Journal of Organometallic Chemistry 694 (2009) 3102–3111

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Synthesis and characterization of several rhenium(I) complexes of 2-acetylpyridine and ferrocenyl carbaldehyde derivatives of 2-hydroxybenzoic acid hydrazide

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ARTICLE INFO

Article history:
Received 18 April 2009
Received in revised form 19 May 2009
Accepted 20 May 2009
Available online 27 May 2009

Keywords:
Hydrazone
Rhenium complexes
Carbonyl complexes
Ferrocene
X-ray

ABSTRACT

The rhenium(I) carbonyl halide (X = Cl and Br) complexes, $[ReX(CO)_3\{H_2(py)L^2\}]$ (**1a**, **1b**) and $[ReX(CO)_3\{H_2(Fc)L^2\}]$ (**2a**, **2b**), of the ligands derived from 2-acetylpyridine and ferrocenyl carbaldehyde derivatives of 2-hydroxybenzoic acid hydrazide [$H_2(py)L^2$ and $H_2(Fc)L^2$, respectively] have been prepared in good yield. The complexes have been characterized by elemental analysis, MS, IR, UV–Vis and ^1H NMR spectroscopic methods and their structures have been elucidated by X-ray diffraction. The ligand forms a five-membered chelate ring but in $H_2(py)L^2$ it is $N_{pyridine}$,N′-bidentate while it is O,N-bidentate in $H_2(Fc)L^2$ complexes.

Reaction of complex **1a** with copper(II) nitrate yields the unexpected aqua complex $[Re\{H(py)L^2\}(H_2O)(CO)_3]$ (**3**) where the ligand is monodeprotonated but maintains the coordination mode observed in **1a**, as shown by X-ray diffraction. However, reaction of **1b** with glycine yields a conformational polymorph of the original compound, **1b′**. The X-ray study shows that the orientation of the O–H phenol group against the carbonyl amide group is the main difference.

1. Introduction

There is growing interest in carbonyl rhenium(I) complexes with 2-pyridine aldehyde and 2-acetylpyridine derivatives as a way to conjugate the $\{M(CO)_3\}^+$ (M = ^{188}Re and ^{99m}Tc) fragment for the labelling of targeting biomolecules. Alberto et al. showed that the ketone or aldehyde is activated by coordination to the *fac*-$[Re(CO)_3]^+$ moiety and that the reaction with several (bio)molecules containing primary amines yields the corresponding N,N′-diimine complexes, with rates of formation several orders of magnitude faster than the reaction between free aldehyde, ketone and amine [1]. This strategy has also been employed to obtain Lipidiol surrogates as possible agents for liver cancer imaging and therapy [2] or to introduce amino acids or esters [3,4]. In addition to labelling properties, the introduction of binding groups such as aza-crown has been carried out in order to assay their properties in cation and molecular recognition studies (see for example Ref. [5]). Furthermore, the luminescent properties of rhenium(I) tricarbonyl N,N′-diimine complexes have demonstrated to have applications in biological imaging as fluorochromes in fluorescence microscopy [6a]. The large Stokes shifts, long lifetimes and good quantum yields allow easy differentiation of their emission from interfering autofluorescence [6b].

Hydrazine derivatives containing N-heterocycles and their complexes exhibit strong antitumor and antivirus activities [7]. The antimicrobial activities of copper complexes of these compounds have also been reported [8]. As a consequence, the 2-acetylpyridine derivatives of these systems are an interesting group of candidates to design molecules for labelling. In contrast, we did not find any evidence that the reaction of 2-acetylpyridine coordinated to rhenium(I) yielded the corresponding hydrazone complexes by reaction with salicylaldehyde hydrazide [9], but the synthesis of the same target complex from the previously isolated ligand is straightforward. As a result, several rhenium(I) acetylpyridine hydrazones have recently been reported [10–12].

Recently, rhenium(I) complexes of 2-acetylpyridine benzoylhydrazone [10] [$H(py)L^1$ in Scheme 1] have been synthesised. The ferrocenyl analog, $H(Fc)L^1$ in Scheme 1, was also prepared because of the potentially improved antitumor and antivirus activities of the ferrocenyl group [13,14] and the possibility of modulating the binding affinity of the ligand for the rhenium fragment by altering the redox state [15]. These studies show that the differences in the coordination of the ligand, κ-N,N′ in $H(py)L^1$ and κ-N,O in $H(Fc)L^1$, cause different spectroscopic behavior (mainly in ^1H NMR spectroscopy).

In this paper, we report a study of hydrazones derived from 2-hydroxybenzoic acid and 2-acetylpyridine and ferrocenyl carbaldehyde [$H_2(py)L^2$ and $H_2(Fc)L^2$ in Scheme 1, respectively]. Both compounds are potentially diprotic ligands and they may act as tetra- or tridentate planar chelating agents that coordinate through

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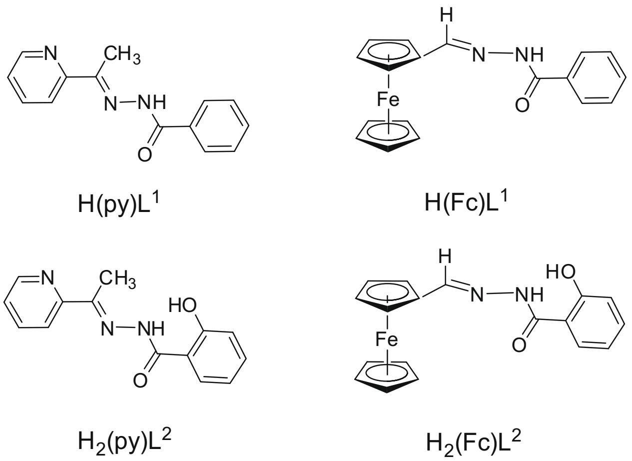
doi:10.1016/j.jorganchem.2009.05.032



Scheme 1.

the phenolic hydroxy, amide oxygen and one/two imine nitrogen atoms. However, in the copper(II) and zinc(II) complexes of the pyridine derivatives reported, we observed exclusively the tridentate monodeprotonated ligand $[H(py)L^2]^-$ [16]. The structural data for $H_2(Fc)L^2$ are even more scarce, although the presence of a bidentate neutral ligand has been reported in a ruthenium(II) complex [17].

2. Results and discussion

2.1. Synthesis and spectroscopic characterization

Reactions of the ligands $H_2(py)L^2$ and $H_2(Fc)L^2$ with the adducts *fac*-$[ReX(CO)_3(CH_3CN)_2]$ afforded orange or red solids that are stable in air, moderately soluble in organic solvents – such as toluene, chloroform and ethanol – and highly soluble in acetone. Elemental analysis and mass spectrometry confirmed the stoichiometries $[ReX(CO)_3\{H_2(py)L^2\}]$ (**1**) and $[ReX(CO)_3\{H_2(Fc)L^2\}]$ (**2**) (Scheme 2).

The mass spectra contain the signal corresponding to the molecular ion although the peaks due to the species $[M-X]^+$ are more intense, as observed in the rhenium(I) complexes of benzoylhydrazones [9,15] and thiosemicarbazone derivatives [18]. A facial geometry around the rhenium atom is suggested by the three strong $\nu(C{\equiv}O)$ IR bands in the range 2027–1892 cm^{-1} in the complexes.

The solutions of ferrocene derivatives show evidence of decomposition when stored for days in sunlight. We have tested the formation of heterodinuclear complexes and co-crystals by reaction of the rhenium derivatives with metallic acetates [zinc(II) or copper(II)], aromatic amines or amino acids, unsuccessfully. In fact, diffusion experiment of an acetone solution of **2a** into a MeOH solution of copper(II) acetate afforded few single crystals of the metallocrown complex $[Fe_{10}(O_2CCH_3)_{10}(OCH_3)_{20}]$, as determined by X-ray diffraction [19]. However, the presence of metal nitrates in aqueous solutions of $H_2(py)L^2$ derivatives yielded some single crystals of $[Re\{H(py)L^2\}(H_2O)(CO)_3]$ (**3**).

2.2. X-ray studies

2.2.1. The crystal and molecular structure of the 2-acetylpyridine-salicyloylhydrazone adducts $[ReX(CO)_3\{H_2(py)L^2\}]$ (*1a*, *1b* and *1b′*)

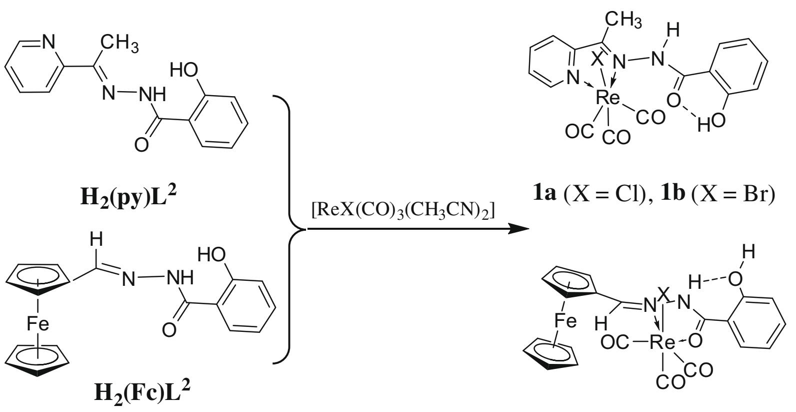
The complexes $[ReX(CO)_3\{H_2(py)L^2\}]$ (**1a**, **1b**) are isotypic and crystallize in the monoclinic $P2_1/n$ space group. The molecular structures of the complexes are shown in Fig. 1A and B along with the atomic numbering scheme used. Selected bond lengths and angles for both complexes are listed in Table 1.

The rhenium atom is coordinated by the N(2) hydrazone and N(3) pyridine atoms, affording a five-membered chelate ring, as well as three carbonyl carbon atoms and a halide atom. The resulting coordination geometry can be described as distorted octahedral [the main distortion being the N(2)–Re–N(3) and C(22)–Re–N(2) angles]. The differences between these angles are statistically insignificant apart from the expected longer Re–Br distance than Re–Cl and the N(2)═C(8) distance in **1a** being clearly shorter than in **1b**. The latter distance in **1a** is statistically equivalent to that observed in the free ligand [1.285(4) Å] [16] and in its hydrochloride form [1.288(2) Å] [20] while that in **1b** is similar to that found in the ferrocene derivatives **2** (*vide infra*).

Other interesting differences with respect to the free ligand structure are the change in the orientation of the pyridine nitrogen atom to allow N,N′ coordination to the rhenium and the loss of the planarity observed in the free form [16] by rotation around the N(1)–N(2) bond. Consequently, the angle between the planes defined by the salicylaldehyde and pyridine groups (see Scheme 3) is greater than 60°.

There is also rotation around the C(1)–C(2) bond, meaning that the intramolecular hydrogen bond N(1)–H···O(2) observed in the free ligand is broken and replaced by the interaction O(2)–H···O(1). The distances between donor–acceptor atoms in both interactions, i.e. the distances N(1)–O(2) in $H_2(py)L^2$ and $[H_3(py)L^2]^+$ and O(2)–O(1) in complexes **1a** and **b**, are very similar (see Table 2).

The molecules are associated into dimers by a weak hydrogen bond N(1)–H···X^i (see Table 2 and Fig. 2A). We observed a similar association in other rhenium(I) halide complexes with hydrazone



1a (X = Cl), **1b** (X = Br)

2a (X = Cl), **2b** (X = Br)

Scheme 2.