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(η^6-Arene)ruthenium complexes with P-coordinated phosphinoferrocene amides bearing extended polar substituents at the amide nitrogen: Synthesis, characterization and cytotoxicity

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ABSTRACT

Heterobimetallic Ru–Fe complexes of the general formula [(η^6-*p*-cymene)$RuCl_2$($Ph_2PfcCONHCH_2CH_2$-COY-κ*P*)], where Y = Me, NH_2, NHEt, NHPh, and NMe_2, and fc = ferrocene-1,1′-diyl, were synthesized from *p*-cymene ruthenium dichloride dimer and phosphinoferrocene carboxamide ligands bearing extended urea or acetamido substituents at the amide nitrogen. All the compounds were fully characterized by analytical and spectroscopic methods and, for one representative, also by single-crystal X-ray diffraction analysis. The cytotoxicity of these complexes was examined. The compounds displayed modest antiproliferative activity towards human ovarian cancer cell lines, the exception being a complex with a terminal *N*-phenylurea moiety which has IC_{50} values of ca. 20 μM.

1. Introduction

In recent years extensive research has been devoted to the development of group 8 complexes as alternatives to platinum drugs as they appear to exhibit fewer side-effects [1]. In particular, considerable advances have been made on the development towards anticancer drugs based on ruthenium with prominent examples including the ruthenium(III) complexes NAMI-A and KP1019, both evaluated in clinical trials [2]. Although they have yet to reach the clinical evaluation stage, ferrocenyl analogues of tamoxifen which target hormone receptors in breast cancer cells, also showed much promise and opened up new paradigms in metal-based drug design [3]. Another class of organometallic complexes that show relevant in vivo properties comprise half-sandwich (η^6-arene)Ru(II) and (η^6-arene)Os(II) complexes [4].

Compared to platinum-based drugs, group 8 compounds tend to be well tolerated in vivo and exhibit low general toxicity. Simple ferrocenium salts were the first iron compounds for which antineoplastic effects were reported [5]. The mechanism of action remains uncertain, however, nuclear DNA, cell membrane, and topoisomerase II have been proposed as possible targets [6]. Other studies showed that ferrocenium salts may generate hydroxyl radicals in physiological solutions which could damage the DNA in a Fenton-type reaction [7].

Various synthetic approaches have been used to covalently link ferrocenes to other metal centres in order to achieve synergistic effects between the two metals [8]. We have recently synthesized and evaluated the cytotoxic properties of a series of Pd(II) and Pt(II) [9], Au(I) [10], and (η^6-arene)Ru(II) [11] complexes employing various functionalized phosphinoferrocene carboxamides as P-monodentate donors. The association of two active metals can, in certain cases, lead to cytotoxicities that are superior to the sum of the individual components. Here we extend the series of heterobimetallic (η^6-*p*-cymene)Ru(II) complexes containing the recently reported phosphinoferrocene carboxamide ligands [12] with extended urea or acetamido substituents at the amide nitrogen (Scheme 1) and their antiproliferative activity on A2780 and A2780cisR human ovarian cancer cells and on non-cancerous human embryonic kidney cells.

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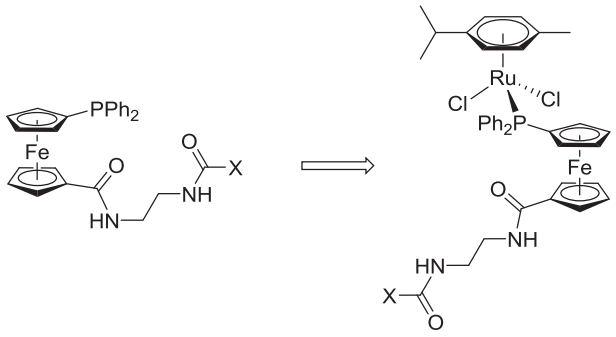


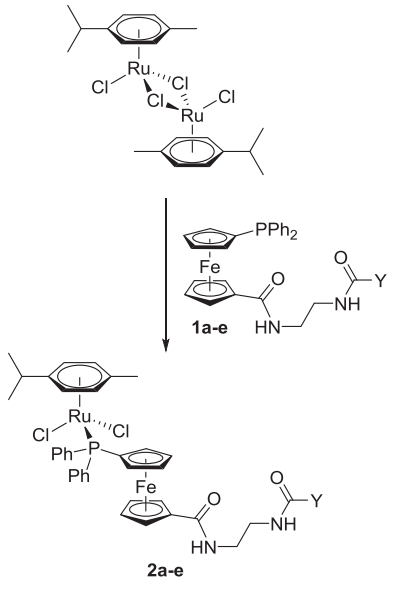
Scheme 1.

2. Results and discussion

2.1. Synthesis and characterization of the Ru–Fe complexes

The heterobimetallic Ru–Fe complexes featuring ligands **1a**–**e** as P-donor monodentate ligands were obtained from the bridge-splitting reaction of the dimer [(η^6-*p*-cymene)RuCl(μ-Cl)]$_2$ (Scheme 2). Compounds **2a**–**e** are obtained as deep red solids and were recrystallized from acetonitrile-diethyl ether. However, as evidenced by NMR spectroscopy and elemental analysis, they tend to crystalize with residual solvent.

The formulation of **2a**–**e** was confirmed by electrospray mass spectra, showing signals attributable to ions resulting by sequential loss of the Ru-bound ligands (*viz.* $[M - Cl]^+$, $[M - Cl - HCl]^+$, $[M - Cl - HCl - cymene]^+$) and ions derived from the liberated phosphine ligand (i.e, $[\mathbf{1} + Na]^+$ and $[\mathbf{1} + Cl]^-$). The ^{1}H and ^{13}C NMR spectra combine the characteristic signature of the Ru-bound cymene ligand [11, 13, 14], the 1′-(diphenylphosphino)ferrocene-1-yl moiety [15], and the ethane-1,2-diyl linker with the signals of the terminal substituents that are varied. The ^{13}C NMR signals of the C=O groups are observed around δ_C 170 ppm (amide CO) and δ_C 156–159 ppm (urea CO). The presence of these moieties is further manifested in the IR spectra showing clearly discernible, strong bands at 1635–1650 and 1540 cm^{-1}, and characteristic bands attributable to the NH stretching vibrations at ca. 3300–3350 cm^{-1}. The ^{31}P NMR resonances of **2a**–**e** are observed in the narrow range δ_P 18.1–18.7 ppm, close to the signal observed for the analogous complex with a P-monodentate 1′-(diphenylphosphino)-1-ferrocenecarboxylic acid (Hdpf) ligand, [(η^6-*p*-cymene)RuCl$_2$(Hdpf-κ*P*)] (δ_P 19.3 ppm) [13].



Y = Me (**a**), NH$_2$ (**b**), NHEt (**c**), NHPh (**d**), and NMe$_2$ (**e**)

Scheme 2. Synthesis of the (*p*-cymene)Ru(II) complexes **2a**–**e**.

2.2. Crystal structure of *2a*

Red, plate-like crystals of **2a** suitable for X-ray diffraction analysis were selected directly from the preparative batch (crystallization from acetonitrile-diethyl ether). The compound crystallizes with one molecule per the asymmetric unit (monoclinic, space group $P2_1/n$). The structure of **2a** is depicted in Fig. 1 and the selected geometric parameters are presented in Table 1.

The molecular structure of **2a** resembles those of other structurally characterized (η^6-*p*-cymene)RuCl$_2$ complexes with phosphinoferrocene donors such as [(μ-dppf-1κ*P*:2κ*P*′){(η^6-*p*-cymene)RuCl$_2$}$_2$] [16] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and, mainly, the analogous complexes containing 1′-functionalized (diphenylphosphino)ferrocene donors, [(η^6-*p*-cymene)RuCl$_2$(Hdpf-κ*P*)] [13], [(η^6-*p*-cymene)RuCl$_2$(Ph$_2$PfcCONHCH$_2$CO$_2$Me-κ*P*)] [14], and [(η^6-*p*-cymene)RuCl$_2$(Ph$_2$PfcCH$_2$OMe-κ*P*)] [17] (fc = ferrocene-1,1′-diyl). The compound adopts the typical piano stool structure with a π-coordinated *p*-cymene and three terminal ligands (legs). Coordination of the η^6-ring to the Ru(II) ion is somewhat asymmetrical (see the range of the individual Ru–C distances in Table 1), though without any notable tilting of the piano stool structure as evidenced by the dihedral angle of the plane of the aromatic ring C(31–36) and the base plane {P, Cl1, Cl2} being only 1.61 (9)° and, further, the relatively minor variation of the Cg^{Ru}-Ru-Cl/P angles. The coordination geometry of the Ru center can alternatively be described as pseudo-octahedral, in which the aromatic ring occupies three adjacent coordination sites (*fac*), with the inter-ligand

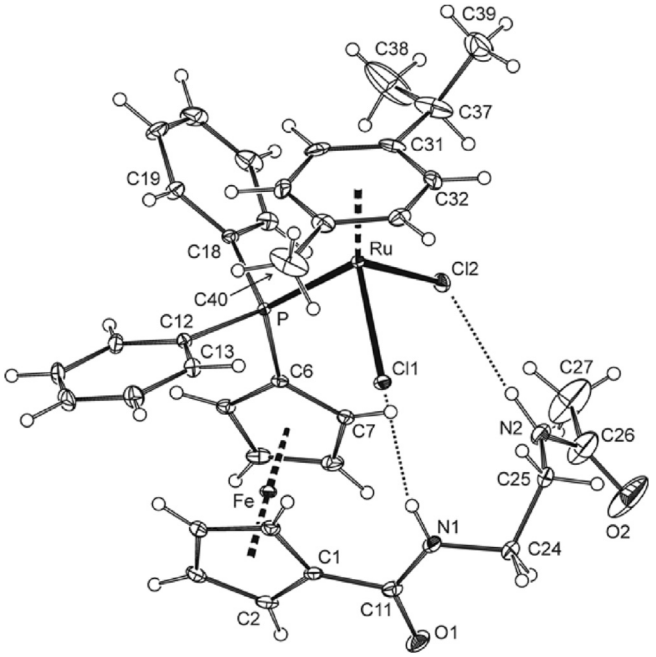


Fig. 1. PLATON plot of the molecular structure of **2a** with displacement ellipsoids set to the 30% probability level. The intramolecular N–H···Cl hydrogen bonds are indicated by dotted lines. For selected distances and angles, see Table 1.