Inorganica Chimica Acta 380 (2012) 211–215

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

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

Synthesis of $[Ru^{II}(\eta^6\text{-}p\text{-cymene})(PPh_3)(L)Cl]PF_6$ complexes with carbohydrate-derived phosphites, imidazole or indazole co-ligands

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ARTICLE INFO

Article history:
Available online 14 October 2011

Young Investigator Award Special Issue

Keywords:
Azoles
Carbohydrates
Nitrogen ligands
Phosphorus ligands
Ru^{II}(arene) compounds

ABSTRACT

Ru^{II}(arene) complexes of the general formula $[Ru^{II}(\eta^6\text{-}p\text{-cymene})(PPh_3)(L)Cl]PF_6$ with L = P- or N-donor systems have been synthesized and characterized. Carbohydrate-derived phosphites, imidazole or indazole have been chosen as co-ligands and different synthetic routes have been explored to obtain the compounds. The organometallics were characterized by elemental analysis, electrospray ionization mass spectroscopy, ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ and 2D NMR spectroscopic methods.

1. Introduction

Organometallic compounds based on the Ru^{II}(arene) structural motif have gained increasing importance in recent years and especially compounds bearing phosphine donor ligands are of interest for many different applications. The Ru^{II}(arene) unit is a very versatile scaffold with regard to its diversity in coordination chemistry and fine-tunable chemical as well as biological properties [1–6]. This class of compounds has been widely investigated spanning a broad range of applications from catalysts for organic transformations [7–10] such as hydrogenation [11,12], free-radical polymerization [13], hydration of terminal alkynes [14–16], hydration of nitriles [17,18], and olefin metathesis reactions [19,20] to the life sciences as metal-based drugs, especially as antimetastatic agents, kinase inhibitors and anticancer agents [1,3,21,22].

The Ru^{II}(arene) moiety bearing the versatile water-soluble phosphine 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA), i.e., the RAPTA family, has exhibited remarkable potential for the development of anticancer drugs [23–27]. The best studied representative RAPTA-C (Fig. 1) has shown excellent antimetastatic activity in *in vivo* tests on animal models [24,28,29]. Many additional derivatives of prototype RAPTA-C have been reported that were equipped with a diversity of ligand sets to design compounds with particular modes of action [1,3,23–25,30–32], including some with two P-donor ligands [25,33]. Some of these derivatives are based on carbohydrate–phosphite ligands, used with the aim to tackle the high demand of rapidly-growing tumors for glucose [34–36]. Such carbohydrate–Ru^{II}(arene) compounds were selectively cytotoxic for tumorigenic cell lines, and dichlorido(η^6-*p*-cymene)(3,5,6-bicyclophosphite-1,2-*O*-cyclohexylidene-α-D-glucofuranoside) ruthenium(II) (Fig. 1) was found to be more cytotoxic than RAPTA-C in *in vitro* assays [34]. The carbohydrate–phosphite coordinated to the Ru center undergoes partial hydrolysis to ultimately form several species. This process can be suppressed by high chloride concentrations or by replacing Ru with osmium and chlorido ligands with dicarboxylates [35,36]. However, the only Ru complexes that have reached clinical trials contain imidazole (HIm) and indazole (HInd). The most important examples are the classic Ru^{III} coordination compounds (H_2Im)[*trans*-$RuCl_4$(DMSO)(HIm)], NAMI-A, and (H_2Ind)-[*trans*-$RuCl_4$(HInd)$_2$], KP1019, both of which are currently undergoing phase I/IIa clinical trials (Fig. 1). NAMI-A is not active against primary tumors, however, it exhibits antimetastatic activity similar to RAPTA compounds [37,38]. In contrast to NAMI-A, KP1019 is active against primary tumors and especially against *in vivo* models bearing colorectal tumors [39,40]. Similarly, imidazole- and indazole-based ligands were used in innovative bioorganometallic approaches to attach biologically active ligand systems to the Ru^{II}(arene) scaffold, for example *via* imidazole-based linkers. While

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doi:10.1016/j.ica.2011.10.007

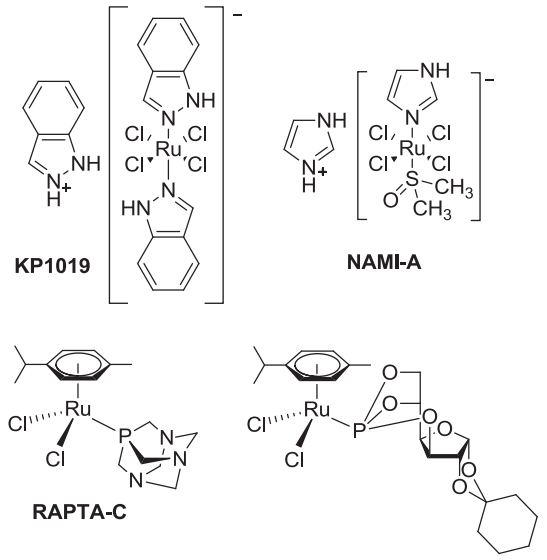


Fig. 1. Chemical structures of biologically active Ru complexes with N- and P-donor ligands.

compounds with the general formulae $[Ru^{II}(\eta^6\text{-arene})Cl_2(L)]$, $[Ru^{II}(\eta^6\text{-arene})Cl(L)_2]X$, and $[Ru^{II}(\eta^6\text{-arene})(L)_3]X_2$ (η^6-arene = benzene, *p*-cymene; L = imidazole, benzimidazole, *N*-methylimidazole, *N*-butylimidazole, *N*-vinylimidazole, *N*-benzoylimidazole; X = Cl, BF_4, BPh_4) did not exhibit significant *in vitro* anticancer activity [41], some derivatives with modified anthracene-based multidrug resistance (MDR) modulators were efficient Pgp inhibitors and active in anticancer screening assays [42].

In this paper, we present the preparation of a series of Ru^{II}(arene) complexes of the general formula $[Ru^{II}(\eta^6\text{-}p\text{-cymene})(PPh_3)(L)Cl]PF_6$ with carbohydrate-derived phosphites, imidazole or indazole co-ligands with potential biological activity.

2. Experimental

2.1. Materials

All reactions were carried out in dry solvents under an inert atmosphere. All chemicals were obtained from commercial suppliers in analytical grade and used as received. The Ru complexes bis[dichlorido(η^6-*p*-cymene)ruthenium(II)] **1** [43], [dichlorido(η^6-*p*-cymene)(triphenylphosphine)ruthenium(II)] **2** [24], [dichlorido(3,5,6-bicyclophosphite-1,2-*O*-isopropylidene-α-D-glucofuranoside)(η^6-*p*-cymene)ruthenium(II)] **3**, [dichlorido(3,5,6-bicyclophosphite-1,2-*O*-cyclohexylidene-α-D-glucofuranoside)(η^6-*p*-cymene) ruthenium(II)] **4** [34] and $[Ru^{II}(\eta^6\text{-}p\text{-cymene})(PPh_3)(CH_3CN)Cl]PF_6$ **7** [44], and the ligands 3,5,6-bicyclophosphite-1,2-*O*-isopropylidene-α-D-glucofuranoside **I** and 3,5,6-bicyclophosphite-1,2-*O*-cyclohexylidene-α-D-glucofuranoside **II** [45] were synthesized according to literature procedures. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded at 25 °C on a Bruker FT NMR spectrometer Avance III 500 MHz at 500.10 (^1H), 125.75 ($^{13}C\{^1H\}$) and 202.44 MHz ($^{31}P\{^1H\}$) or on a Bruker DPX 400 MHz at 400.13 (^1H), 100.63 ($^{13}C\{^1H\}$) and 161.98 MHz ($^{31}P\{^1H\}$) and the 2D NMR spectra were collected in a gradient-enhanced mode. Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Elemental analysis was determined by the Laboratory for Elemental Analysis, Faculty of Chemistry, University of Vienna, on a Perkin-Elmer 2400 CHN Elemental Analyzer. Electrospray ionization mass spectra were recorded on a Bruker esquire$_{3000}$.

2.1.1. [Chlorido(3,5,6-bicyclophosphite-1,2-*O*-isopropylidene-α-D-glucofuranoside)(η^6-*p*-cymene)(triphenylphosphine)ruthenium(II)] hexafluorophosphate **5**

A solution of $[Ru^{II}(\eta^6\text{-}p\text{-cymene})(PPh_3)(CH_3CN)Cl]PF_6$ (144 mg, 0.2 mmol) and 3,5,6-bicyclophosphite-1,2-*O*-isopropylidene-α-D-glucofuranoside (50 mg, 0.2 mmol) in CH_2Cl_2 (15 mL) was stirred for 2 h at room temperature. The solvent was reduced to about 3–5 mL and the product was precipitated by addition of pentane (20–25 mL). The orange yellow powder was filtered, washed with pentane (2× 5 mL) and dried under vacuum.

Yield: 176 mg (95%), m.p. 177–178 °C (decomp.). Elemental analysis, *Anal.* Calc. for $C_{37}H_{42}O_6P_3F_6ClRu$: C, 47.98; H, 4.57. Found: C, 47.69; H, 4.36%. MS (ESI^+): *m*/*z* 781.4 $[M-PF_6]^+$.

^1H NMR (500.10 MHz, $CDCl_3$, 25 °C): δ = 7.64–7.45 (m, 30H, $H^{a,b}_{Ar}$), 6.18 (d, *J* = 6.3 Hz, 1H, H^b_{Ar}), 6.13 (d, *J* = 6.0 Hz, 1H, H^b_{Ar}), 6.09 (d, *J* = 6.0 Hz, 1H, H^a_{Ar}), 6.06 (d, *J* = 6.5 Hz, 1H, H^a_{Ar}), 5.97 (tr, *J* = 3.8 Hz, 2H, $H^{a,b}$-1), 5.80 (d, *J* = 6.3 Hz, 2H, $H^{a,b}_{Ar}$), 5.45 (d, *J* = 6.3 Hz, 1H, H^b_{Ar}), 5.28 (d, *J* = 6.3 Hz, 1H, H^a_{Ar}), 4.98–4.89 (m, 2H, $H^{a,b}$-5), 4.58 (d, *J* = 3.5 Hz, 1H, H^b-2), 4.49 (d, *J* = 2.2 Hz, 1H, H^a-3), 4.43 (d, *J* = 1.9 Hz, 1H, H^b-3), 4.42 (d, *J* = 3.5 Hz, 1H, H^a-2), 4.24 (tr, *J* = 9.8 Hz, 1H, H^a-6), 4.20–4.14 (m, 3H, $H^{a,b}$-4, H^b-6), 3.71 (m, 1H, H^a-6′), 3.40 (m, 1H, H^b-6′), 2.81 (m, 1H, CH^a), 2.73 (m, 1H, CH^b), 1.94 (s, 3H, $CH_3{}^b$), 1.86 (s, 3H, $CH_3{}^a$), 1.46 (s, 6H, $CH_3{}^{a,b}$), 1.33 (s, 6H, $CH_3{}^{a,b}$), 1.27–1.25 (m, 12H, $CH_3{}^{a,b}$) ppm. $^{31}P\{^1H\}$ NMR (202.44 MHz, $CDCl_3$, 25 °C): δ = 144.7 (d, *J* = 87 Hz, sugar–P^b), 144.4 (d, *J* = 89 Hz, sugar–P^a), 32.7 (d, *J* = 89 Hz, $PPh_3{}^b$), 32.5 (d, *J* = 89 Hz, $PPh_3{}^a$), −144.3 (septet, PF_6) ppm.

The diastereomer **5a** crystallized at 4 °C from saturated chloroform solution within 72 h. The yellow crystals were filtered, washed with diethylether and dried under vacuum.

^1H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 7.68–7.46 (m, 15H, H_{Ar}), 6.07 (m, 2H, H_{Ar}), 6.00 (d, *J* = 3.4 Hz, 1H, H-1), 5.95 (d, *J* = 6.0 Hz, 1H, H_{Ar}), 5.46 (d, *J* = 6.0 Hz, 1H, H_{Ar}), 4.94 (m, 1H, H-5), 4.51 (s, 1H, H-3), 4.43 (d, *J* = 3.4 Hz, 1H, H-2), 4.23 (tr, *J* = 9.8 Hz, 1H, H-6), 4.16 (d, *J* = 2.0 Hz,1H, H-4), 3.80 (m, 1H, H-6′), 2.86 (m, 1H, CH), 1.82 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.30–1.24 (m, 6 H, CH_3) ppm. $^{31}P\{^1H\}$ NMR (161.98 MHz, $CDCl_3$, 25 °C): δ = 144.7 (d, *J* = 88 Hz, sugar–P), 32.9 (d, *J* = 88 Hz, PPh_3), −144.2 (septet, PF_6) ppm.

2.1.2. [Chlorido(3,5,6-bicyclophosphite-1,2-*O*-cyclohexylidene-α-D-glucofuranoside)(η^6-*p*-cymene)(triphenylphosphine)ruthenium(II)] hexafluorophosphate **6**

A solution of $[Ru^{II}(\eta^6\text{-}p\text{-cymene})(PPh_3)(CH_3CN)Cl]PF_6$ (144 mg, 0.2 mmol) and 3,5,6-bicyclophosphite-1,2-*O*-cyclohexylidene-α-D-glucofuranoside (58 mg, 0.2 mmol) in CH_2Cl_2 (15 mL) was stirred for 2 h at room temperature. The solvent was reduced to about 3–5 mL and the product was precipitated by addition of pentane (20–25 mL). The orange yellow powder was filtered, washed with pentane (2× 5 mL) and dried under vacuum.

Yield: 185 mg (96%), m.p. 178–180 °C (decomp.). Elemental analysis, *Anal.* Calc. for $C_{40}H_{46}O_6P_3F_6ClRu$: C, 49.72; H, 4.80. Found: C, 49.44; H, 4.53%. MS (ESI^+): *m*/*z* 821.5 $[M-PF_6]^+$.

^1H NMR (500.10 MHz, $CDCl_3$, 25 °C): δ = 7.64–7.45 (m, 30H, $H^{a,b}_{Ar}$), 6.17 (d, *J* = 6.0 Hz, 1H, H^a_{Ar}), 6.10 (m, 2H, $H^{a,b}_{Ar}$), 6.00 (d, *J* = 6.3 Hz, 1H, H^b_{Ar}), 5.96 (tr, *J* = 3.8 Hz, 2H, $H^{a,b}$-1), 5.79 (m, 2H, $H^{a,b}_{Ar}$), 5.46 (d, *J* = 6.6 Hz, 1H, H^a_{Ar}), 5.31 (d, *J* = 6.3 Hz, 1H, H^b_{Ar}), 4.97–4.87 (m, 2H, $H^{a,b}$-5), 4.55 (d, *J* = 3.5 Hz, 1H, H^a-2), 4.50 (d, *J* = 2.5 Hz, 1H, H^b-3), 4.45 (d, *J* = 2.2 Hz, 1H, H^a-3), 4.39 (d, *J* = 3.9 Hz, 1H, H^b-2), 4.24 (tr, *J* = 9.8 Hz, 1H, H^b-6), 4.20–4.13 (m, 3H, $H^{a,b}$-4, H^a-6), 3.71 (m, 1H, H^b-6′), 3.42 (m, 1H, H^a-6′), 2.79 (m, 1H, CH^b), 2.71 (m, 1H, CH^a), 1.92 (s, 3H, $CH_3{}^a$), 1.84 (s, 3H, $CH_3{}^b$), 1.69–1.49 (m, 16H, $CH_2{}^{a,b}$), 1.43–1.35 (m, 4H, $CH_2{}^{a,b}$), 1.25–1.20 (m, 12H, $CH_3{}^{a,b}$) ppm. $^{31}P\{^1H\}$ NMR (202.44 MHz, $CDCl_3$, 25 °C): δ = 144.6 (d, *J* = 87 Hz, sugar–P), 144.5 (d, *J* = 87 Hz, sugar–P), 32.3 (d, *J* = 89 Hz, PPh_3), 32.4 (d, *J* = 87 Hz, PPh_3), −144.3 (septet, PF_6) ppm.

*2.1.3. [Chlorido(η^6-p-cymene)(1H-indazole)(triphenylphosphine) ruthenium(II)] hexafluorophosphate **8***

A solution of indazole (26 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) was added to a solution of [Ru^{II}(η^6-*p*-cymene)(PPh_3)(CH_3CN)Cl]PF_6 (144 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) and stirred for 2 h at room temperature. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (3–5 mL) and the product was precipitated by addition of pentane (20–25 mL). The orange yellow powder was filtered, washed with pentane (2× 5 mL) and dried under vacuum.

Yield: 150 mg (94%), m.p. 235 °C (decomp.). Elemental analysis, *Anal.* Calc. for $C_{35}H_{35}N_2P_2F_6ClRu$: C, 52.80; H, 4.43; N, 3.52. Found: C, 53.02; H, 4.39; N, 3.24%. MS (ESI^+): *m/z* 651.2 [M−PF_6]$^+$.

^{1}H NMR (500.10 MHz, $CDCl_3$, 25 °C): δ = 11.18 (s, 1H, NH_{ind}), 8.71 (s, 1H, H_{ind}), 7.76 (d, *J* = 8.2 Hz, 1H, H–Ar_{ind}), 7.30–7.37 (m, 15H, PPh_3), 7.11–7.16 (m, 2H, H–Ar_{ind}), 6.32 (d, *J* = 5.5 Hz, 1H, H–Ar), 6.09 (d, *J* = 6.0 Hz, 1H, H–Ar), 5.48 (d, *J* = 6.0 Hz, 1H, H–Ar), 5.23 (d, *J* = 6.1 Hz, 1H, H–Ar), 2.43–2.49 (m, 1H, $CH(CH_3)_2$), 1.70 (s, 3H, CH_3), 1.11 (d, *J* = 6.9 Hz, 3H, $CH(CH_3)_2$), 1.06 (d, *J* = 6.9 Hz, 3H, $CH(CH_3)_2$) ppm. ^{13}C{^{1}H} NMR (125.75 MHz, $CDCl_3$, 25 °C): δ = 143.1 (C_{ind}), 139.7 (C_{ind}), 134.2 (d, *J* = 9.1 Hz, C–Ar), 131.3 (C–Ar), 129.0 (d, *J* = 49.0 Hz, C–Ar), 128.7 (C–Ar), 128.4 (d, *J* = 10.0 Hz, C–Ar), 123.9 (C–Ar), 122.2 (C–Ar), 121.3 (C–Ar), 115.4 (d, *J* = 8.2 Hz, C–Ar), 108.9 (C–Ar), 104.1 (C–Ar), 95.8 (d, *J* = 6.4 Hz, C–Ar), 89.9 (C–Ar), 88.3 (C–Ar), 83.2 (C–Ar), 31.1 ($CH(CH_3)_2$), 23.1 ($CH(CH_3)_2$), 20.9 ($CH(CH_3)_2$), 18.3 (CH_3) ppm. ^{31}P{^{1}H} NMR (202.44 MHz, $CDCl_3$, 25 °C): δ = 36.4 (s, PPh_3), −144.1 (septet, PF_6) ppm.

*2.1.4. [Chlorido(η^6-p-cymene)(imidazole)(triphenylphosphine) ruthenium(II)] hexafluorophosphate **9***

A solution of imidazole (15 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) was added to a solution of [Ru^{II}(η^6-*p*-cymene)(PPh_3)(CH_3CN)Cl]PF_6 (144 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) and stirred for 2 h at room temperature. The solvent was removed, the residue was dissolved in CH_2Cl_2 (3–5 mL) and the product was precipitated by addition of pentane (20–25 mL). The orange yellow powder was filtered, washed with pentane (2× 5 mL) and dried under vacuum.

Yield: 147 mg (99%), m.p. 138 °C (decomp.). Elemental analysis, *Anal.* Calc. for $C_{31}H_{33}N_2P_2F_6ClRu$: C, 49.91; H, 4.46; N, 3.75. Found: C, 50.12; H, 4.31; N, 3.47%. MS (ESI^+): *m/z* 601.3 [M−PF_6]$^+$.

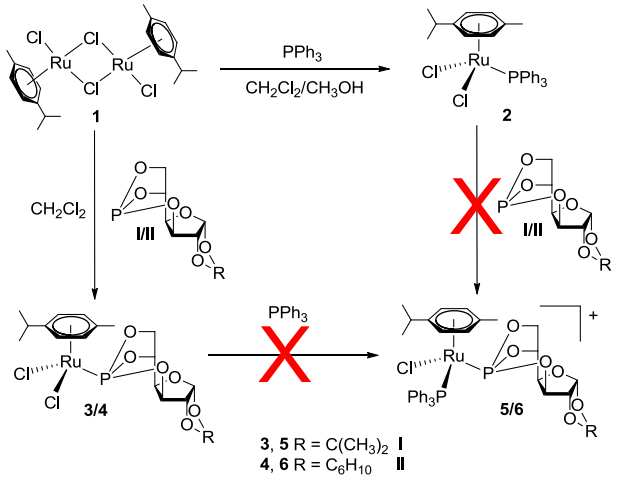
^{1}H NMR (500.10 MHz, CD_3OD, 25 °C): δ = 7.86 (s, 1H, H_{im}), 7.50–7.53 (m, 3H, PPh_3), 7.40–7.42 (m, 12H, PPh_3), 7.25 (t, *J* = 1.4 Hz, 1H, H_{im}), 7.08 (d, *J* = 0.8 Hz, 1H, H_{im}), 6.97 (d, *J* = 1.6 Hz, 1H, H_{im}), 6.02 (dd, *J* = 6.1 Hz, *J* = 1.1 Hz, H–Ar), 5.80 (dd, *J* = 6.1 Hz, *J* = 1.4 Hz, 1H, H–Ar), 5.68 (d, *J* = 6.0 Hz, 1H, H–Ar), 5.15 (d, *J* = 6.1 Hz, 1H, H–Ar), 2.33–2.38 (m, 1H, $CH(CH_3)_2$), 1.75 (s, 3H, CH_3), 1.15 (d, *J* = 7.0 Hz, 3H, $CH(CH_3)_2$), 1.11 (d, *J* = 7.0 Hz, 3H, $CH(CH_3)_2$). ^{13}C{^{1}H} NMR (125.75 MHz, CD_3OD, 25 °C): δ = 134.1 (d, *J* = 10.0 Hz, C_{im}), 132.2 (C–Ar), 130.7 (d, *J* = 2.6 Hz, C_{im}), 130.6 (d, *J* = 47.2 Hz, C–Ar), 128.1 (d, *J* = 10.0 Hz, C_{im}), 117.7 (C–Ar), 113.4 (d, *J* = 6.4 Hz, C–Ar), 102.6 (C–Ar), 93.2 (d, *J* = 6.4 Hz, C–Ar), 88.1 (C–Ar), 88.0 (C–Ar), 87.9 (C–Ar), 86.8 (C–Ar), 30.7 ($CH(CH_3)_2$), 21.7 ($CH(CH_3)_2$), 20.0 ($CH(CH_3)_2$), 16.8 (CH_3) ppm. ^{31}P{^{1}H} NMR (202.44 MHz, CD_3OD, 25 °C): δ = 35.8 (s, PPh_3), −144.5 (septet, PF_6) ppm.

3. Results and discussion

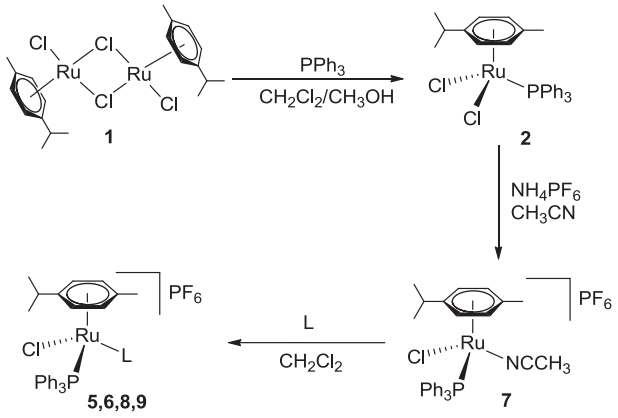
3.1. Synthesis and characterization

Within our quest for new derivatives of the RAPTA family, we have prepared a series of heteroleptic Ru^{II}(arene) compounds, bearing both P,P- and P,N-donor systems. Such bis-phosphine Ru^{II}(arene) organometallics have been studied as catalysts and structure–activity correlations have been established [45–52]. Furthermore, analogous [Ru^{II}(arene)(L)(PPh_3)Cl] complexes with sugar–phosphite, imidazole and indazole as co-ligands were prepared. Several strategies were pursued to prepare such heteroleptic compounds. Direct substitution of one chloride of [Ru^{II}(η^6-*p*-cymene)(P-ligand)Cl_2] (P-ligand = PPh_3 or carbohydrate–phosphite) by either triphenylphosphine or a carbohydrate–phosphite to yield **5** and **6** was not successful in aprotic solvents, such as dichloromethane and chloroform (Scheme 1). Instead of substitution of a chloride, a mixture of compounds containing the starting material, the desired products and P-ligand exchange products were obtained at elevated temperature and prolonged reaction time. The same reaction in protic solvent systems like methanol and at low temperature was also not successful and resulted in degradation of the sugar–phosphite at elevated temperature (50–60 °C).

In another attempt, [Ru^{II}(η^6-*p*-cymene)(acetonitrile)(P-ligand)Cl]$^+$ was selected as a precursor to replace the more labile acetonitrile by another P-based ligand, following a strategy reported earlier (Scheme 2) [44]. This approach was successful and heteroleptic organometallic compounds of the general formula [Ru^{II}(η^6-*p*-cymene)(Ph_3P)(sugar–P)Cl]PF_6 **5** (sugar–P = 3,5,6-bicyclophosphite-1,2-*O*-isopropylidene-α-D-glucofuranoside) and **6** (sugar–P = 3,5,6-bicyclophosphite-1,2-*O*-cyclohexylidene-α-D-glucofurano side) were synthesized in CH_2Cl_2 in very good yield under mild conditions (Scheme 2). Both complexes were characterized by 1D



Scheme 1. Synthetic strategy to heteroleptic Ru complexes by direct substitution of a chloride by a second P-based ligand.



Scheme 2. Synthetic scheme for the preparation of **5**, **6**, **8**, and **9** from precursor **7** (L = **I**, **II**, indazole or imidazole, respectively).

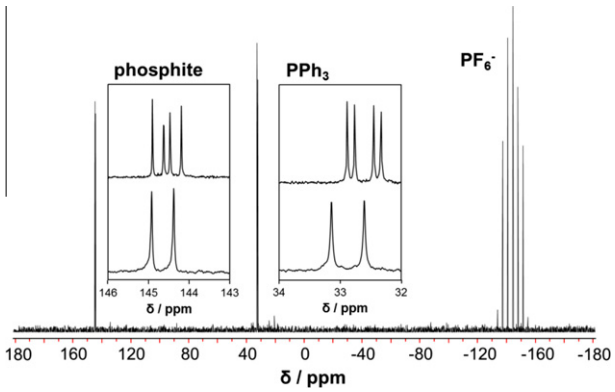


Fig. 2. $^{31}P\{^{1}H\}$ NMR spectrum of **5**. The insets show zooms into the relevant regions of the spectrum for compounds **5** (top) and **5a** (bottom), indicating the isolation of a single diastereomer from the diastereomeric mixture. The slight shift of the signal at 33 ppm (and of the PF_6^-; data not shown) is related to recording the data at two different instruments, however, the coupling constant is equal ($J \approx 88$ Hz).

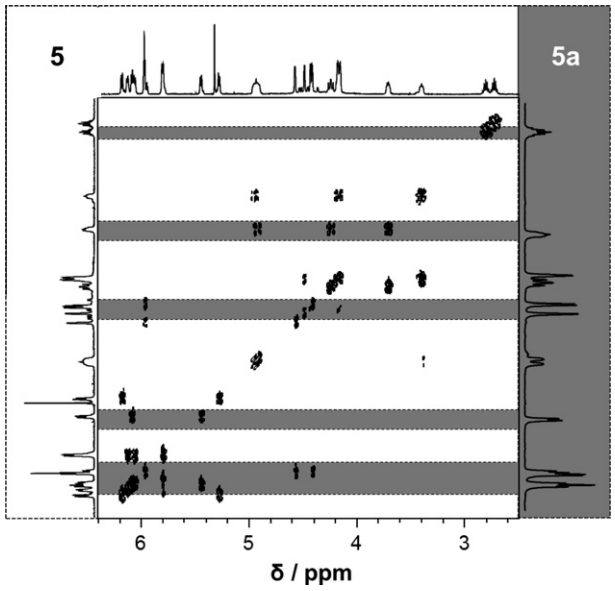


Fig. 3. $^{1}H,^{1}H$-COSY NMR spectrum of the diastereomeric mixture of **5**, overlaid with the signals assigned to diastereomer **5a**.

and 2D NMR spectroscopy, ESI-MS and elemental analysis. The electrospray ionization mass spectra (ESI-MS) of **5** and **6** display the expected ions and isotopic abundances at m/z 781.4 for **5** and m/z 821.5 for **6**. Compounds **5** and **6** are present as a mixture of diastereomers as confirmed by $^{31}P\{^{1}H\}$ NMR spectroscopy data. Two sets of signals (two doublets each) are found for the diastereomeric mixtures of **5** and **6** at *ca.* 32 (PPh_3) and 144 ppm (sugar–P) with a $^{2}J_{P-Ru-P}$ coupling constant of 87 Hz, corroborating the coordination of both phosphorous ligands to the Ru center (Fig. 2). Further indication for the presence of different phosphorus-based co-ligands at the Ru center is a low field-shift of the signal assignable to the phosphite from 144 to 130 ppm accompanied by a change in multiplicity from singlet to doublet [34].

In order to separate the diastereomers, a saturated solution of **5** in chloroform was prepared and allowed to crystallize at 4 °C (72 h). This resulted in yellow crystals of **5a** which were characterized by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy. The ^{1}H NMR spectra (Fig. 3) contained only a single set of signals, as compared to two sets for diastereomeric **5**, and a similar observation was made in the $^{31}P\{^{1}H\}$ NMR spectra (Fig. 2). Based on these data sets we conclude that we isolated the single diastereomer **5a**, however, the exact configuration remains elusive.

Compounds **8** and **9** were prepared following a similar procedure by using indazole and imidazole instead of the phosphite–carbohydrate moiety (Scheme 2). Three tautomeric forms for indazole are known and coordination to metal ions *via* N1 or N2 have been recently documented by X-ray diffraction and NMR spectroscopy [53], with binding to N2 being the most frequent coordination mode. Complexes **8** and **9** were characterized by standard analytical methods as described above. A notable feature is a coupling between the P atom and the C atoms of PPh_3, indazole and imidazole ligands. In contrast to the carbohydrate bearing complexes **5** and **6**, **8** and **9** can only be present as enantiomers but not as diastereomers. However, a dynamic equilibrium causes inversion of the stereocenter and does not allow separation of the two components [54]. Therefore, the $^{31}P\{^{1}H\}$ NMR spectra for both compounds contained only a singlet at approximately 36 ppm for triphenylphosphine and a septet at −144 ppm assignable to PF_6^-.

4. Conclusions

Ru^{II}(arene) complexes bearing ligands with P- or N-donor atoms have potential in both metallodrug research and as catalysts. In an attempt to prepare compounds bearing heteroleptic P,P- or P,N-ligand systems, we have synthesized a series of organometallic compounds based on the $Ru^{II}(\eta^6$-*p*-cymene$)(PPh_3)$ fragment bearing sugar-derived phosphites, imidazole and indazole co-ligands and characterized them by standard analytical methods. A synthetic route *via* the acetonitrile-containing intermediate $[Ru^{II}(\eta^6$-*p*-cymene$)(CH_3CN)(PPh_3)Cl]^+$ has proven to provide access to such compounds, whereas the direct replacement of a chlorido ligand in $[Ru^{II}(\eta^6$-*p*-cymene$)$(P-ligand$)Cl_2]$ was not successful. The complexes based on chiral phosphite-modified sugars give rise of diastereomers upon coordination to the Ru center. We were successful in isolating one of the diastereomers by crystallization from chloroform, as shown by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy.

Acknowledgements

We thank the Higher Education Commission of Pakistan (M.H.), the Austrian Exchange Service (ÖAD), the Hochschuljubiläumsstiftung Vienna, and COST D39 and CM0902 for financial support. This research was supported by a Marie Curie Intra European Fellowship within the 7th European Community Framework Programme Project 220890-SuRuCo (A.A.N.). We gratefully acknowledge Prof. Markus Galanski for recording the 2D NMR spectra and Patricia Schaaf for assistance in synthesis.

References

[1] P.J. Dyson, Chimia 61 (2007) 698.
[2] A.F.A. Peacock, P.J. Sadler, Chem. Asian J. 3 (2008) 1890.
[3] C.G. Hartinger, P.J. Dyson, Chem. Soc. Rev. 38 (2009) 391.
[4] A. Casini, C.G. Hartinger, A.A. Nazarov, P.J. Dyson, Top. Organomet. Chem. 32 (2010) 57.
[5] W.-H. Ang, A. Casini, G. Sava, P.J. Dyson, J. Organomet. Chem. 696 (2011) 989.
[6] G. Gasser, I. Ott, N. Metzler-Nolte, J. Med. Chem. 54 (2011) 3.
[7] K. Umezawa-Vizzini, T.R. Lee, Organometallics 22 (2003) 3066.
[8] T.J. Geldbach, P.J. Dyson, J. Am. Chem. Soc. 126 (2004) 8114.
[9] E. Bustelo, P.H. Dixneuf, Adv. Synth. Catal. 347 (2005) 393.
[10] L. Qiu, F.Y. Kwong, J. Wu, W.H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou, A.S.C. Chan, J. Am. Chem. Soc. 128 (2006) 5955.
[11] P. Crochet, M.A. Fernández-Zumel, C. Beauquis, J. Gimeno, Inorg. Chim. Acta 356 (2003) 114.
[12] R. Venkateswaran, J.T. Mague, M.S. Balakrishna, Inorg. Chem. 46 (2007) 809.
[13] F. Simal, A. Demonceau, A.F. Noels, Angew. Chem., Int. Ed. 38 (1999) 538.
[14] M. Tokunaga, Y. Wakatsuki, Angew. Chem., Int. Ed. 37 (1998) 2867.
[15] H.D. Hansen, J.H. Nelson, Organometallics 19 (2000) 4740.
[16] V. Cadierno, P. Crochet, S.E. Garcia-Garrido, J. Gimeno, Dalton Trans. (2004) 3635.

[17] I.N. Stepanenko, B. Cebrian-Losantos, V.B. Arion, A.A. Krokhin, A.A. Nazarov, B.K. Keppler, Eur. J. Inorg. Chem. (2007) 400.
[18] S.M. Ashraf, I. Berger, A.A. Nazarov, C.G. Hartinger, M.P. Koroteev, E.E. Nifant'ev, B.K. Keppler, Chem. Biodiversity 5 (2008) 1640.
[19] R. Akiyama, S. Kobayashi, Angew. Chem., Int. Ed. 41 (2002) 2602.
[20] M. Bassetti, F. Centola, D. Semeril, C. Bruneau, P.H. Dixneuf, Organometallics 22 (2003) 4459.
[21] E. Meggers, Chem. Commun. (2009) 1001.
[22] G. Süss-Fink, Dalton Trans. 39 (2010) 1673.
[23] C.S. Allardyce, P.J. Dyson, D.J. Ellis, S.L. Heath, Chem. Commun. (2001) 1396.
[24] C. Scolaro, A. Bergamo, L. Brescacin, R. Delfino, M. Cocchietto, G. Laurenczy, T.J. Geldbach, G. Sava, P.J. Dyson, J. Med. Chem. 48 (2005) 4161.
[25] C. Scolaro, A.B. Chaplin, C.G. Hartinger, A. Bergamo, M. Cocchietto, B.K. Keppler, G. Sava, P.J. Dyson, Dalton Trans. (2007) 5065.
[26] S. Chatterjee, S. Kundu, A. Bhattacharyya, C.G. Hartinger, P.J. Dyson, J. Biol. Inorg. Chem. 13 (2008) 1149.
[27] C.A. Vock, A.K. Renfrew, R. Scopelliti, L. Juillerat-Jeanneret, P.J. Dyson, Eur. J. Inorg. Chem. (2008) 1661.
[28] A. Bergamo, A. Masi, P.J. Dyson, G. Sava, Int. J. Oncol. 33 (2008) 1281.
[29] P. Nowak-Sliwinska, J.R. van Beijnum, A. Casini, A.A. Nazarov, G. Wagnieres, J. Med. Chem. 54 (2011) 3895.
[30] W.H. Ang, L.J. Parker, A. De Luca, L. Juillerat-Jeanneret, C.J. Morton, M. Lo Bello, M.W. Parker, P.J. Dyson, Angew. Chem., Int. Ed. 48 (2009) 3854.
[31] A.K. Renfrew, A.D. Phillips, A.E. Egger, C.G. Hartinger, S.S. Bosquain, A.A. Nazarov, B.K. Keppler, L. Gonsalvi, M. Peruzzini, P.J. Dyson, Organometallics 28 (2009) 1165.
[32] B. Wu, M.S. Ong, M. Groessl, Z. Adhireksan, C.G. Hartinger, P.J. Dyson, C.A. Davey, Chem. Eur. J. 17 (2011) 3562.
[33] A.K. Renfrew, A.E. Egger, R. Scopelliti, C.G. Hartinger, P.J. Dyson, C. R. Chim. 13 (2010) 1144.
[34] I. Berger, M. Hanif, A.A. Nazarov, C.G. Hartinger, R.O. John, M.L. Kuznetsov, M. Groessl, F. Schmitt, O. Zava, F. Biba, V.B. Arion, M. Galanski, M.A. Jakupec, L. Juillerat-Jeanneret, P.J. Dyson, B.K. Keppler, Chem. Eur. J. 14 (2008) 9046.
[35] M. Hanif, A.A. Nazarov, C.G. Hartinger, W. Kandioller, M.A. Jakupec, V.B. Arion, P.J. Dyson, B.K. Keppler, Dalton Trans. 39 (2010) 7345.
[36] M. Hanif, S.M. Meier, W. Kandioller, A. Bytzek, M. Hejl, C.G. Hartinger, A.A. Nazarov, V.B. Arion, M.A. Jakupec, P.J. Dyson, B.K. Keppler, J. Inorg. Biochem. 105 (2011) 224.
[37] M. Magnarin, A. Bergamo, M.E. Carotenuto, S. Zorzet, G. Sava, Anticancer Res. 20 (2000) 2939.
[38] M. Cocchietto, G. Sava, Pharmacol. Toxicol. 87 (2000) 193.
[39] C.G. Hartinger, S. Zorbas-Seifried, M.A. Jakupec, B. Kynast, H. Zorbas, B.K. Keppler, J. Inorg. Biochem. 100 (2006) 891.
[40] M.A. Jakupec, M. Galanski, V.B. Arion, C.G. Hartinger, B.K. Keppler, Dalton Trans. (2008) 183.
[41] C.A. Vock, C. Scolaro, A.D. Phillips, R. Scopelliti, G. Sava, P.J. Dyson, J. Med. Chem. 49 (2006) 5552.
[42] C.A. Vock, W.H. Ang, C. Scolaro, A.D. Phillips, L. Lagopoulos, L. Juillerat-Jeanneret, G. Sava, R. Scopelliti, P.J. Dyson, J. Med. Chem. 50 (2007) 2166.
[43] M.A. Bennett, A.K. Smith, J. Chem. Soc., Dalton Trans. (1974) 233.
[44] A.B. Chaplin, C. Fellay, G. Laurenczy, P.J. Dyson, Organometallics 26 (2007) 586.
[45] A.B. Chaplin, Chimia 62 (2008) 217.
[46] P.J. Dyson, D.J. Ellis, G. Laurenczy, Adv. Synth. Catal. 345 (2003) 211.
[47] H. Horvath, G. Laurenczy, A. Katho, J. Organomet. Chem. 689 (2004) 1036.
[48] A.B. Chaplin, P.J. Dyson, Organometallics 26 (2007) 2447.
[49] A.B. Chaplin, P.J. Dyson, Organometallics 26 (2007) 4357.
[50] C.A. Mebi, R.P. Nair, B.J. Frost, Organometallics 26 (2007) 429.
[51] S. Bolano, G. Ciancaleoni, J. Bravo, L. Gonsalvi, A. Macchioni, M. Peruzzini, Organometallics 27 (2008) 1649.
[52] A. Garcia-Fernandez, J. Diez, A. Manteca, J. Sanchez, M.P. Gamasa, E. Lastra, Polyhedron 27 (2008) 1214.
[53] G.E. Buchel, I.N. Stepanenko, M. Hejl, M.A. Jakupec, B.K. Keppler, V.B. Arion, Inorg. Chem. 50 (2011) 7690.
[54] R. Lang, K. Polborn, T. Severin, K. Severin, Inorg. Chim. Acta 294 (1999) 62.