Neutral and cationic half-sandwich arene ruthenium, Cp*Rh and Cp*Ir oximato and oxime complexes: Synthesis, structural, DFT and biological studies

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ARTICLE INFO

ABSTRACT

The reaction of [(p-cymene)RuCl$_2$]$_2$ and [Cp*MCl$_2$]$_2$ (M = Rh/Ir) with chelating ligand 2-pyridyl cyanoxime {pyC(CN)NOH} leads to the formation of neutral oximato complexes having the general formula [(arene)M{pyC(CN)NO}Cl] {arene = p-cymene, M = Ru, (**1**); Cp*, M = Rh (**2**); Cp*, M = Ir (**3**)}. Whereas the reaction of 2-pyridyl phenyloxime {pyC(Ph)NOH} and 2-thiazolyl methyloxime {tzC(Me)NOH} with precursor compounds afforded the cationic oxime complexes bearing formula [(arene)M{pyC(ph)NOH}Cl]$^+$ and [(arene)M{tzC(Me)NOH}Cl]$^+$ {arene = p-cymene M = Ru, (**4**), (**7**); Cp*, M = Rh (**5**), (**8**); Cp*, M = Ir (**6**), (**9**)}. The cationic complexes were isolated as their hexafluorophosphate salts. All these complexes were fully characterized by analytical, spectroscopic and X-ray diffraction studies. The molecular structures of the complexes revealed typical piano stool geometry around the metal center within which the ligand acts as a NN′ donor chelating ligand. The Chemo-sensitivity activities of the complexes evaluated against HT-29 (human colorectal cancer), and MIAPaCa-2 (human pancreatic cancer) cell line showed that the iridium-based complexes are much more potent than the ruthenium and rhodium analogues. Theoretical studies were carried out to have a deeper understanding about the charge distribution pattern and the various electronic transitions occurring in the complexes.

1. Introduction

The study of half-sandwich arene ruthenium (arene = p-cymene and its derivatives) Cp*Rh and Cp*Ir complexes represents one of the most versatile subject in the field of organometallic chemistry because of their potential applications in various areas [1–6]. These complexes bearing the general formula [(arene)(M)(L)X]$^+$ (M = Ru, Rh and Ir, L is a chelating ligand and X is a halide) have been extensively studied as potential metal-based anticancer drugs [7–11]. The coordination sphere of the metal center in these half-sandwich complexes is stabilized by the arene moiety which protects the metal's oxidation state occupying three coordinating sites, the chelating ligand L which controls the reactivity through various interactions and the M–Cl bond which easily gets dissociated and produces the active site for the metal ion to target biomolecules [12,13]. It is seen that the leaving group, the chelating ligand and the arene substituent strongly influence the biological and structure activity relationship of these complexes [14]. Sadler et al. carried out number of experiments with chelating N,N–, N,O– and O,O– ligands to study the SAR activity of cytotoxic ruthenium(II) complexes by increasing the size of the arene ring [15]. Also it has been proposed by various research groups that the cytotoxicity of half-sandwich metal complexes increases with increase in size of the arene substituent [16–18]. These complexes have also displayed their remarkable activity as catalyst in various organic transformation reactions such as hydrogenation, water oxidation and C–H activation [19–21]. In recent years many half-sandwich complexes with NN′ chelating nitrogen donor ligands have been accomplished in our laboratory [22].

Oxime ligands in particular have developed a keen interest in the field of coordination chemistry [23]. The oxime ligand can act as an ambidentate ligand and can coordinate with metal ions either

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through nitrogen or oxygen atoms [24]. Cyanoximes having the general formula {HO−N=C(CN)-R}, where R is an electron with-drawing group represents an important class of biologically active compounds and transition metal complexes of cyanoximes have shown pronounced cytotoxicity and antimicrobial activity [25,26]. The presence of the cyano group as a substituent close to the oxime fragment increases the acidity of the oxime several thousand times greater than that of common oximes [27]. The anions of 2-pyridyl oximes serve as a versatile ligand for preparation of complexes with unusual topologies exhibiting interesting magnetic properties [28]. Oximes have the capability to remain intact in the co-ordination sphere of the metal by undergoing O−H bond cleavage to afford oximate derivatives [29]. Despite having a rich diversified chemistry of metal oxime and oximato complexes, it is noteworthy that only a few half-sandwich platinum group metal oxime com-plexes have been reported to date [30,31].

In our present work we report the synthesis of ruthenium, rhodium and iridium half-sandwich oximato and oxime complexes, their biological activity and theoretical studies. Ligands used in the present study are shown in Chart 1.

2. Experimental

2.1. Materials and methods

All reagents were purchased from commercial sources and used as received without further purification. $RuCl_3 \cdot nH_2O$, $RhCl_3 \cdot nH_2O$, $IrCl_3 \cdot nH_2O$ was purchased from Arora Matthey limited. 2-acetylthiazole and 2-benzoylpyridine were obtained from Aldrich, 2-pyridylacetonitrile was obtained from Alfa Aesar and hydroxyl-amine hydrochloride was obtained from himedia. The solvents were purified and dried according to standard procedures [32]. The starting precursor metal complexes [(p-cymene)RuCl₂]₂ and [Cp*MCl₂]₂ (M = Rh/Ir) were prepared according to the literature methods [33,34]. The oxime ligands 2-pyridyl cyanoxime, 2-pyridyl phenyloxime and 2-thiazolyl methyloxime were synthesized ac-cording to published procedures [29,35and36]. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer by using KBr pellets in the range of 400−4000 cm⁻¹. ¹H NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer using DMSO-d_6 as solvents. Absorption spectra were recorded on a Perkin-Elmer Lambda 25 UV/Vis spectrophotometer in the range of 200−800 nm at room temperature in acetonitrile. Mass spectra were recorded using Q-Tof APCI-MS instrument (model HAB 273). Elemental analyses of the complexes were performed on a Perkin-Elmer 2400 CHN/S analyzer.

2.2. Structure determination by X-ray crystallography

Suitable single crystals of complexes (**1**), (**2**) and (**3**), were ob-tained by slow diffusion of hexane into acetone solution and crystals of complexes (**4**), (**5**), (**7**) and (**8**) were obtained by diffusing hexane into DCM solution. Single crystal X-ray diffraction data for the complexes were collected on an Oxford Diffraction Xcalibur Eos
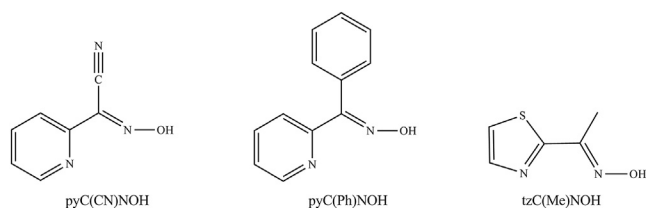
Gemini diffractometer at 293 K using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The strategy for the data collec-tion was evaluated using the CrysAlisPro CCD software. Crystal data were collected by standard "phi−omega scan" techniques and were scaled and reduced using CrysAlisPro RED software. The structures were solved by direct methods using SHELXS-97 and refined by full-matrix least squares with SHELXL-97 refining on F² [37,38]. The positions of all the atoms were obtained by direct methods. Metal atoms in the complex were located from the E-maps and non-hydrogen atoms were refined anisotropically. The hydrogen atoms bound to the carbon were placed in geometrically con-strained positions and refined with isotropic temperature factors, generally 1.2 U$_{eq}$ of their parent atoms. Crystallographic and structure refinement parameters for the complexes are summa-rized in Table 1, and selected bond lengths and bond angles are presented in Table 2. Figs. 1−3 were drawn with ORTEP3 program whereas Figs. S2-S6 was drawn by using MERCURY 3.6 program [39].

The crystal structure of complex (**5**) contains disordered hexane molecule, which has been removed by SQUEEZE method [40]. Crystal structure of complex (**6**) contains fourfold disordered sol-vent molecule, which has been refined and removed by SQUEEZE method. Crystal structure of complex (**8**) contains solvent molecule in their solved structure.

2.3. Biological studies

The complexes (**1−9**) were dissolved in DMSO at 100 mM and stored at −20 °C until required. The cytotoxicity of the complexes was studied against HT-29 (human colorectal cancer) and MIAPaCa-2 (human pancreatic cancer) cell line. Cells were seeded into 96 well plates at 1×10^3 cells per well and incubated at 37 °C in a CO₂ enriched (5%), humidified atmosphere overnight to adhere. The cells were exposed to a range of drug concentrations in the range of 0−100 μM for four days before cell survival was deter-mined using the MTT assay [41]. To each well MTT (0.5 mg/ml) in phosphate buffered saline was added and was further incubated at 37 °C for 4 h. The MTT was then removed from each well and the formazan crystals formed were dissolved in 150 μM DMSO and the absorbance of the resulting solution was recorded at 550 nm using an ELISA spectrophotometer. The percentage of cell inhibition was calculated by dividing the absorbance of treated cell by the control value absorbance (exposed to 0.1% DMSO). The IC₅₀ values were determined from plots of % survival against drug concentration. Each experiment was repeated three times and a mean value ob-tained and stated as IC₅₀ (μM) ± SD.

2.4. Computational methodology

The geometry optimization of all the complexes were done in the gas phase using the Density Functional Theory (DFT) based B3LYP method in conjugation with 6-31G** basis set for lighter atoms (H, C, N, O, Cl, S, P and F) and LANL2DZ [42,43] basis set for heavier atoms (Ru, Rh and Ir). LANL2DZ is a widely used Effective Core Potential (ECP) basis set which considers the core electrons as chemically inactive and performs only on the valence electrons and thus reduces the computational cost. Harmonic frequency calcu-lations were carried out at the same level to ensure that the ge-ometries are minima at the potential energy surface (PES). Natural Bond Orbital (NBO) [44] analysis was carried out to get charges on individual atoms present in the complexes. Time dependent-Density Functional Theory (TD-DFT) [45] has been employed to evaluate the absorption spectra and the electronic transitions of the metal complexes. In order to incorporate the effect of the solvent around the molecule, the Polarizable Continuum Model (PCM) [46]

Chart 1. Ligands used in this study.

pyC(CN)NOH   pyC(Ph)NOH   tzC(Me)NOH