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Synthesis, catalytic properties and biological activity of new water soluble ruthenium cyclopentadienyl PTA complexes $[(C_5R_5)RuCl(PTA)_2]$ (R = H, Me; PTA = 1,3,5-triaza-7-phosphaadamantane)†

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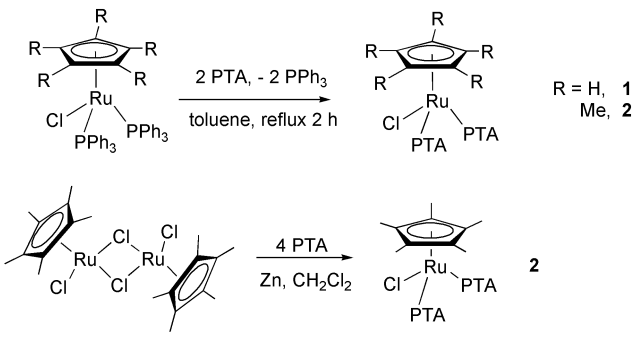
Received (in Cambridge, UK) 15th October 2002, Accepted 25th November 2002
First published as an Advance Article on the web 18th December 2002

The new water soluble ruthenium complexes $[(C_5R_5)RuCl(PTA)_2]$ (R = H, Me; PTA = 1,3,5-triaza-7-phosphaadamantane) were synthesised and characterised. Their evaluation as regioselective catalysts for hydrogenation of unsaturated ketones in aqueous biphasic conditions and as cytotoxic agents towards the TS/A adenocarcinoma cell line is briefly presented.

In recent years, aqueous homogeneous catalysis has received increased attention, due to greater environmental awareness and cost effectiveness thanks to easier catalyst recycling.[1] Some water-soluble organometallic compounds have been used in nuclear medicine, diagnostics and therapy.[2] Water solubility can be obtained using polar group-substituted phosphines or cyclopentadienyls,[3] or by using neutral water-soluble ligands such as 1,3,5-triaza-7-phosphaadamantane (PTA) whose late transition metal coordination chemistry has been developed mainly by Joó, Darensbourg and coworkers.[4,5] PTA complexes were used in catalytic processes including hydrogenation of aldehydes,[5a,b] olefins[5c] and allyl alcohols,[6] in aqueous biphasic conditions. Hydrogenation of aqueous carbonate to formate has also been investigated.[7] The pH-dependent cytotoxicity of $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2(PTA)]$ has been shown by Dyson *et al.*[8] Remarkably, water-soluble PTA complexes incorporating C_5R_5 coligands have never been described in spite of their obvious potentialities in both aqueous catalysis and biological activity.

We present here preliminary results describing the novel water-soluble complexes $[(C_5R_5)RuCl(PTA)_2]$ [R = H (**1**), Me (**2**)] and providing a first assessment of their catalytic and biological activity. The complexes were synthesised according to Scheme 1 and obtained in moderate to good yield.†

NMR data† confirm that two PTA ligands are P-bonded to the $(C_5R_5)Ru$ moiety, while the low conductivity in water indicates the metal coordination of chloride. The molecular structure of $\mathbf{2}\cdot C_2H_4Cl_2$ was determined by single-crystal X-ray diffraction study and is shown in Fig. 1.‡ Two independent molecules were found in the asymmetric unit showing no significant differences in their metrical parameters. The overall geometry of the complex is very similar to that observed for three-legged piano-stool complexes of the type $[(C_5R_5)MXL_2]$ such as $[CpRuCl(PPh_3)_2]$,[9a] and $[Cp^*Fe(dppe)(\eta^1\text{-}P_4)]BPh_4$,[9b] with the Cp* ring essentially planar ($d_{RuC(ave)}$ = 1.86 Å). One chlorine ligand (d_{RuCl} = 2.46 Å) and two PTA molecules ($d_{RuP(ave)}$ = 2.28 Å, in the range expected for Ru-PTA complexes)[5a,8] complete the coordination polyhedron around the metal, with P(1)–Ru–P(2) angle at 93.3°. Complexes **1** and **2** are air stable solids which easily dissolve in water ($S_{25\,°C}$ = 40 mg cm^{-3} for **1** and 25 mg cm^{-3} for **2**) and chlorinated organic solvents. Aqueous solutions of **1** and **2** are exceedingly stable and the complexes were recovered unchanged after 16 h refluxing. Prolonged heating in D_2O did not cause deuterium incorporation in either the cyclopentadienyl ring or PTA ligands.



Scheme 1

Both complexes are active in regioselective hydrogenation of benzylidene acetone (**3**) to 4-phenylbutan-2-one (**4**) in H_2O–*n*-octane. By-products 4-phenylbutan-2-ol (**5**) and 4-phenylbut-3-en-2-ol (**6**) were formed in small amount or traces, as summarised in Table 1. Catalytic tests with **1** at 80 °C, 450 psi of H_2, showed very high selectivity to **4** (90%) at low conversion (26%) after 13 h. At 130 °C **1** gave higher activity (78% at 13 h), with a decrease in selectivity towards **4** (76%), likely due to over-hydrogenation in a two-step reaction fashion. The presence of an excess of PTA (Table 1, entry 6) caused a decrease in conversion as expected for a dissociative mechanism. Comparable selectivity to **4** (94%) at moderate conversion (40%) was observed at 80 °C using **2**. The activity of **2** does not depend dramatically on the temperature, as a maximum conversion of 38.7% was observed at 130 °C. However, higher temperature caused a drop in selectivity (84%). The catalyst is confined to the water phase and **1** could be recycled at least three times showing moderate loss of activity and a slight increase of selectivity for **4** (Table 2). Formation of metal

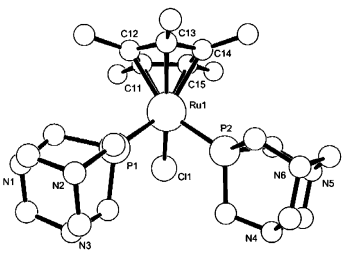


Fig. 1 X-Ray crystal structure of $Cp^*Ru(PTA)_2Cl$, **2**. Hydrogen atoms and solvent omitted for clarity.

† Electronic supplementary information (ESI) available: synthesis, $^{31}P\{^1H\}$, ^1H, ^{13}C NMR characterisation and elemental analysis of **1** and **2**. See http://www.rsc.org/suppdata/cc/b2/b210102e/

DOI: 10.1039/b210102e

aggregates was ruled out by comparison with results obtained using Ru/SiO_2 under the same conditions (Table 2, entry 14). Detailed HP-NMR experiments were carried out at variable temperature to obtain a better insight into the formation of organometallic species nearing the catalytic conditions. In a typical experiment, a solution of **1** and **3** (1:20 ratio) in H_2O–THF-d_8 (1:1) was pressurised with 450 psi of H_2 in a 10 mm NMR sapphire tube. At 25 °C only the singlet at −23.6 ppm due to **1** was observed in the $^{31}P\{^1H\}$ spectrum. By heating to 50 °C, a sharp singlet at −12.0 ppm appeared, becoming the major species (*ca*. 2:1 ratio to **1**) after 150 min at 80 °C. We attribute this signal to the new hydride $[CpRuH(PTA)_2]$ (**7**), based on the singlet to doublet splitting (^2J(HP) 36 Hz) in the proton coupled ^{31}P NMR spectrum and on an independent synthesis of the complex.§ At the end of the NMR experiment, the room temperature solution contained only **1** and **7** in *ca*. 1:2 ratio. Depressurisation under nitrogen did not change this ratio suggesting a very high stability of **7** in solution. In a separate HP-NMR experiment, **7** was formed in the absence of the substrate under the conditions described above, suggesting heterolytic activation of H_2 by **1**.[10] The presence of **7** in catalysis was confirmed by ^{31}P NMR analysis of the reaction mixture taken from an autoclave run. In contrast with what was expected, in all experiments no sign of PTA dissociation was observed.

Proton coupled ^{31}P HP-NMR experiments performed in H_2O–THF-d_8 with **2** (δ −34.4, s, 25 °C) and **3** under the conditions described above evidenced fast conversion at 50 °C to the dihydride $[Cp^*Ru(H)_2(PTA)_2]Cl$ (**8**) (−21.4 ppm, t, ^2J(HP) 33 Hz; ^1H NMR −10.08 ppm, t), which slowly gave the monohydride $[Cp^*Ru(H)(PTA)_2]$ (**9**) (−21.7 ppm, d, ^2J(HP) 36 Hz; ^1H NMR −14.58 ppm, t) after leaving the tube at 80 °C for 30 min. After 150 min at 80 °C, the solution contained **9**, **8**, **2** and PTA oxide (**10**).¶ After depressurisation and venting with nitrogen, the signals due to **8** and **9** disappeared leaving, after 16 h at room temperature, a 1:1 mixture of **2** and **10**, similar to that observed after a catalytic experiment in an autoclave under comparable conditions (100 °C, 450 psi).

The combination of catalytic tests and NMR experiments suggest that **1** and **2** behave differently under hydrogen pressure at high temperature. Whilst **1** forms the monohydrido complex **7** at 50 °C, complex **2** converts at first into the dihydride **8** which only at higher temperature is converted into the corresponding monohydrido species **9**.[10] Under HP-NMR tube conditions, we observed that hydride loss from **8** to **9** is easier in the presence of solvents with Lewis base properties such as THF. The different behaviour of **1** and **2** towards H_2 activation may be explained by the higher nucleophilicity of Ru in **2** compared to **1** due to Cp* which should favour oxidative addition against heterolytic splitting. Formation of PTA oxide could be related to faster deactivation of **2** in catalysis. Work is in progress to elucidate the influence of anions and different Cp substituents on the activity and selectivity in catalytic hydrogenation.

Table 1 Aqueous biphasic hydrogenation of **3** using complexes **1** and **2**[a]

Entry	Catalyst	% conv. (h)[b]	**4**[b] (%)	**5**[b] (%)	**6**[b] (%)
1	**1**	39.1 (3)	34.7	2.0	2.4
2	**1**	52.7 (6)	43.6	3.8	5.3
3	**1**	78.5 (13)	60.0	13.6	4.9
4	**1**	99.7 (21)	74.8	21.9	3.0
5	**1**[c]	22.9 (13)	15.4	1.2	6.3
6	**1**[d]	26.3 (13)	23.7	1.6	1.0
7	**2**	24.3 (3)	19.7	1.2	3.4
8	**2**	32.1 (6)	26.3	1.2	4.6
9	**2**	38.7 (13)	32.5	1.4	4.8
10	**2**[d]	40.0(13)	37.4	1.7	0.9

[a] Conditions: **3**, 1.8 mmol; catalyst, 9×10^{-3} mmol; *n*-octane, 30 cm^3; H_2O, 15 cm^3; 130 °C; H_2, 450 psi; 1200 rpm. [b] GC values based on pure samples. [c] PTA, 18×10^{-3} mmol added. [d] 80 °C.

Table 2 Recycling of **1** in aqueous biphasic hydrogenation of **3**[a]

Entry	Cycle	% conv.[b]	**4**[b] (%)	**5**[b] (%)	**6**[b] (%)
11	1	32.5	27.9	1.7	2.9
12	2	24.4	21.9	1.1	1.4
13	3	20.5	19.2	0.8	0.5
14	Ru/SiO_2[c]	99.9	35.0	64.5	0.4

[a] Conditions: **3**, 1.8 mmol; catalyst, 9×10^{-3} mmol; *n*-octane, 30 cm^3; H_2O, 15 cm^3; 130 °C; H_2, 450 psi; 1200 rpm, 3 h. [b] GC values based on pure samples. [c] Ru load 1.7% w/w.

The biological activity of compounds **1** and **2** was preliminarily tested on the proliferation of TS/A murine adenocarcinoma tumor cells. While **1** is devoid of antiproliferative effects at any tested concentration and at any time of tumor cell exposure, **2** inhibits tumor cell proliferation. This activity starts at 10 μM concentration and is maximal (−62.6% *vs.* controls) after 48 h treatment. A longer time of tumor cell exposure of 72 h did not increase such antiproliferative effects.

In summary, we have synthesised precursors of a new series of $[(C_5R_5)RuX(PTA)_2]$ water soluble complexes which could be applied to regioselective C=C catalytic hydrogenation and are potential starting materials for stable water soluble organometallic hydrides. Furthermore, **2** showed significant activity as an inhibitor of specific tumor cell proliferation.

We acknowledge CNR/Agenzia 2000, CNR/CONACYT, MCYT (Spain) INTAS (00179), NATO and EC through COST and RTN (HPRN-CT-2002-00176) for promoting this scientific activity.

Notes and references

‡ Crystals of **2**·$C_2H_4Cl_2$ were grown at −18 °C from a diluted pentane–dichloroethane solution. A Nonius Kappa CCD diffractometer was used with combined φ–ω-scans. Cell refinement, data reduction, and the empirical absorption correction were done by Denzo and Scalepack programs. Empirical formula $C_{24}H_{43}Cl_3N_6P_2Ru$; M 685.01; T 213(2) K; λ 0.71073 Å; crystal system, triclinic; space group, $P\bar{1}$; unit cell dimensions a = 12.5986(2), b = 16.2139(3), c = 16.3454(3) Å, α = 64.0661(8), β = 82.934(1), γ = 80.159(1)°; V 2954.1(1) $Å^3$; Z = 4; ρ 1.541 Mg m^{-3}; μ 0.751 mm^{-1} Reflections collected/unique 25086/13313 [R_{int} = 0.0180]. CCDC 195496. See http://www.rsc.org/suppdata/cc/b2/b210102e/ for crystallographic data in CIF or other electronic format.

§ Complex **7** was synthesised by refluxing **1** in benzene under nitrogen with a 5-fold excess of NaOMe for 3 h. Extraction with CH_2Cl_2 and usual workup gave a 5:1 mixture of **7** and **1**. $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 81.01 MHz) δ −12.96 (s). ^1H NMR (CD_2Cl_2, 200.13 MHz) δ −14.46 (t, ^2J(HP) 36.0 Hz, 1H, RuH).

¶ **9** + **8** (48%, superimposed signals), **2** (47%), **10** (5%). PTA oxide **10**, ^{31}P NMR: (H_2O–THF-d_8, 166.98 MHz) δ −4.57, septet, ^2J(PH) 10 Hz.

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