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Polyhedron 26 (2007) 4373–4382
POLYHEDRON
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Synthesis, spectral characterization and cytotoxicity of Ru–bipyridyl complexes containing hexakis(pyrazol-1-yl)benzene (hpzb) as a co-ligand

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Received 11 May 2007; accepted 18 May 2007
Available online 12 June 2007

Abstract

A novel ruthenium bisbipyridine complex, $[Ru(bpy)_2(hpzb)](PF_6)_2$ (**1**) (hpzb = hexakis(pyrazol-1-yl)benzene) was obtained in the reaction between $[Ru(bpy)_2Cl_2]$, the tritopic ligand hpzb and NH_4PF_6. A high selectivity has been found in the reaction and when the hpzb ligand was made to react with more than one ruthenium fragment, it coordinated selectively only to the first metallic fragment, and it was not possible to introduce two or three ruthenium centres. A similar complex with a deuterated bipyridine has also been obtained. The reaction with the methylated ligand hexakis(3,5-dimethylpyrazol-1-yl)benzene does not take place. A complete assignment of all the proton and carbon NMR signals of **1** was carried out. The orientation of the free pyrazolyl groups is also discussed. The redox properties and the anticancer activity of complex **1** have been studied.

Keywords: Ruthenium; N-ligands; Pyrazole; NMR spectroscopy; Electrochemistry; Cytotoxic activity

1. Introduction

The coordination chemistry of multitopic N-donor ligands has been an area of great interest in recent years and has found applications in fields such as catalysis and supramolecular chemistry. The use of ligands containing N-substituted pyrazoles is very common [1]. In this field, polypyrazolylborates (scorpionates) [2] and polypyrazolylmethanes [3] have been widely used, as have polypyrazolylazines [4]. However, polypyrazolylbenzenes have been used less frequently. The coordination chemistry of (pyrazol-1-ylmethyl) derivatives of type **A** (''coelenterands'') [3–14] has been explored and so has that of other types of ligands (**B** and **C**) in which the pyrazolyl heterocycle is not directly bonded to the benzene ring (Scheme 1). The use of ligands of type **B** gives mononuclear complexes or helicates [15,16] while type **C** gives rise to dinuclear derivatives [17]. (Pyrazol-1-yl)benzenes of type **D** containing two [18–22], three [23] or four [24] pyrazolyl units have been used as ligands. However, hexakis(pyrazol-1-yl)benzene (hpzb) (Scheme 2), a ligand of the ''propellene'' class that has been studied systematically by several of us [25–30], has very seldom been used in coordination chemistry.

We have previously studied the coordination chemistry of hpzb with transition metals of groups 10 and 11, namely Pd, Pt, Cu [31] and Ag [32]. If one considers that the ligand

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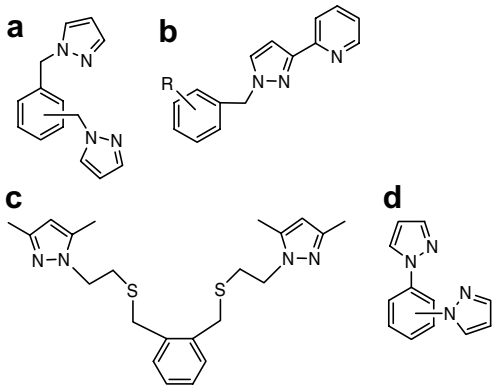
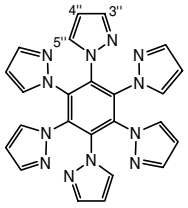
doi:10.1016/j.poly.2007.05.043



Scheme 1.



Scheme 2.

has three bidentate positions, we have prepared complexes with one, two or three metals occupying these positions. The incorporation of three metallic centres was only possible with a small metallic fragment. As far as the fluxionality of the compounds is concerned, two types of processes were found: metallotropic shift and rotation of the uncoordinated pyrazolyl rings.

In the free ligand, each pyrazol-1-yl group can adopt two perpendicular conformations depending on the orientation of the N-2 lone pair ($u = up$, $d = down$) with regard to the benzene plane. This situation leads to several isomers. The hpzb ligand exists in the solid state in two conformations (polymorphism) – *ududud* and *udduud*. According to AM1 and SAM calculations [26], these conformations have torsion angles close to 90° with the *ududud* disposition giving the most stable conformer. NMR studies in solution have shown that, depending on the solvent and/or concentration, the *ududud* isomer is either the only one detected or is the major isomer along with the *udduud* isomer as the minor component. The fact that two isomers can be observed separately indicates that restricted rotation of the pyrazolyl rings exists in the free hpzb ligand at room temperature. The same conclusion was deduced for the monometallic derivatives, while those containing two metallic centres exhibited free rotation at room temperature of the two uncoordinated pyrazolyl rings situated *para* to one another [31].

In this work we decided to focus our attention on the study of the coordination ability of hpzb with the chiral fragment *cis*-$[Ru(bpy)_2]^{2+}$. Although complexes have been described that contain the $[Ru(bpy)_2]^{2+}$ fragment bonded to pyrazolyl-derived ligands [33–35], the coordination of hpzb to this potentially octahedral fragment has not previously been explored. It was of interest to evaluate if any selectivity existed in the coordination and also to assess the possible presence of fluxional processes.

On the other hand, ruthenium-based anticancer drugs are making significant advances as an attractive alternative to classical platinum chemotherapies. Specifically, polypyridyl–Ru complexes have been investigated as potential anticancer drug candidates, given their photoluminescence properties and both the ability of Ru to coordinate DNA nucleobases and the ability of polypyridyl ligands to intercalate DNA [36]. Because of that, we decided to explore the possible anticancer activity of the ruthenium complexes containing bpy and our ligand hpzb.

2. Results and discussion

2.1. Synthesis and characterization

The reaction of hpzb [27,28] with the system $[RuCl_2(bpy)_2]/2NH_4PF_6$ [37] was carried out (Eq. (1)) [35]. The ruthenium containing precursor has been used in anticipation that such a compound, besides providing the possibility of its substitution by two N donors, could also be exploited for its biological studies in view of earlier reports [36]. The reaction was performed in 1:1, 1:2 and 1:3 hpzb:Ru ratios. The same product, **1**, was obtained in all cases (even after prolonged reaction times of 36 h) as a dark-red solid. Elemental analysis of complex **1** shows the stoichiometry to be $[Ru(bpy)_2(hpzb)](PF_6)_2$ (see Eq. (1)) (clearly a racemic mixture would be present). The mass spectrum is also consistent with coordination of the ligand to only one metal fragment. In fact, peaks corresponding to the loss of one or two counteranions or other fragments from the proposed formula are also observed. It is worth highlighting the selectivity in the coordination of the ligand to only one metal fragment. It is possible that the ruthenium centre is sufficiently electrophilic to reduce considerably the donor ability of the uncoordinated pyrazolyl rings once the first metal centre is present. Undoubtedly, bonding of one hpzb ligand to three metal centres would involve a high level of steric hindrance:

$$[RuCl_2(bipy)_2] + hpzb + 2NH_4PF_6 \rightarrow [Ru(bipy)_2(hpzb)](PF_6)_2, 1 + 2NH_4Cl \quad (1)$$

A different behaviour to that found with hpzb has been observed with the similar ligand hexakis(3,5-dimethylpyrazol-1-yl)benzene that contains substituted pyrazolyl rings. It did not react with the same ruthenium complex, possibly due to steric factors.

The ^1H NMR spectrum of compound **1** shows a very complicated pattern that consists of 34 different signals, all of which have the same integration. This observation is consistent with the presence of six different spin systems for the pyrazolyl rings and four different spin systems for