_{1g}$, $^{3}T_{2g}$, $^{1}T_{1g}$ and $^{1}T_{2g}$ in the order of increasing energy. Hence, four bands are possible corresponding to the $^{1}A_{1g} \rightarrow {}^{3}T_{1g}$, $^{1}A_{1g} \rightarrow {}^{3}T_{2g}$, $^{1}A_{1g} \rightarrow {}^{1}T_{1g}$ and $^{1}A_{1g} \rightarrow {}^{1}T_{2g}$ transitions. In the electronic spectra of all the organometallics, two bands appeared in the regions of 450-470 nm and 270-320 nm

corresponding to the transitions $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g,}$ respectively. Sometimes the higher energy transition is totally obscured by intense charge transfer bands. Other higher energy bands can be assigned as ligand $\pi \rightarrow \pi^*$ and other ligand to metal charge-transfer transitions. These data suggest octahedral geometry for all the Ru (II) organometallics[25].

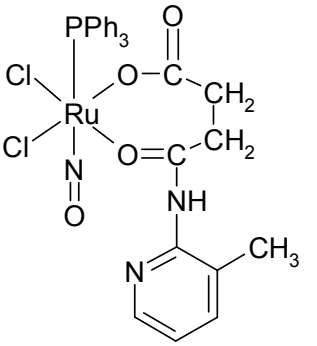
On the basis of analytical and spectral analysis, octahedral structures **(Scheme 1)** have been tentatively proposed for all of the Ru (II) organometallics with amide ligands.



$RuCl_2(NO)(PPh_3)$ (MPYPA)



$RuCl_2(NO)(PPh_3)$ (MPYAA)



$RuCl_2(NO)(PPh_3)$ (MPYSA)

Scheme 1. Structures of Ru (II) organometallics containing amide ligands

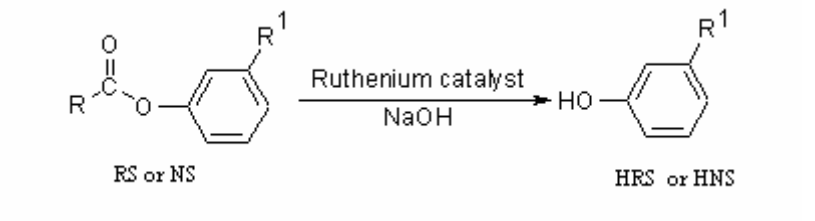
Catalytic applications

Chemistry of hydrolysis and colored product formation

Rivastigmine tartrate (RS) or neostigmine bromide (NS) contains an aromatic ester group which on base hydrolysis catalyzed by ruthenium organometallics produces its hydrolyzed product (HRS or HNS). A plausible mechanism[26] has been proposed for the ruthenium catalyzed hydrolysis of RS and NS.

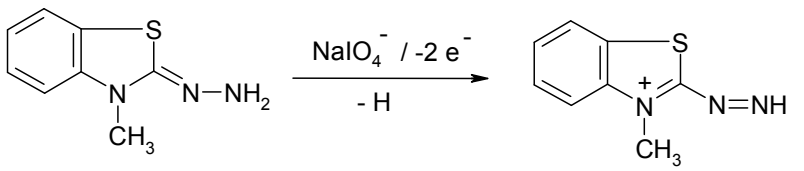
When treated with periodate, MBTH undergoes oxidation with loss of two electrons and one proton to form an electrophilic intermediate (Step 1), which couples with hydrolyzed products due to the presence of phenolic hydroxyl groups by electrophilic attack on the most nucleophilic site of the aromatic ring viz. the position para to the phenolic hydroxylic group. The resulting intermediate species is spontaneously oxidized with periodate to form the colored oxidative coupling product (Step-2)[12] **(Scheme 2)**.

Hydrolysis

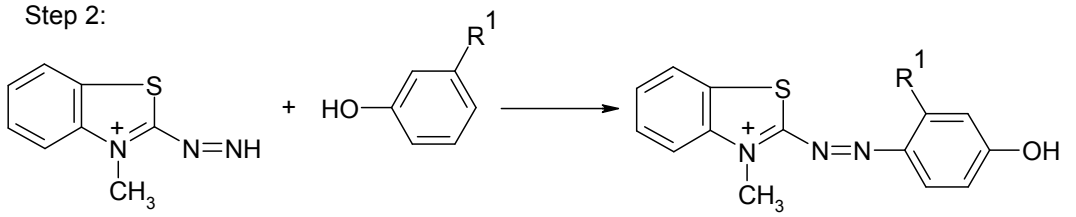


Color product

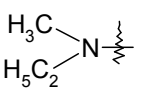
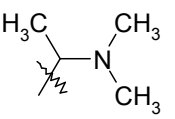
Step 1:

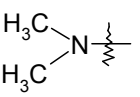
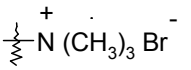


Step 2:



where

R =  and R^1 =  for rivastigmine as free base and

R =  and R^1 =  for neostigmine as bromide

Scheme 2 : Hydrolysis and color product formation

Percent yields of hydrolyzed product

The percent yields of hydrolyzed products of rivastigmine tartrate and neostigmine bromide formed using their pharmaceuticals with all the ruthenium catalysts were determined spectrophotometrically and the yields of HNS and HRS were found in the range of 85.12-89.12 %.

CONCLUSIONS

Three new Ru (II) organometallics containing carboxy amide ligands were synthesized from $RuCl_3(NO)(PPh_3)_2$. Octahedral structures have been assigned to these organometallics. These organometallics were found to be efficient for the faster hydrolysis ester containing drug viz. rivastigmine tartrate and neostigmine bromide. These reactions require less reaction times and produces high product yields.

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