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Short communication

Ru(III)-catalyzed oxidation of pyridoxine and albuterol in pharmaceuticals

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Ru(III) complexes with coordinated amide were synthesized and characterized by elemental, IR, mass, electronic, ESR spectral analysis, magnetic and conductance measurements and octahedral structures have been proposed. These complexes were used as catalysts for the oxidation of pyridoxine and albuterol in pharmaceuticals in presence of hydrogen peroxide. The role of co-oxidant and the effect of reaction time on the yields of oxidation products which were spectrophotometrically determined by condensing them with sulfanilic acid in acid medium were investigated. Structures of the oxidation products were established with the help of IR and NMR spectral analysis.

1. Introduction

The development of ruthenium-catalyzed methods [1] for the oxidation of primary [2] and secondary [3] alcohols to produce carbonyl derivatives remains an important one in pharmaceutical products [4]. But, these methods require either the presence of a co-oxidant [5] or a prolonged oxidation time [6] leading to environmental problems. Pyridoxine [7], the first isolated vitamin B6, is oxidized to pyridoxal in biological system. Albuterol [7] is a beta-adrenergic stimulant which has a highly selective action on the receptors in bronchial smooth muscle, there by causing relaxation of bronchial muscle fibres. In literature, some oxidation methods of pyridoxine as hydrochloride (5-hydroxy-6-methyl-3,4-pyridine dimethanol, hydrochloride, PYE) to pyridoxal (3-hydroxy-5-(hydroxy methyl)2-methyl-4-pyridine carboxaldehyde, PYL) [8] and albuterol (α^1[(*tert*-butyl amino)methyl]4-hydroxy *m*-xylene α,α^1-diol sulfate, 2:1 salt, AB) to its oxidation product (5-[(*tert*-butyl amino)acetyl]-2-hydroxy benzaldehyde, OPAB) [9] were reported. Even though some complexes were synthesized using the [$RuCl_3(PPh_3)_3$] [10–12], no amide complex of this precursor was synthesized so far. Hence, Ru(III) complexes with coordinated amide of the type $RuCl_2(PPh_3)_2(L_2)$ (Complex-1–12) were synthesized using the precursor [$RuCl_3(PPh_3)_3$] and used as catalysts for the oxidation of pyridoxine and albuterol (in pure form and pharmaceutical formulations) in presence of hydrogen peroxide with lesser oxidation times without using a co-oxidant. PYL and OPAB were condensed with sulfanilic acid (SA) in acid medium [13] for their spectrophotometric determination.

2. Experimental

2.1. Instruments

The melting points of all the ligands and complexes were determined on a Buchi-510 melting point apparatus. The percentages of carbon, hydrogen, nitrogen were determined using a PerkinElmer CHN analyzer. The IR spectra were recorded in KBr pellets on PerkinElmer-283 spectrophotometer. The scanning rate was 6 min in the range of 4000–200 cm^{-1}. MICROMASS-7070 spectrometer operating at 70 eV using a direct inlet system was used for mass spectra. UV–visible spectra were recorded with Shimadzu UV-160A, a UV–visible double beam spectrophotometer with matched quartz cells of path length 1 cm. ESR spectra were recorded on JEOL-JES-FE-3X spectrometer. Gouy balance calibrated with $Hg[Co(NCS)_4]$ was used for the determination of magnetic susceptibilities of complexes in solid state at room temperature. Conductance measurements were done on 10^{-3} M solution of compounds in dichloromethane at room temperature using Digisun Digital conductivity meter model DL-909.

2.2. Materials and reagents

$RuCl_3{\cdot}3H_2O$ (Johnson Matthey & Co. Ltd.), acetone (Qualigens) and diethyl ether (Qualigens) were used as such. The precursor $RuCl_3(PPh_3)_3$ [10] and the 12 amide ligands viz. 2-(anilinocarbonyl) benzoicacid (ACBA); 4-anilino-4-oxo but-2-enoicacid (AOBEA);

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Table 1
Physical and analytical data of Ru(III) complexes with coordinated amide

Complex no.	Complex/formula	Mp (°C)	Color	Yield (g)	*Analysesfound*(*calculated*)(%)			
					C	H	N	Ru
1.	$RuCl_2(PPh_3)_2$(ACBA), $C_{50}H_{40}Cl_2NO_3P_2Ru$	242	Green	0.269 (72%)	64.06 (64.10)	4.24 (4.27)	1.47 (1.49)	10.82 (10.79)
2.	$RuCl_2(PPh_3)_2$(AOBEA), $C_{46}H_{38}Cl_2NO_3P_2Ru$	235	Green	0.261 (74%)	62.22 (62.30)	4.32 (4.28)	1.60 (1.58)	11.36 (11.39)
3.	$RuCl_2(PPh_3)_2$(AOBA), $C_{46}H_{40}Cl_2NO_3P_2Ru$	231	Green	0.251 (71%)	62.11 (62.16)	4.55 (4.50)	1.59 (1.57)	11.33 (11.37)
4.	$RuCl_2(PPh_3)_2$(NACBA), $C_{54}H_{42}Cl_2NO_3P_2Ru$	249	Brown	0.295 (75%)	65.77 (65.72)	4.29 (4.25)	1.44 (1.41)	10.26 (10.24)
5.	$RuCl_2(PPh_3)_2$(NAOBEA), $C_{50}H_{40}Cl_2NO_3P_2Ru$	245	Brown	0.272 (73%)	64.02 (64.10)	4.31 (4.27)	1.46 (1.49)	10.83 (10.79)
6.	$RuCl_2(PPh_3)_2$(NAOBA), $C_{50}H_{42}Cl_2NO_3P_2Ru$	243	Brown	0.265 (71%)	64.01 (63.96)	4.51 (4.47)	1.49 (1.49)	10.72 (10.76)
7.	$RuCl_2(PPh_3)_2$(BACBA), $C_{51}H_{40}Cl_2N_3O_3P_2Ru$	279	Black	0.288 (74%)	62.63 (62.70)	4.13 (4.09)	4.35 (4.30)	10.33 (10.34)
8.	$RuCl_2(PPh_3)_2$(BAOBEA), $C_{47}H_{38}Cl_2N_3O_3P_2Ru$	275	Black	0.281 (76%)	60.83 (60.90)	4.14 (4.10)	4.56 (4.53)	10.88 (10.90)
9.	$RuCl_2(PPh_3)_2$(BAOBA), $C_{47}H_{40}Cl_2N_3O_3P_2Ru$	271	Black	0.266 (72%)	60.71 (60.77)	4.34 (4.31)	4.56 (4.52)	10.91 (10.88)
10.	$RuCl_2(PPh_3)_2$(PHCBA), $C_{50}H_{41}Cl_2N_2O_3P_2Ru$	242	Green	0.269 (71%)	63.01 (63.09)	4.27 (4.31)	2.96 (2.94)	10.60 (10.62)
11.	$RuCl_2(PPh_3)_2$(OPHBEA), $C_{46}H_{39}Cl_2N_2O_3P_2Ru$	234	Green	0.259 (72%)	61.20 (61.26)	4.36 (4.32)	3.13 (3.10)	11.17 (11.20)
12.	$RuCl_2(PPh_3)_2$(OPHBA), $C_{46}H_{41}Cl_2N_2O_3P_2Ru$	231	Green	0.274 (76%)	61.05 (61.12)	4.57 (4.54)	3.13 (3.10)	11.15 (11.18)

4-anilino-4-oxobutanoicacid (AOBA); 2-[(1-naphthyl amino) carbonyl] benzoic acid (NACBA); 4-(1-naphthylamino)4-oxobut-2-enoicacid (NAOBEA); 4-(1-naphthyl amino)-4-oxobutanoicacid (NAOBA); 2-[(1*H*-benzimidazol-2-yl amino)carbonyl]benzoic acid (BACBA); 4-(1*H*-benzimidazol-2-ylamino)-4-oxobut-2-enoic acid (BAOBEA); 4-(1*H*-benzimidazol-2-ylamino)-4-oxobutanoicacid (BAOBA); 2-[(2-phenylhydrazino) carbonyl] benzoicacid (PHCBA); 4-oxo-4-(2-phenylhydrazino)but-2-enoic acid (OPHBEA); 4-oxo-4-(2-phenyl hydrazino)butanoic acid (OPHBA) were synthesized as previously reported [14]. Hydrogen peroxide solution (Merck, 30%) was used as it is. 0.1N hydrochloric acid solution (Qualigens) was prepared by diluting 9.1 ml of conc. hydrochloric acid solution to 1000 ml with double distilled water. 0.1N sulfanilic acid solution (Merck) was prepared by dissolving 1.071 g in 100 ml of double distilled water.

2.3. *Drug solutions*

Standard stock solutions of pyridoxine hydrochloride or albuterol sulfate (1 mg/ml) were prepared by dissolving 100 mg of pure pyridoxine hydrochloride or albuterol sulfate in 100 ml of double distilled water. The stock solutions were diluted with double distilled water to get the working pure drug solutions of 100 μg/ml. An accurately weighed amount of tablet powder equivalent to 100 mg of pyridoxine hydrochloride or albuterol sulfate was extracted separately with chloroform (4 × 20 ml) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in 100 ml of double distilled water to achieve a concentration of 1 mg/ml. This solution was diluted with double distilled water to get the working pharmaceutical solutions of 100 μg/ml.

2.4. *Recommended procedures*

2.4.1. *Synthesis of ruthenium(III) catalysts*

To $RuCl_3(PPh_3)_3$ solution (0.4 mmol in 20 ml acetone), ligand solution (0.4 mmol in 20 ml acetone) was added and the reaction mixture was stirred magnetically for 3 h. The resulting solution was concentrated to 5 ml under reduced pressure and a few ml of diethylether was added to initiate the crystallization. The precipitate formed was separated by suction filtration, washed with diethylether and dried in vacuum. The crystalline compound obtained was recrystallized using dichloromethane and diethylether mixture.

2.4.2. *Ruthenium-catalyzed oxidation method*

In a 100 ml round bottom flask, 4 ml of pyridoxine hydrochloride or albuterol sulfate solution (pure or pharmaceutical formulation), hydrogen peroxide (4 ml for PYE and 6 ml for AB) and 0.01 mmol of Ru(III) catalyst were taken. The contents of the flask were refluxed (15 min for PYE and 30 min for AB) at 60 °C. The contents of the flask were cooled and transferred separately into 20-ml-calibrated tubes. Now, sulfanilic acid solution (2 ml for PYL and 4 ml for AB) was added and the tubes were heated for 5 min in boiling water bath. Pink color was developed slowly. The tubes were cooled and 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 PYL and OPAB formed during oxidation process were determined from their respective calibration curves.

3. Results and discussion

3.1. *Characterization of Ru(III) complexes with coordinated amide*

3.1.1. *Physical and analytical data*

Twelve Ru(III) complexes with coordinated amide were synthesized using the precursor, $RuCl_3(PPh_3)_3$. The percentages of carbon, hydrogen and nitrogen were determined experimentally using CHN analyzer. The percentage of ruthenium in complexes was determined by literature method [15]. The physical and analytical data (Table 1) for the newly synthesized Ru(III) complexes is in good agreement with the proposed molecular formulae viz. $RuCl_2(PPh_3)_2(L_2)$.

3.1.2. *Infrared spectral analysis*

The infrared spectra of the free amide ligands and precursor are compared with the Ru(III) complexes to elucidate the binding mode of the amide ligands to ruthenium. The non-involvement of amide nitrogen in coordination is confirmed by the consistent stretching frequencies of amide nitrogen in the range of 3375–3264 cm^{-1} in ligand and complexes spectra. However, in the IR spectra of Ru(III) complexes having ligands derived from benzimidazoles viz. BACBA, BAOBEA and BOABA, $\upsilon_{N\text{-}H}$ (benzimidazole) modes are observed at 3360, 3368 and 3365 cm^{-1}, respectively. Similarly, in the IR spectra of complexes having ligands derived from phenylhydrazines viz. PHCBA, OPHBEA and OPHBA, $\upsilon_{N\text{–}H}$ (phenylhydrazine) modes are observed at 3362, 3367 and 3360 cm^{-1}, respectively. Stretching frequencies of amide oxygen of complexes have undergone negative shifts by 30–40 cm^{-1} from 1670 cm^{-1} of free amide ligands indicating the coordination of amide oxygen to ruthenium [16]. In free ligands, strong absorption bands are found around 1710 and 1340 cm^{-1} corresponding to $\upsilon_{C=O}$ stretching and $\delta_{O\text{–}H}$ deformation modes of vibration. In complexes spectra, these bands are not observed, but new bands are observed in the ranges of 1548–1529 and 1388–1348 cm^{-1} corresponding to υ_{COO^-} (asymmetric) and υ_{COO^-} (symmetric) vibrations indicating the participation of oxygen atom of carboxylic group in chelation [12]. Similarly, a strong absorption band in precursor spectrum as well as complexes