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Synthesis, spectral characterization and catalytic activity of Co(II) complexes of drugs: Crystal structure of Co(II)–trimethoprim complex

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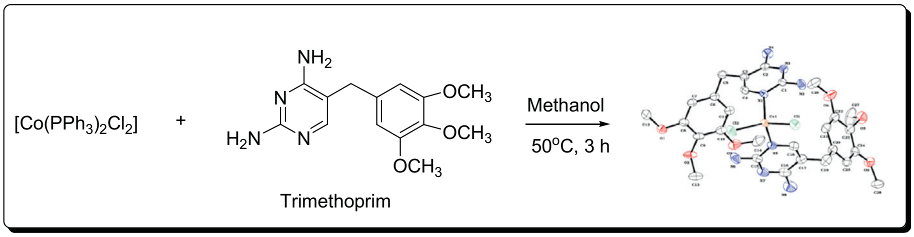
HIGHLIGHTS

- Four new Co(II)–drug complexes were characterized using several spectral techniques.
- Single crystal XRD indicated that Co(II)–trimethoprim complex is tetrahedral.
- Co(II)–ofloxacin complex exhibited excellent catalytic activity in aryl–aryl coupling.

GRAPHICAL ABSTRACT



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ABSTRACT

New Co(II) complexes with drugs such as trimethoprim (TMP), cimetidine (CTD), niacinamide (NAM) and ofloxacin (OFL) as ligands were synthesized. The complexes were characterized by analytical analysis, various spectral techniques such as FT-IR, UV–Vis, magnetic measurements and molar conductivity. The magnetic susceptibility results coupled with the electronic spectra suggested a tetrahedral geometry for the complexes. The coordination mode of trimethoprim ligand and geometry of the complex were confirmed by single crystal X-ray studies. In this complex the metal ion possesses a tetrahedral geometry with two nitrogen atom from two TMP ligands and two chloride ions coordinated to it. The catalytic activity of the complexes in aryl–aryl coupling reaction was screened and the results indicated that among the four complexes [Co(OFL)Cl(H_2O)] exhibited excellent catalytic activity.

Introduction

The biaryl motif plays a considerable role in organic chemistry by its common presence in a vast array of natural products, pharmaceuticals, agrochemicals and materials [1]. Increasing attentions have been paid to the development of efficient synthetic methods for biaryl formation. Homo- and cross-coupling are the most commonly used methods to construct biaryl structure. Historically, the copper-catalyzed coupling, known as Ullmann reaction, was the first efficient method to synthesize symmetrical biaryls [2]. Since Ullmann reaction is always performed under tough conditions, various mild methods relying on the use of nickel or palladium have been developed [3]. However, the metal catalysts together with the ligands are expensive and toxic. Recently, such reaction was elevated to a high plateau by Gosmini et al. who reported an efficient procedure for reductive homo-coupling of aryl halide catalyzed by $CoBr_2$[4]. Excessive yields were obtained using substrates with electron-donating substituents.

Oxidative homo-coupling of aryl-metal reagents is another efficient synthetic method for the construction of symmetrical biaryls. Although many organometallic reagents (ArM; M = B, Sn, Si, Zn, Mn and Mg) can be used for this reaction, Grignard reagents were no doubt the best choice for large-scale preparation because of their convenient and economical preparation directly from aryl halides. However, most homo-couplings involving Grignard reagent need stoichiometric use of transition metal halides such as $TiCl_4$[5], TlCl [6], $VO(OEt)Cl_2$[7], $FeCl_3$[8], $CoCl_2$[9] and $CuCl_2$[10], making the reactions neither atom-economical nor green. More recently, Nagano and Hayashi [11] and Cahiez et al. [12] have developed iron-catalyzed homo-couplings of Grignard reagents using 1,2-dihalogenoethanes as oxidant. Such procedures may be attractive

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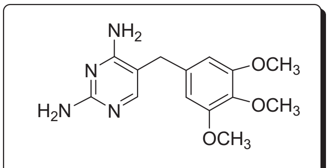
alternatives to those reactions using stoichiometric amounts of metal salts. Cahiez et al. also developed a more economical procedure for the homo-coupling catalyzed by $MnCl_2$ or $FeCl_3$ by using atmospheric oxygen as oxidant [13]. Similar reactions were performed smoothly with $FeCl_3$/bipyridine/O_2 system by Lei group [14]. Though many metal salts/complexes were reported to catalyze aryl–aryl coupling reactions, the search is still on as it is an important reaction in organic chemistry.

The main objective of the present endeavor is to prepare four co-ordinated Co(II)–drug complexes and to use as a catalyst in aryl–aryl coupling reaction. Drugs such as trimethoprim, cimetidine, niacinamide and ofloxacin were used as ligands because they are poly functional organic molecules and are known to behave as good ligands in the preparation of coordination complexes. Though few complexes involving the chosen drugs have also been reported in literature, our aim to prepare four coordinated Co(II) complexes by using $[CoCl_2(PPh_3)_2]$ as a precursor complex, as these type of complexes are known to possess excellent catalytic activity in aryl–aryl coupling reactions [15–17]. Also, in general, complexes with drugs as ligands were screened for their biological activity but not as catalysts. Synthesis, spectral characterization and catalytic activity of these complexes are reported and discussed in the forthcoming pages. The crystal structure of Co(II)–trimethoprim complex is also reported and discussed.

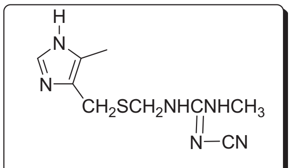
Experimental

Chemicals

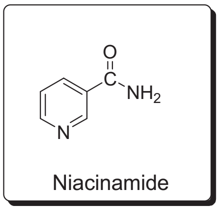
All the chemicals used in the present study were of high purity analytical grade (Merck, India) and were used as received. The drugs trimethoprim, cimetidine, niacinamide and ofloxacin were obtained as gift samples from locally available pharmaceutical companies and were used as received. The purity of the drugs was ascertained using its m.p. (Trimethoprim Found: 138–139 °C, Lit.: 138–140 °C; Cimetidine Found: 142–143 °C, Lit.: 139–144 °C; Niacinamide Found: 128–129 °C, Lit.: 128–131 °C; and Ofloxacin Found: 271–272 °C Lit.: 270–273 °C). The structures of the drugs are shown below.



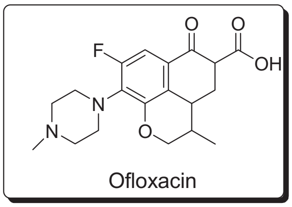
Trimethoprim



Cimetidine



Niacinamide



Ofloxacin

Instrumentation

The UV–Vis spectra were recorded on a double beam spectrophotometer (JASCO 460 Plus, Japan). The FT-IR spectra were recorded on a JASCO, Japan 460 Plus spectrometer using KBr disk. Elemental analysis for CHN was performed at the Sophisticated Analytical Instrument Facility, Cochin University of Science and Technology, Kochi (Elemeater Vario EL III). Conductance measurements of 10^{-3} M solution in DMSO were made on a SYSTRONICS, India conductivity bridge. The room temperature magnetic moments were determined using a Gouy balance.

X-ray crystallography

Crystallographic data measurements were made at the Sophisticated Analytical Instrument Facility, Indian Institute of Technology, Madras on a Bruker axs kappa APEX-II CCD Diffractometer with Mo Ka radiation ($k = 0.71073$ A^3) by the w scan mode. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes. Crystal structure refinements were carried using SHELXTL Ver. 6.12 W96/98/NT/2000/ME [18].

Synthesis of the metal complexes

The precursor complex $[Co(PPh_3)_2Cl_2]$ was prepared as reported earlier [15]. Methanolic solutions of the ligand (2 mmol) and the precursor complex (2 mmol) were mixed and heated at 50 °C for 3 h with constant stirring. Then the mixture was evaporated to a volume of half of its original volume in vacuum and left to cool to room temperature. The precipitated complex was filtered in vacuum and washed with diethyl ether. The products were recrystallized from methanol.

Catalytic activity

The catalytic activity of these complexes in aryl–aryl coupling reaction has been tested. In a typical experiment, magnesium turnings (320 mg; 0.013 mol) were taken in a two necked round bottom flask fitted with a $CaCl_2$ guard tube. A crystal of iodine was added to activate the magnesium. Bromobenzene (distilled over P_2O_5, 0.5 ml of total 1.275 ml; 0.012 mol) in 5 ml of THF was added with stirring. Appearance of turbidity and bubbles indicated the initiation of the reaction. The remaining bromobenzene in 5 ml of THF was added (in 20 min) drop wise and stirred for 35 min till all the magnesium gets dissolved. To this reaction mixture 1.03 ml (0.01 mol) of bromobenzene in 5 ml of THF and the Co(II) complex (0.00012 mol) were added and refluxed for an optimum period i.e. 6 h. Then the reaction mixture was cooled and hydrolyzed with saturated solution of aq. NH_4Cl. The THF extract on evaporation of the solvent gave the product. The biphenyl product was compared with an authentic sample on TLC and M. p. 69–72 °C. The yield of the product was calculated based on the amount of bromobenzene taken.

Result and discussion

The reactions of $[Co(PPh_3)_2Cl_2]$ with the chosen drugs gave the Co(II)–drug complexes. These complexes are stable solids at room temperature and are soluble in solvents such as CH_2Cl_2, acetonitrile, DMF and DMSO. The elemental analyses of the complexes, magnetic moments and molar conductance data are summarized in Table 1. All the Co(II) complexes exhibited magnetic moment values in the range of 3.21–3.65 BM, which suggested tetrahedral geometry around the metal ion in these complexes [19]. The molar conductance indicated that the Co(II)–CTD complex is an 1:1 electrolyte while other complexes are non-electrolyte in nature