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Palladium(II), platinum(II) and gold(I) complexes containing chiral diphosphines of the Josiphos and Walphos families – Synthesis and evaluation as anticancer agents

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ABSTRACT

A series of palladium(II) and platinum(II) complexes ([$PdCl_2$(J003)] (**1**), [$PdCl_2$(W001)] (**2**), [$PtCl_2$(J003)] (**3**) and [$PtCl_2$(W001)] (**4**), where J003 = the Josiphos ligand (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine and W001 = the Walphos ligand (*R*)-1[(*R*)-2-(2′-diphenylphosphinyl) ferrocenyl]ethyldo(bis-3,5-trifluoromethylphenyl)phosphine), were prepared from the reaction of the diphosphine ligands with [$PdCl_2$(NCMe)$_2$] or [$PtCl_2$(cod)] and characterised by multinuclear NMR spectroscopy, mass spectrometry and elemental analyses. Single crystal X-ray structures were used to confirm the proposed structures. Attempts to use the same ligands to prepare isoelectronic d^8 Au(III) analogues of the palladium and platinum complexes resulted in the reduction of Au(III) to Au(I) and isolation of the Au(I) complexes [AuCl(J003)] (**5**), [Au_2Cl_2(J003)] (**6**) and [Au_2Cl_2(W001)] (**7**). The cytotoxicity of the four chiral, bidentate ferrocenylphosphine palladium and platinum complexes was investigated against HeLa cells and were found to have low to moderate cytotoxicity. In general, the two Josiphos complexes showed better cytotoxicity compared to the Walphos complexes, irrespective of the metal used.

1. Introduction

The importance of ferrocene and its applications in several areas of chemistry have been well documented and extensively reviewed [1]. One such application is its functionalization to diphosphine compounds. Due to their abundance and easy functionalization it is no surprise that diphosphine derivatives are the auxiliary ligands of choice in many coordination compounds. In recent years, the use of chiral diphoshinoferrocenes in areas of chemistry such as asymmetric catalysis has gained prominence [2]. Chiral diphosphine ligands of the Josiphos and Walphos structural families (Fig. 1) have been widely used and are known to impart very high degrees of enantio selectivity to several transition-metal-catalyzed reactions [3]. Furthermore, it is easy to vary the nature of the two ligating moieties attached to the same cyclopentadienyl ring independently from each other [4].

Another area where diphosphinoferrocene ligands have been used is in preparing gold(I) anticancer agents [5]. In this regard, emphasis has been on non-ferrocenyl diphoshines and disubstituted ferrocenyl phosphines such as diphenylphoshinoferrocene (dppf). Gold(III), being isoelectronic to platinum(II), has always been seen as a potential source of anticancer agents similar to cisplatin. In a project where we sought to prepare palladium(II), platinum(II) and gold(III) complexes, with chiral phosphines, viz. Josiphos ligand (*R*)-1-[(*S*)-2-diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (J003) and the Walphos ligand (*R*)-1 [(*R*)-2-(2′-diphenylphosphinyl)ferrocenyl]ethyldo(bis-3,4-trifluoromethylphenyl)phosphine) (W001), we reacted palladium(II), platinum(II) or gold(III) starting materials with these diphosphines, with the knowledge that chiral phosphines can be discriminate between healthy and diseased cells. Here we report the synthesis and structures of Josiphos and Walphos diphosphine complexes of the above-mentioned group 10 and 11 metals, as well as their antitumor activity on HeLa cells.

2. Results and discussion

2.1. Synthesis

Complexation of the chiral Josiphos and Walphos diphosphine ligands with palladium were performed in dichloromethane using [$PdCl_2$(NCMe)$_2$] as the metal precursor (Scheme 1). Using the Josiphos ligand J003, [$PdCl_2$(J003)] (**1**) was obtained as an orange solid in 86% yield, while the Walphos ligand gave [$PdCl_2$(W001)] (**2**) as a red solid in 60% yield. Complexation of the same chiral

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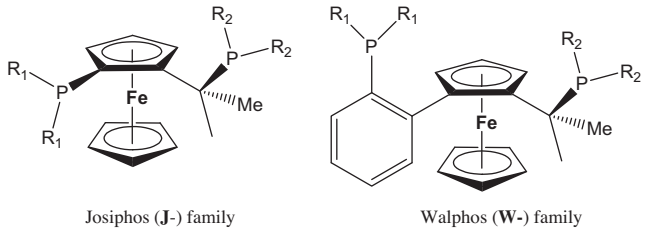


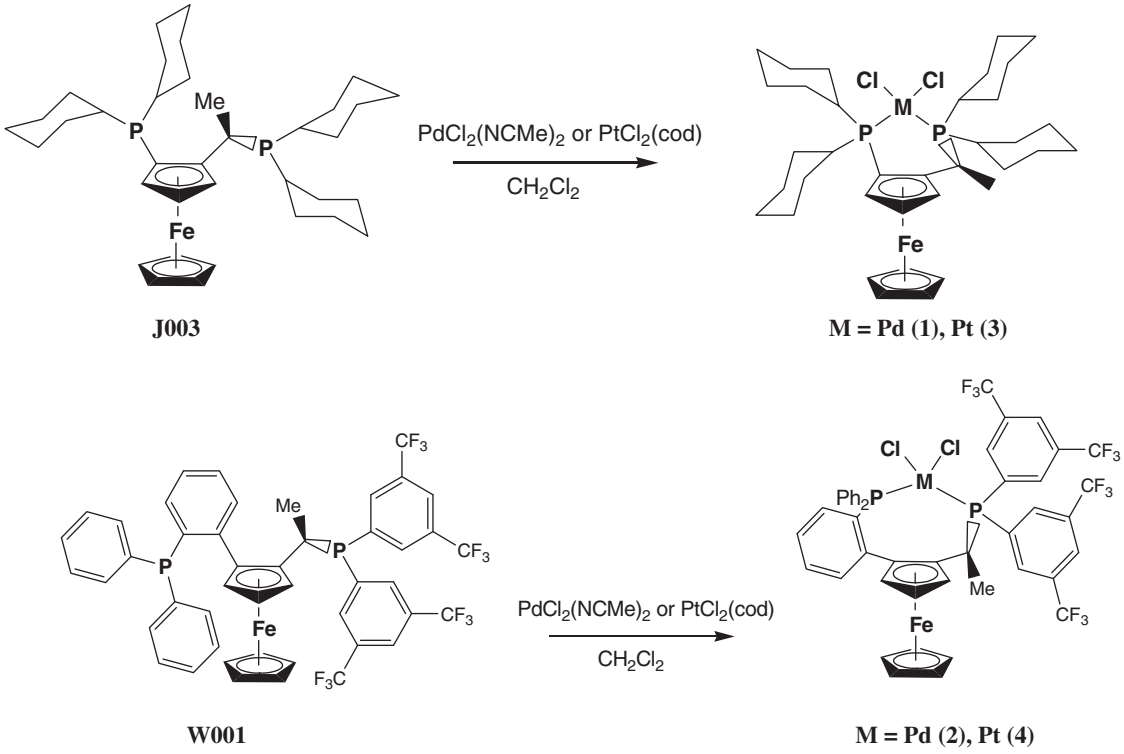
Fig. 1. Framework structures of the Josiphos and Walphos families of ferrocene-based chiral diphosphine ligands; J003: $R_1 = R_2$ = cyclohexyl; W001: R_1 = phenyl; R_2 = 3,5-trifluoromethylphenyl.

diphosphine ligands with platinum were performed using [$PtCl_2$(cod)] as the metal precursor (Scheme 1). In both instances the complexes were obtained as orange solids, with a 61% yield for [$PtCl_2$(J003)] (**3**) and 65% yield for [$PtCl_2$(W001)] (**4**).

Single crystals of **1** and **3** suitable for X-ray crystallographic studies were obtained by slow evaporation of dichloromethane solutions of the complexes at room temperature. The molecular structure of [$PdCl_2$(J003)] (**1**) is shown in Fig. 2 and that of [$PtCl_2$(J003)] (**3**) in Fig. 3. Their crystal data are presented in Table 1 and selected bond distances and angles are given in Table 2. In **1**, the geometry around the Pd atom is distorted square planar with two *cis* chlorines and two phosphorus atoms. The structure is similar to that of the analogous palladium complex [$PdCl_2$(J002)] (J002 = FcCHMeP^{t}Bu$_2$(PCy_2), cf. Fig. 1) in which the two phosphorus atoms carry tert-butyl (^{t}Bu) and cyclohexyl (Cy) substituents [6]. The P(2)–Pd(1)–P(1) and Cl(2)–Pd(1)–Cl(1) bond angles of 96.23(3)° and 88.44(3)° in **1** are in the same range as those observed for [$PdCl_2$(J002)] (97.03° and 86.48°, respectively). However, the P(2)–Pd(1)–P(1) bond angles in **1** and [$PdCl_2$(J002)] are larger than those found in [FcCHMePCy$_2$(PPh_2)PdMe_2(J001)] (93.26(9)°) (J001 = FcCHMePCy$_2$(PPh_2), cf. Fig. 1) [7]. The Pd–P bond distances in **1** for Pd(1)–P(1) and Pd(1)–P(2) are 2.2717(7) and 2.2702(7) Å, respectively. These Pd–P bond distances are in agreement with the expected donor ability of the two PCy_2 groups on the palladium atom. The Pd(1)–P(2) bond distances in **1** is similar to 2.276 Å reported for [$PdCl_2$(J002)] [6] where P(2) is also directly attached to the cyclopentadienyl ring. In contrast, the Pd(1)–P(1) distance of 2.327(3) Å in [PdMe_2(J001)] is significantly longer than in **1**. Despite the similar Pd–P bond distances in **1**, the Pd–Cl distances are different. For Pd(1)–Cl(1) the distance is 2.3781(7) Å while for Pd(1)–Cl(2) it is 2.3416(7) Å. Generally an increase of the P–Pd–P angle in achiral ferrocenyl diphosphine compounds results in lengthening of Pd–P bonds and a decrease of the Cl–Pd–C1 angle and Pd–C1 bond distances [8]. The discrepancies observed between **1** and [PdMe_2(J001)] can thus be ascribed to the electron-withdrawing effect of the chlorine in the former, relative to the donor effects of the methyl groups in the latter.

Similarly, the structure of [$PtCl_2$(J003)] (**3**) can be described as a distorted square planar geometry with two *cis* chlorine and two *cis* phosphorus atoms. The P(2)–Pt(1)–P(1) and Cl(2)–Pt(1)–Cl(1) bond angles of 96.41(6)° and 85.76(6)° are in the same range as observed by Ghent et al. [6] for [$PtCl_2$(J002) (97.33(3)° and 83.54(3)°, respectively). The Pt(1)–P(1) and Pt(1)–P(2) bond distances in **3** are 2.2641(18) and 2.2517(17) Å, respectively, and the Pt(1)–Cl(1) and Pt(1)–Cl(2) distances are 2.3713(17) and 2.3669(16) Å, respectively. The Pt–Cl bond *trans* to the PCy_2 directly attached to the cyclopentadienyl ring in **3** (2.3669(16) Å) and in [$PtCl_2$(J002)] (2.3696(9) Å) are also similar.

Attempts to prepare the corresponding d^8 gold(III) complexes resulted in reduction of the gold(III) precursor, H[$AuCl_4$]·4H_2O, to produce gold(I) complexes, as has also been observed for reactions with the achiral diphsophine ligands bis(diphenylphosphino)ferrocene (dppf) and bis(diisopropylphosphino)ferrocence (dippf) recently been reported by us [9]. The gold(I) complexes could thus be prepared from either [AuCl(tht)] (tht = tetrahydrothiophene) or H[$AuCl_4$]·4H_2O (Schemes 2 and 3). The ^{1}H NMR spectra of these chiral diphosphine gold complexes are complicated by their



Scheme 1. Schematic description of synthetic routes to complexes **1**–**4**.