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Organometallic complexes that interconvert between trimeric and monomeric structures as a function of pH and their effect on human cancer and fibroblast cells

Wee Han Ang [a], Zacharias Grote [a], Rosario Scopelliti [a], Lucienne Juillerat-Jeanneret [b], Kay Severin [a,*], Paul J. Dyson [a,*]

[a] Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland
[b] University Institute of Pathology, Centre Hospitalier Universitaire Vaudois (CHUV), CH 1011 Lausanne, Switzerland

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ABSTRACT

Organometallic half-sandwich complexes based on ruthenium with aminomethyl-substituted 3-hydroxy-2-pyridone ligands exist in aqueous solution as monomeric O,O′-chelate complexes or trimeric metallamacrocycles depending upon the pH. We hypothesized that administration of the compounds as stable trimers, which subsequently convert to active monomers at the reduced pH of the cancer environment, could facilitate their delivery to cancer cells without undergoing deactivation. Thus, the compounds were evaluated against cancer and fibroblast cell lines *in vitro*. A series of rhodium complexes, which exist mainly as monomers at neutral pH, were also studied for comparative purposes.

1. Introduction

Platinum-based coordination compounds have proven to be extremely important anticancer agents with widespread clinical use [1]. Coordination compounds based on other metal centers have also been evaluated in cancer chemotherapy [2] and organometallic compounds are under intensive investigation [3]. The organometallic compound titanocene dichloride was shown to exhibit antitumor activity in the 1970's [4], and although it entered clinical evaluations it has not gained clinical approval [5]. The ferrocifens, ferrocenyl derivatives of tamoxifen, show considerable promise in hormone-related cancers and paved the way for the rational development of organometallic pharmaceuticals [6,7].

Two coordination compounds based on ruthenium, viz. [ImH][*trans*-$RuCl_4$(DMSO)Im] (NAMI-A) [8] and [ImH][*trans*-$RuCl_4Im_2$] (KP1019) [9], are currently under clinical investigation, which has inspired greater interest in the medicinal properties of this metal, including in part recent studies on organoruthenium compounds [10]. Ruthenium(II)–arene compounds with imidazole [11], alanine and guanine derived co-ligands [12], ethylenediamine [13], disulfoxide [14], and 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane (pta) and analogous sugar [15] co-ligands have been evaluated. These compounds have been extensively tested *in vitro* and to a limited extent *in vivo* [16], although there is not always a good correlation between *in vitro* and *in vivo* data [17].

Combining the ruthenium(II)–arene fragment with maltolato ligands is an interesting prospect since maltolato systems have found applications in various medicinal applications [18]. Indeed, a series of such compounds has been reported, but it was found that they readily form inactive hydroxo-bridged dimers, following hydrolysis and rapid deprotonation at physiological pH [19]. Dinuclear ruthenium(II)–arene complexes with maltol-derived pyridonato-ligands, on the other hand, were shown to be highly cytotoxic towards human cancer cell lines [20]. In this paper, we describe a series of trinuclear ruthenium(II)–arene complexes with pyridonato-ligands that can fragment to mononuclear complexes according to the pH. We hypothesized that such a mechanism could facilitate their delivery to cancer cells without undergoing deactivation, and in this paper we describe our experiments to test this hypothesis. In addition a series of related rhodium(III)–pentamethylcyclopentadienyl (Cp^*) complexes were also studied.

2. Results and discussion

The half-sandwich complexes based on the (η^6-cymene)Ru (**M1**) and the (η^5-Cp^*)Rh (**M2**) organometallic fragments are

* Corresponding authors. Fax: +41 21 693 98 85 (P.J. Dyson).
E-mail address: paul.dyson@epfl.ch (P.J. Dyson).

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shown in Scheme 1. They were obtained in situ by reaction of the respective $[(\pi\text{-ligand})MCl_2]_2$ precursors with amino-substituted 3-hydroxy-2-pyridone ligands (**L1**–**L3**) in aqueous solution. The spectroscopic data and the behavior of the complexes as a function of pH have been reported previously [21,22]. Interesting differences were observed between the Ru and the Rh complexes: whereas the (η^6-cymene)Ru complexes **1**–**3** are trimers, the (η^5-Cp*)Rh complexes **4**–**6** are predominantly monomers in aqueous solution at neutral pH. It should be noted that the Ru-trimers are remarkably stable compounds. Aqueous solutions of the trimers can be handled in air for several hours without decomposition and they tolerate high salt concentrations (e.g. 100 mM phosphate buffer). Furthermore, it has recently been shown that structurally related trimers remain intact in a complex biological matrix such as reconstituted human serum [23].

The aminomethyl-substituted 3-hydroxy-2-pyridone ligands **L1**–**L3** can be obtained by Mannich reactions as described in the literature [24]. The structure of the ligand **L3** in the solid state has now been established by X-ray crystallography and is shown in Fig. 1.

The crystallographic analysis reveals that the ligand is in its preferred pyridone form and not in the tautomeric 2,3-dihydroxypyridine form. As a consequence, the C1–O1 bond (1.281(3) Å) is significantly shorter than the C2–O2 bond (1.371(3) Å). Intermolecular hydrogen bonds between N1–H1 and O1 (1.98 Å) and between O2–H2 and O1 (1.99 Å) result in a ribbon-like connection of the ligands in the solid state (Fig. 1, bottom).

The solid state structures of mononuclear ruthenium(II)–arene complexes containing aminomethyl-substituted 3-hydroxy-2-pyridone ligands have been reported previously [21a], but crystallographic data for analogous Cp*Rh complexes are missing. We managed to obtain single crystals of complex **5** containing the Cp*Rh fragment **M2** and ligand **L2**. This was achieved by dissolving a mixture of $[Cp^*RhCl_2]_2$ and two equivalents of **L2** in chloroform and layering the resulting solution with diethyl ether. The crystallographic analysis revealed that **5** exhibits the expected 'piano-stool' geometry with an O,O′-bound, monoanionic pyridonate ligand (Fig. 2). Since the complex was obtained from an unpolar organic solvent, the third coordination site opposite to the Cp* ligand is occupied by a chloro ligand and not by a water ligand as expected for aqueous solutions of **5** [21a]. The bond lengths of the two Rh–O bonds (Rh1–O1 = 2.1385(18) Å and Rh1–O2 =

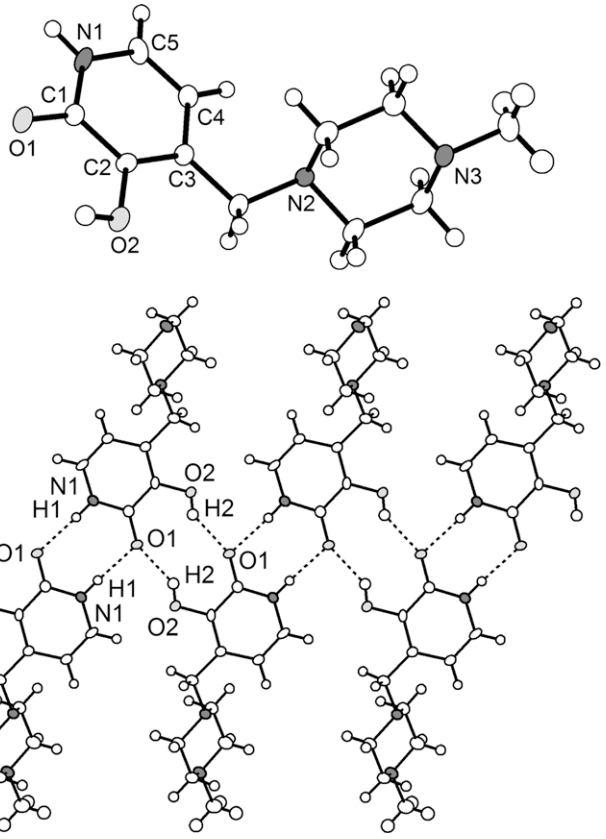
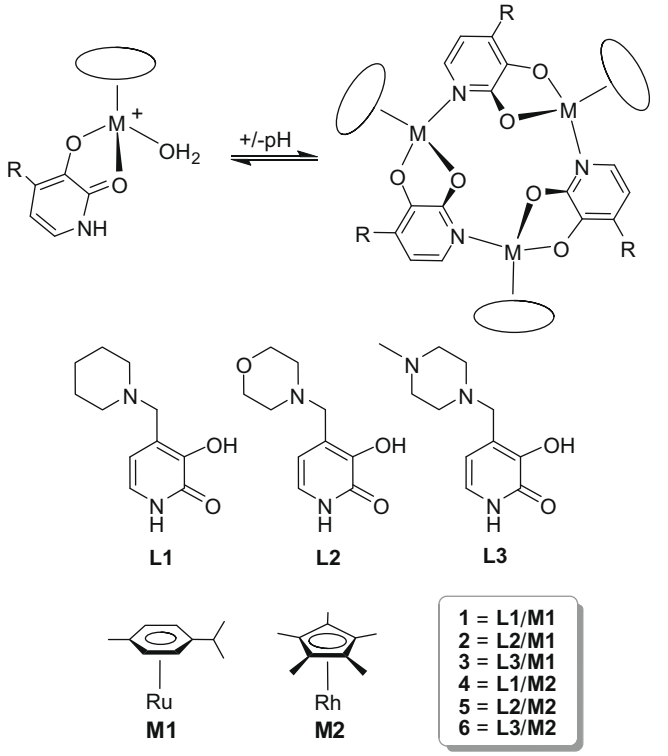


Fig. 1. Graphic representation of the molecular structure of ligand **L3** (top). The 3-hydroxy-2-pyridone groups form a hydrogen bond network with intermolecular NH···O and OH···O interactions (bottom). The thermal ellipsoids are at the 50% probability level.



Scheme 1. Structures of the complexes employed in this study; at pH 7 compounds **1**–**3** are trimeric, whereas **4**–**6** are predominantly monomeric.

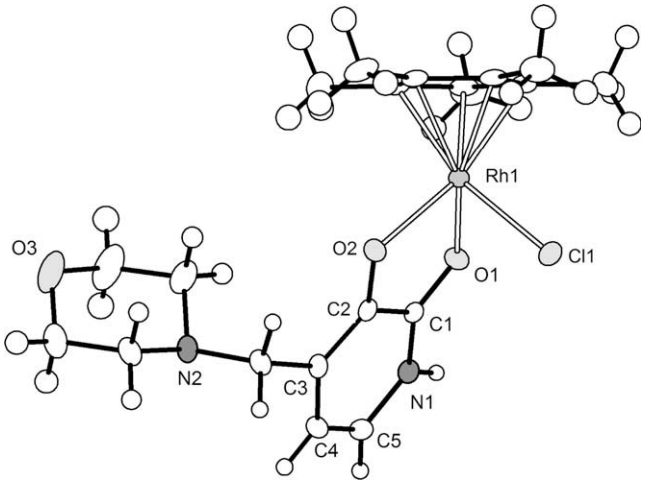


Fig. 2. Graphic representation of the molecular structure of complex **5**. The thermal ellipsoids are at the 50% probability level. Key bond lengths (Å) and angles (°) for **5** include: Rh1–O1 = 2.1385(18), Rh2–O2 = 2.1349(17), Rh1–Cl1 = 2.4208(7), C2–O2 = 1.335(3), C1–O1 = 1.285(3); Cl1–Rh1–O1 = 86.89(5), Cl1–Rh1-O2 = 89.33(5), O1–Rh1–O2 = 78.31(7).