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# Synthesis, Characterization, and DNA Binding of New Water-Soluble Cyclopentadienyl Ruthenium(II) Complexes Incorporating Phosphines

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The new water-soluble ruthenium(II) chiral complexes $[RuCpX(L)(L')]^{n+}$ (X = Cl, I. L = $PPh_3$; L′ = PTA, mPTA; L = L′ = PTA, mPTA) (PTA = 1,3,5-triaza-7-phosphaadamantane; mPTA = *N*-methyl-1,3,5-triaza-7-phosphaadamantane) have been synthesized and characterized by NMR and IR spectroscopy and elemental analysis. The salt $mPTA(OSO_2CF_3)$ was also prepared and fully characterized by spectroscopic techniques. X-ray crystal structures of $[RuClCp(PPh_3)(PTA)]$ (**2**), $[RuCpI(PPh_3)(PTA)]$ (**3**), and $[RuCpI(mPTA)(PPh_3)](OSO_2CF_3)$ (**9**) have been determined. The binding properties toward DNA of the new hydrosoluble complexes have been studied using the mobility shift assay. The ruthenium chloride complexes interact with DNA depending on the hydrosoluble phosphine bonded to the metal, while the corresponding compounds with iodide, $[RuCpI(PTA)_2]$ (**1**), $[RuCpI(PPh_3)(PTA)]$ (**3**), $[RuCpI(mPTA)_2](OSO_2CF_3)_2$ (**6**), and $[RuCpI(mPTA)(PPh_3)](OSO_2CF_3)$ (**9**), do not bind to DNA.

## Introduction

During the past decades great attention has been paid to studying the interaction of several nucleobases with transition metal fragments.[1] In this wide area of chemistry, we have contributed by studying the interaction of purines, which are among the most important components of DNA, with transition metal complexes.[2] These nucleobases behave as effective ligands for a wide range of metal ions,[1,2] adopting different coordination modes as a function of the electronic and steric properties of the additional donor groups coordinated to the metal center. Our studies have been carried out on both Pd and Pt complexes that are among the most biologically active metals.[1,2] Jointly with these studies, we are involved in the synthesis of new water-soluble ruthenium complexes that are useful for bringing about catalytic reactions in water and biphasic conditions.[3] These complexes provide interesting solutions to most of the important disadvantages of homogeneous catalysis in organic solvents.[4]

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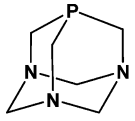
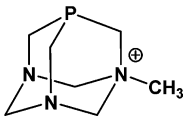
Noticeably, ruthenium complexes have shown important biological activity and are becoming more and more important in bioinorganic chemistry.[5] Indeed, three main properties make ruthenium compounds amenable to be investigated for medicinal applications: (i) the excellent rate of ligand exchange; (ii) the wide range of accessible oxidation states; and (iii) the ability of ruthenium to mimic iron binding to a variety of biological molecules. However, many of the ruthenium complexes are barely soluble in aqueous solution, a condition that has to be fulfilled to allow for both efficient administration and transport through living organisms. Solubility of ruthenium compounds has been increased by using dialkyl sulfoxide derivatives, such as in [*trans*-$RuCl_4$-(DMSO)Im][ImH] (NAMI-A), which is now recognized as the most successful ruthenium-based anticancer compound and has recently entered clinical trials,[6] and by using water-soluble phosphines, which has provided access to interesting hydrosoluble complexes.[7] In particular, the extensive and pioneering work by Sadler and co-workers on the antitumor properties of organometallic piano-stool compounds[8] has shown that this class of complexes are effective antitumoral agents and has shed some light on the mechanism ruling the interaction between the biomolecule and ruthenium. Interestingly, Ru(II) complexes are far more reactive toward DNA than Ru(III) and Ru(IV)[5] and it is therefore probable that the anticancer activity shown by several Ru(III) complexes would involve initial reduction to Ru(II). Moreover, strong evidence has been accumulated, showing that metal-to-protein interactions are also extremely important in promoting the anticancer activity of ruthenium compounds and it has been demonstrated that such interactions could occur with ruthenium ions in either oxidation states.[1,8]

Recently, we described the first water-soluble ruthenium cyclopentadienyl complexes containing hydrosoluble phosphines coordinated to the metal, namely, $[RuClCp'(PTA)_2]$ (Cp′ = Cp, Cp*; PTA = 1,3,5-triaza-7-phosphaadamantane), a pair of water-soluble piano-stool ruthenium complexes,[9] which showed modest biological activity. Remarkably, this activity is lower than that found for other piano-stool ruthenium complexes containing PTA[10] and therefore it should be attributed to the other ligands bonded to the metal. In keeping with this hypothesis, the recently reported piano-stool complexes $[RuCl_2(PTA)([9]aneS_3)]$ and $[RuCl(PTA)_2([9]aneS_3)](OSO_2CF_3)$ ([9]aneS$_3$ = 1,4,7-trithiacyclononane)[11] show comparable cytotoxic activity with $[RuClCp^*(PTA)_2]$[9] and $[RuCl_2(p\text{-cymene})(PTA)]$,[10] suggesting a negligible role of the cyclopentadienyl and *p*-cymene ligands in the biological activity. The question of addressing the biological role for the different donor ligands coordinated to ruthenium can likely be accurately answered by planning a systematic study on a wide family of RuCp compounds containing different water-soluble phosphines. From such a study we could obtain important information for the rational design of new DNA-binding agents capable of recognizing specific sequences or structures and henceforth modifying specific DNA functions.

Here, we address this study reporting on the synthesis and the characterization of a series of water-soluble piano-stool ruthenium complexes of general formula $[RuCpX(L)(L')]^{n+}$ (X = Cl, I. L = $PPh_3$, L′ = PTA, mPTA; L = L′ = PTA, mPTA. PTA = 1,3,5-triaza-7-phosphaadamantane; mPTA = *N*-methyl-1,3,5-triaza-7-phosphaadamantane), sharing an identical structural motif with different combinations of water-soluble phosphines such as PTA (**I**) and *N*-alkylated-PTA (**II**).[12] In addition, we show that these complexes, stable to both hydrolysis and oxygen, exhibit remarkable activity toward DNA in the darkness that is clearly depending on the nature and number of the donor ligands (water-soluble phosphines and halogen).




(**I**)




(**II**)

## Experimental Section

**General Procedures.** All chemicals were reagent grade and, unless otherwise stated, were used as received by commercial suppliers. The solvents were all degassed and distilled according to standard procedures.[13] All reactions and manipulations were routinely performed under a dry nitrogen atmosphere by using standard Schlenk-tube techniques. The hydrosoluble phosphines PTA[14] and mPTA(**I**)[15,16] and the complexes $[RuClCp(PTA)_2]$[9] and

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$[RuClCp(PPh_3)_2]$[17] were prepared as described in the literature. $CD_3OD$ for NMR measurements (Cortec-Euriso-top) was dried over molecular sieves (0.4 nm). $^1H$ and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 300.13 MHz ($^1H$) and 75.47 MHz ($^{13}C$), respectively. Peak positions are relative to tetramethylsilane and were calibrated against the residual solvent resonance ($^1H$) or the deuterated solvent multiplet ($^{13}C$). $^{31}P\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectra were recorded on the same instrument operating at 121.49 and 282.40 MHz, respectively. Chemical shifts for $^{31}P\{^1H\}$ NMR were measured relative to external 85% $H_3PO_4$ and for $^{19}F\{^1H\}$ NMR to $CFCl_3$ with downfield values taken as positive in both cases. Infrared spectra were recorded as KBr disks using an FT-IR ATI Mattson Infinity Series. Elemental analyses (C, H, N, S) were performed on a Fisons Instruments EA 1108 elemental analyzer.

**Synthesis of [RuCpI(PTA)$_2$] (1).** This compound was synthesized by a slightly modified procedure to that described in the literature.[18] A solution of $[RuClCp(PTA)_2]$ (0.10 g, 0.14 mmol) in 15 mL of MeOH was reacted by KI (0.022 g, 0.13 mmol) at refluxing temperature. After 1 h, the orange precipitated formed was filtered while hot, washed with MeOH (2 × 5 mL), and vacuum-dried. Yield: 0.08 g, 68%. $S_{25°C} = 10$ mg/mL. Elemental analysis for $C_{17}H_{29}N_6P_2RuI$ (607.38): found, C 33.31, H 5.03, N 13.53%; calcd, C 33.62, H 4.81, N 13.84%. $^1H$ NMR (300.13 MHz, 20 °C, $CDCl_3$): $\delta$ (ppm) 3.99−4.20 (m, $CH_2P_{(PTA)}$, 12 H), 4.48−4.46 (m, $CH_2N_{(PTA)}$, 12 H), 4.65 (s, Cp, 5 H). $^1H$ NMR ($D_2O$): $\delta$ (ppm) 3.91−4.10 (m, $CH_2P_{(PTA)}$, 12 H), 4.48 (bs, $CH_2N_{(PTA)}$, 12 H), 4.75 (bs, Cp, 5 H). $^{13}C\{^1H\}$ NMR (75.47 MHz, 20 °C, $CDCl_3$): $\delta$ (ppm) 59.63 (t, $^1J_{CP} = 8.6$ Hz, $CH_2P_{(PTA)}$), 73.30 (s, $CH_2N_{(PTA)}$), 76.83 (s, Cp). $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ (ppm) 56.37 (t, $^1J_{CP} = 8.6$ Hz, $CH_2P_{(PTA)}$), 70.60 (s, $CH_2N_{(PTA)}$), 77.65 (s, Cp). $^{31}P\{^1H\}$ NMR (121.49, 20 °C, $CDCl_3$): $\delta$ (ppm) −30.11 (s, PTA). $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ (ppm) −28.51 (s, PTA).

**Synthesis of [RuClCp(PPh$_3$)(PTA)] (2).** Solid PTA (0.65 g, 4.24 mmol) was slowly added to a vigorously stirred solution of $[RuClCp(PPh_3)_2]$ (3.00 g, 4.13 mmol) in 65 mL of toluene. The mixture was gradually heated to a boiling temperature and gently refluxed for 2 h. After the solution was cooled to room temperature, the yellow powder of $[RuClCp(PPh_3)(PTA)]$ (**2**) was collected by filtration and washed with $Et_2O$ (2 × 3 mL). Crystals adequate for X-ray determination were obtained by slow evaporation from a $CH_3Cl$:*n*-hexane (1:1) solution. Yield: 2.30 g, 89%. $S_{25°C} = 1.5$ mg/mL. Elemental analysis for $C_{29}H_{32}N_3ClP_2Ru$ (621.06): found, C 55.93, H 5.31, N 6.57%; calcd, C 56.08, H 5.19, N 6.77%. Elemental analysis for crystals $C_{29}H_{32}ClN_3P_2Ru\cdot 1CHCl_3\cdot 0.25H_2O$ (744.94): found, C 48.15, H 4.62, N 5.42%; calcd, C 48.37, H 4.53, N 5.64%. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 3.73−4.01 (m, $PCH_{2(PTA)}$, 6 H), 4.23−4.46 (m, $NCH_{2(PTA)}$, 6 H), 4.41 (s, Cp, 5 H), 7.32−7.64 (m, aromatic protons, 15 H). $^{13}C\{^1H\}$ NMR: $\delta$ (ppm) 55.37 (AXX′ system, $^1J_{CPX} = 13.3$ Hz, $^1J_{CPX'} = 2.0$ Hz, $NCH_2P_{(PTA)}$), 73.19 (d, $^1J_{CP} = 5.8$ Hz, $NCH_2N_{(PTA)}$), 78.70 (t, $^1J_{CP} = 2.1$ Hz, Cp), 128.05−138.72 (m, aromatic carbons). $^{31}P\{^1H\}$ NMR: $\delta$ (ppm) −34.96 (d, $^1J_{PP} = 34.7$, PTA), 48.16 (d, $PPh_3$).

**Synthesis of [RuCpI(PPh$_3$)(PTA)] (3).** An excess of solid KI (0.12 g, 0.07 mmol) was added to a solution of **2** (0.03 g, 0.05 mmol) in 15 mL of MeOH and then kept at refluxing temperature for 30 min. The orange precipitate obtained was filtered while hot, washed with MeOH (2 × 5 mL) and EtOH (2 × 2 mL), and vacuum-dried. Crystals good enough for X-ray diffraction were obtained by slow evaporation from a $CHCl_3$ solution. Yield: 0.04 g, 70%. $S_{25°C} < 0.1$ mg/mL. Elemental analysis for $C_{29}H_{32}N_3IP_2Ru$ (712.52): found, C 48.56, H 4.71, N 5.44%; calcd, C 48.89, H 4.53, N 5.90%. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 3.54−4.08 (m, $CH_2P_{(PTA)}$, 6 H), 4.24−4.46 (m, $CH_2N_{(PTA)}$, 6 H), 4.46 (s, Cp, 5 H), 7.34−7.59 (m, aromatic protons, 15 H). $^{13}C\{^1H\}$ NMR: $\delta$ (ppm) 57.16 (d, $^1J_{CP} = 14.2$, $CH_2P_{(PTA)}$), 73.04 (s, $CH_2N_{(PTA)}$, 6 H), 79.13 (s, Cp), 127.77−139.09 (aromatic carbons). $^{31}P\{^1H\}$ NMR: $\delta$ (ppm) −39.50 (d, $^1J_{PP} = 43.28$ Hz, PTA), 47.88 (d, $PPh_3$).

**Synthesis of mPTA(OSO$_2$CF$_3$) (4).** $MeOSO_2CF_3$ (0.14 mL, 1.27 mmol) was added via a syringe to a stirred PTA (0.1 g, 0.64 mmol) $CHCl_3$ solution (10 mL). The white suspension which formed was refluxed for 30 min and cooled at room temperature. The white precipitate which separated was filtered, washed with $CHCl_3$ (2 × 1 mL), and air-dried. Yield: 0.0485 g, 23.7%. $S_{25°C} = 240$ mg/mL. Elemental analysis for $C_8H_{15}N_3F_3O_3PS$ (321.25): found, C 29.70, H 4.72, N 12.86; S 9.56%; calcd, C 29.90, H 4.71, N 13.08, S 9.96%. IR (KBr, $cm^{-1}$): $\nu$(OSO) 1264. $^1H$ NMR ($D_2O$): $\delta$ (ppm) 2.67 (s, $CH_3N_{(mPTA)}$, 3 H), 3.83 (ABPYY′X system, $^2J_{H_AH_B} = 15.0$ Hz, $^2J_{H_{A,B}P} = 14.1$ Hz, $^4J_{H_BH_Y(CH_3NCH_2P)} = 0.4$ Hz, $^4J_{H_BH_{Y'}(CH_3NCH_2P)} = 0.3$ Hz, $^4J_{H_AH_X(NCH_2N)} = 1.5$ Hz, $NCH_2P_{(mPTA)}$, 4 H), 4.28 (AMPX system, $^2J_{H_AP} = 6.7$ Hz, $^4J_{H_AH_M(NCH_2P)} = 0.4$ Hz, $^4J_{H_AH_X(CH_3NCH_2N)} = 0.3$ Hz, $CH_3NCH_2P_{(mPTA)}$, 2 H), 4.45 (ABMX system, $^2J_{H_AH_B} = 13.8$ Hz, $^4J_{H_AH_M(NCH_2P)} = 1.5$ Hz, $^4J_{H_BH_X(CH_3NCH_2N)} = 0.5$ Hz, $NCH_2N_{(mPTA)}$, 2 H), 4.81 (ABMQX system, $^2J_{H_AH_B} = 12.0$ Hz, $^4J_{H_AH_M(CH_3NCH_2P)} = 0.3$ Hz, $^4J_{H_AH_Q(NCH_2P)} = 0.3$ Hz, $^4J_{H_BH_X(NCH_2N)} = 0.5$ Hz, $CH_3NCH_2N_{(mPTA)}$, 4 H). $^{13}C\{^1H\}$ NMR: $\delta$ (ppm) 45.27 (d, $^1J_{CP} = 21.4$ Hz, $NCH_2P_{(mPTA)}$), 49.92 (s, $CH_3N_{(mPTA)}$), 56.45 (d, $^1J_{CP} = 33.6$ Hz, $CH_3N\mathbf{C}H_2P_{(mPTA)}$), 69.10 (s, $NCH_2N_{(mPTA)}$), 80.01 (s, $CH_3N\mathbf{C}H_2N_{(mPTA)}$), 119.24 (q, $^1J_{CF} = 316.8$ Hz, $OSO_2CF_3$). $^{31}P\{^1H\}$ NMR: $\delta$ (ppm) −85.10 (s, mPTA). $^{19}F\{^1H\}$ NMR (282.40, 20 °C, $D_2O$): $\delta$ (ppm) −78.98 (s, $OSO_2CF_3$).

**Synthesis of [RuClCp(mPTA)$_2$](OSO$_2$CF$_3$)$_2$ (5).** $RuCl_3\cdot xH_2O$ (0.03 g, 0.145 mmol) in 5 mL of EtOH and freshly cracked cyclopentadiene (1 mL, 0.02 mmol) were added to a stirred solution of $mPTA(OSO_2CF_3)$ (0.1 g, 0.312 mmol) in 10 mL of EtOH. The mixture was refluxed for 6 h, filtered through sintered glass while hot, and then evaporated to dryness under vacuum. The crude yellow solid was taken with 1 mL of EtOH and precipitated with 5 mL of $Et_2O$. The yellow solid obtained was filtered, washed with $Et_2O$ (2 × 1 mL), and vacuum-dried. Yield: 0.016 g, 12.9%. $S_{25°C} = 80$ mg/ mL. Elemental analysis for $C_{21}H_{35}N_6ClF_6O_6P_2RuS_2$ (844.13): found, C 29.75, H 4.52, N 9.54, S 7.22%; calcd, C 29.88, H 4.18, N 9.96, S 7.60%. IR (KBr, $cm^{-1}$): $\nu$(OSO) 1269. $^1H$ NMR ($D_2O$): $\delta$ (ppm) 2.82 (s, $CH_3N_{(mPTA)}$, 6 H), 3.92−4.16 (m, $CH_2P_{(mPTA)}$, 12 H), 4.19−4.98 (m, $CH_2N_{(mPTA)}$, 12 H), 4.85 (s, Cp, 5 H). $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ (ppm) 49.30 (s, $CH_3N_{(mPTA)}$), 50.76 (bd, $^1J_{CP} = 57.5$ Hz, $NCH_2P_{(mPTA)}$), 57.99 (bd, $^1J_{CP} = 58.0$ Hz, $CH_3N\mathbf{C}H_2P_{(mPTA)}$), 67.80 (bd, $^2J_{CP} = 8.6$ Hz, $NCH_2N_{(mPTA)}$), 80.29 (s, $CH_3N\mathbf{C}H_2N_{(mPTA)}$), 80.36 (s, Cp), 119.54 (q, $^1J_{CF} = 317.0$ Hz, $OSO_2CF_3$). $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ (ppm) −10.74 (s, mPTA). $^{19}F\{^1H\}$ NMR ($D_2O$): $\delta$ (ppm) −78.84 (s, $OSO_2CF_3$).

**Synthesis of [RuCpI(mPTA)$_2$](OSO$_2$CF$_3$)$_2$ (6).** Solid NaI (0.053 g, 0.35 mmol) was added to a solution of **5** (0.05 g, 0.059 mmol) in 10 mL of $MeOH/H_2O$ (1:1) and stirred at room temperature for 15 min. The mixture was gradually heated to the boiling temperature and then gently refluxed for 1 h. The resulting red solution was filtered through Celite and the solvent evaporated to leave a red yellowish solid which was taken with $CHCl_3$ (3 mL). The resulting solution was filtered and the solvent removed under vacuum to give **6** as a yellowish red powder. Yield: 0.050 g, 90.2%. $S_{25°C} = 32$ mg/mL. Elemental analysis for $C_{21}H_{35}N_6IF_6O_6P_2RuS_2$

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(935.58): found, C 26.75, H 3.98, N 8.64, S 6.52%; calcd, C 26.96, H 3.77, N 8.98, S 6.85%. IR (KBr, $cm^{-1}$): $\nu$(OSO) 1271. $^1H$ NMR ($D_2O$): $\delta$ (ppm) 2.80 (s, $CH_3N_{(mPTA)}$, 6 H), 3.80−4.20 (m, $CH_2P_{(mPTA)}$, 12 H), 4.34−5.12 (m, $CH_2N_{(mPTA)}$, 12 H), 4.90 (s, Cp, 5 H). $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ (ppm) 49.32 ($CH_3N_{(mPTA)}$), 51.18 (bd, $^1J_{CP}$ = 57.0 Hz, $NCH_2P_{(mPTA)}$), 58.1 (bd, $^1J_{CP}$ = 51.9 Hz, $CH_3N\mathbf{C}H_2P_{(mPTA)}$), 67.70 (bd, $^2J_{CP}$ = 8.6 Hz, $NCH_2N_{(mPTA)}$), 80.11 (s, $CH_3N\mathbf{C}H_2N_{(mPTA)}$), 80.17 (s, Cp), 120.27 (q, $^1J_{CF}$ = 318.1 Hz, $OSO_2CF_3$). $^{31}P\{^1H\}$ NMR: $\delta$ (ppm) −15.02 (s, mPTA). $^{19}F\{^1H\}$ NMR: $\delta$ (ppm) −79.02 (s, $OSO_2CF_3$).

**Synthesis of [RuClCp(mPTA)($PPh_3$)]($OSO_2CF_3$) (7).** Solid **4** (0.08 g, 0.28 mmol) was added to a stirred solution of [RuClCp($PPh_3$)$_2$] (0.1 g, 0.14 mmol) in 5 mL of acetone and slowly warmed to reflux which was maintained for 4 h. During this time **7** separated out as a yellow-orange powder, which was collected by filtration while hot, washed with acetone (2 × 2 mL), and vacuum-dried. Yield: 0.077 g, 71%. $S_{25°C}$ = 1.1 mg/mL. Elemental analysis for $C_{31}H_{35}N_3ClF_3O_3P_2RuS$ (785.16): found, C 47.24, H 4.52, N 5.12, S 3.82%; calcd, C 47.42, H 4.49, N 5.35, S 4.08%. IR (KBr, $cm^{-1}$): $\nu$(OSO) 1251. $^1H$ NMR ($CD_3OD$): $\delta$ (ppm) 2.58 (bs, $CH_3N_{(mPTA)}$, 3 H), 3.44−3.96 (m, $CH_2P_{(mPTA)}$, 6 H), 4.07−4.36 (m, $CH_2N_{(mPTA)}$, 6 H), 4.59 (s, Cp, 5 H), 7.45−7.53 (m, aromatic protons, 15 H). $^1H$ NMR (DMSO-$d_6$): $\delta$ (ppm) 2.50 (bs, $CH_3N_{(mPTA)}$, 3 H), 3.12−3.77 (m, $CH_2P_{(mPTA)}$, 6 H), 4.09−4.95 (m, $CH_2N_{(mPTA)}$, 6 H), 4.54 (s, Cp, 5 H), 7.45−7.47 (m, aromatic protons, 15 H). $^{13}C\{^1H\}$ NMR (DMSO-$d_6$): $\delta$ (ppm) 48.87 (s, $CH_3N_{(mPTA)}$), 49.17 (d, $^1J_{CP}$ = 12.7 Hz, $NCH_2P_{(mPTA)}$), 51.97 (d, $^1J_{CP}$ = 15.3 Hz, $CH_3N\mathbf{C}H_2P_{(mPTA)}$), 59.44 (s, $NCH_2N_{(mPTA)}$), 58.76 (s, $CH_3N\mathbf{C}H_2N_{(mPTA)}$), 79.3 (s, Cp), 121.08 (q, $^1J_{CF}$ = 321.4 Hz, $OSO_2CF_3$), 128.54−134.03 (aromatic carbons). $^{31}P\{^1H\}$ NMR ($CD_3OD$): $\delta$ (ppm) −15.38 (d, $^1J_{PP}$ = 43.9, mPTA), 46.31 (d, $PPh_3$). $^{31}P\{^1H\}$ NMR (DMSO-$d_6$): $\delta$ (ppm) −15.57 (d, $^1J_{PP}$ = 43.3, mPTA), 47.27 (d, $PPh_3$). $^{19}F\{^1H\}$ NMR ($CD_3OD$): $\delta$ (ppm) −80.11 (s, $OSO_2CF_3$). $^{19}F\{^1H\}$ NMR (DMSO-$d_6$): $\delta$ (ppm) −77.72.

**Synthesis of [RuCpI(mPTA)($PPh_3$)]Cl (8).** Solid [RuClCp($PPh_3$)$_2$] (0.10 g, 0.14 mmol) was added to a solution of mPTA (**I**) (0.16 g, 0.54 mmol) in 30 mL of 2-propanol. The resulting mixture was stirred at refluxing temperature for 6 h. The orange precipitate obtained was filtered while hot and dissolved in 2 mL of $CHCl_3$. Addition of 4 mL of $Et_2O$ gave an orange precipitate which was filtered off, washed with $Et_2O$ (2 × 2 mL), and vacuum-dried. Yield: 0.07 g, 70%. $S_{25°C}$ = 0.4 mg/mL. Elemental analysis for $C_{30}H_{35}N_3ClIP_2Ru$ (763.00): found, C 46.82, H 4.94, N 5.21%; calcd, C 47.23, H 4.62, N 5.51%. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 3.00 (s, $CH_3N_{(mPTA)}$, 3 H), 3.92−4.02 (m, $CH_2P_{(mPTA)}$, 6 H), 4.71−5.56 (m, $CH_2N_{(mPTA)}$, 6 H), 4.77 (s, Cp, 5 H), 7.28−7.56 (aromatic protons, 15 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta$ (ppm) 48.68 (s, $CH_3N_{(mPTA)}$), 51.92 (d, $^1J_{CP}$ = 15.8 Hz, $NCH_2P_{(mPTA)}$), 54.35 (d, $^1J_{CP}$ = 15.3 Hz, $CH_3N\mathbf{C}H_2P_{(mPTA)}$), 63.16 (s, $NCH_2N_{(mPTA)}$), 69.65 (s, $CH_3N\mathbf{C}H_2N_{(mPTA)}$), 80.62 (s, Cp), 128.16−138.34 (aromatic carbons). $^{31}P\{^1H\}$ NMR: $\delta$ (ppm) −18.32 (d, $^1J_{PP}$ = 40.7 Hz, mPTA), 46.37 (d, $PPh_3$).

**Synthesis of [RuCpI(mPTA)($PPh_3$)]($OSO_2CF_3$)·$2H_2O$ (9·$2H_2O$).** This complex was prepared by three different procedures.

(A) Compound **8** (0.20 g, 0.26 mmol) and $NH_4OSO_2CF_3$ (0.04 g, 0.26 mmol) were dissolved in 5 mL of $CHCl_3$. The yellow solution obtained was left at room temperature for 1 h. By slow evaporation of the solvent, yellow crystals formed, which were filtered and dried in the air. The crystals were of good quality suitable for analysis by X-ray diffraction methods.

(B) To a solution of **8** (0.20 g, 0.26 mmol) in 20 mL of $CHCl_3$ was added $AgOSO_2CF_3$ (0.07 g, 0.27 mmol), causing the formation of a white precipitate. After 1 h at refluxing temperature the resulting red-orange mixture was filtered through Celite and the solvent was completely evaporated. The red-orange solid was washed with $Et_2O$ (2 × 5 mL) and vacuum-dried.

(C) The red solution obtained by refluxing for 1 h a solution of **7** (0.10 g, 0.26 mmol) and NaI (0.02 g, 0.27 mmol) in 5 mL of MeOH was cooled and evaporated to 1 mL. Addition of 3 mL of $Et_2O$ gave a reddish orange precipitate which was filtered, washed with $Et_2O$ (2 × 1 mL), and vacuum-dried.

Yield: 0.08 g, 34% (method A); 0.20 g, 89%. Elemental analysis (taken on a crystalline sample obtained from method A) $C_{31}H_{35}N_3F_3IO_3P_2RuS_1\cdot 2H_2O$ (912.64): found, C 40.44, H 4.44, N 4.42, S 3.22%; calcd, C 40.80, H 4.31, N 4.60, S 3.51%. Elemental analysis (taken on a powdered sample obtained from method B) $C_{31}H_{35}N_3O_3F_3IRuP_2S_1$ (876.61): found, C 42.24, H 4.27, N 4.52, S 3.42%; calcd, C 42.47, H 4.02, N 4.79, S 3.66%. IR (KBr, $cm^{-1}$): $\nu$(OSO) 1258. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 2.78 (s, $CH_3N_{(mPTA)}$, 3 H), 3.74−4.12 (m, $CH_2P_{(mPTA)}$, 6 H), 4.31−5.17 (m, $CH_2N_{(mPTA)}$, 6 H), 4.68 (s, Cp, 5 H), 7.41−7.56 (aromatic protons, 15 H). $^{13}C\{^1H\}$ NMR: $\delta$ (ppm) 48.91 (s, $CH_3N_{(mPTA)}$), 51.34 (d, $^1J_{CP}$ = 15.8 Hz, $NCH_2P_{(mPTA)}$), 51.34 (d, $^1J_{CP}$ = 15.8 Hz, $CH_3N\mathbf{C}H_2P_{(mPTA)}$), 59.27 (s, $N\mathbf{C}H_2N_{(mPTA)}$), 69.59 (s, $CH_3N\mathbf{C}H_2N_{(mPTA)}$), 81.90 (s, Cp), 120.46 (q, $^1J_{CF}$ = 319.76 Hz, $OSO_2CF_3$), 129.03−135.15 (aromatic carbons). $^{31}P\{^1H\}$ NMR: $\delta$ (ppm) −18.63 (d, $^1J_{PP}$ = 41.5 Hz, mPTA), 46.30 (d, $PPh_3$). $^{19}F\{^1H\}$ NMR: $\delta$ (ppm) −78.35 (s, $OSO_2CF_3$).

**Stability Tests for the Ruthenium Complexes [RuCpX(L)(L′)]$^{n+}$ (X = Cl, I. L= $PPh_3$, L′ = PTA, mPTA; L = L′ = PTA, mPTA) toward $H_2O$ and $O_2$.** In a standard procedure, 0.01 g of ruthenium complexes, but 7 and 9, were introduced into a 5 mm NMR tube and dissolved in degassed $CDCl_3$ (1.0 mL). The solution was then cooled to ca. 0 °C and dry $O_2$ was slowly bubbled throughout the solution for 2 min via a long syringe needle. $^{31}P\{^1H\}$ NMR monitoring showed no change within 1 week. No decomposition was also observed after 1 week, maintaining the temperature at 40 °C. Due to poor solubility in $CDCl_3$, the complexes 7 and 9 were dissolved in $CD_3OD$ where they showed a similar lack of reactivity toward $O_2$.

A similar stability experiment performed in $D_2O$ showed that **1**, **2**, **5**, **6**, **7**, and **9** did not decompose within 1 week at room temperature. At 40 °C however decomposition was observed within 2 days. Compounds **3** and **8** were not soluble enough in water to accomplish the above experiment. However, dissolving 0.02 g of complexes **3** and **8** in 10 mL of aerated water causes decomposition at 40 °C within 2 days (IR and NMR analysis) with the formation of green-colored solutions likely containing paramagnetic ruthenium species which prevented the recording of NMR spectra.

**DNA Mobility Shift Assays.** Reactions between DNA and the ruthenium complexes were performed in a 20 $\mu$L final volume containing 10 mM sodium phosphate buffer at physiological pH 7.0, 1 $\mu$g of the pBluescript-KSII plasmid (3 Kbp, from Stratagene), and appropriate amounts of a freshly prepared solution of the Ru complex in water, to achieve the desired metal-to-base pair stoichiometry. Reaction mixtures were incubated for 14 h at 37 °C in the dark. 10 $\mu$L samples were withdrawn and analyzed by electrophoresis in 1% agarose gels freshly prepared in TAE buffer (40 mM tris(hydroxymethyl)aminomethane, 20 mM sodium acetate, 1 mM EDTA, pH 8.0). Running was conducted in TAE buffer at a constant voltage of 3 V/cm. DNA bands were visualized by incubation of the gel with 1 $\mu$g/mL ethidium bromide in TAE buffer for 30 min and photographed under UV light. For each active compound we registered the Ri (ruthenium-to-base molar ratio) value at which complete transformation of the supercoiled-to-relaxed form of the plasmid was attained.

**Table 1.** Crystallographic Data

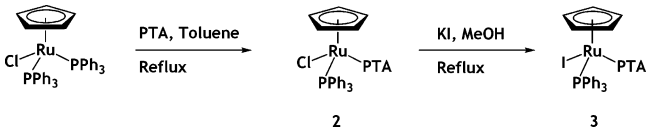
| | **2**·$CHCl_3$·$0.25H_2O$ | **3** | **9**·$2H_2O$ |
|---|---|---|---|
| formula | $C_{30}H_{32.5}N_3Cl_4O_{0.25}P_2Ru$ | $C_{29}H_{32}N_3IP_2Ru$ | $C_{31}H_{35}N_3F_3IO_5P_2RuS$ |
| $M_r$ | 743.90 | 712.49 | 908.59 |
| space group | $Pca2_1$ | $P21/n$ | $P2_1/c$ |
| cryst syst | orthorhombic | monoclinic | monoclinic |
| $a$/Å | 17.7148(7) | 9.8910(4) | 20.5735(7) |
| $b$/Å | 17.1794(7) | 18.8230(7) | 20.7874(7) |
| $c$/Å | 21.1886(9) | 14.4419(6) | 9.3689(3) |
| α/deg | 90 | 90 | 90 |
| $\beta$/deg | 90 | 98.4990(10) | 101.9200(10) |
| $\gamma$/deg | 90 | 90 | 90 |
| $V$/Å$^3$ | 6448.3(5) | 2659.24(18) | 3920.4(2) |
| Z | 8 | 4 | 4 |
| $D_c$/g cm$^{-3}$ | 1.533 | 1.780 | 1.539 |
| $F$(000) | 3020 | 1416 | 1808 |
| $M$(Mo Kα)/cm$^{-1}$ | 9.43 | 18.96 | 13.75 |
| measd reflns | 28649 | 12571 | 17744 |
| unique reflns | 8343 | 3817 | 5583 |
| $R_{int}$ | 0.0473 | 0.0431 | 0.0402 |
| obsd reflns [$I \geq 2\sigma(I)$] | 7889 | 3115 | 4278 |
| $\theta_{min}-\theta_{max}$/deg | 1.6−23 | 1.8−23 | 1.4−23 |
| *hkl* ranges | −19, 19; −19, 18; −23, 19 | −10, 9; −20, 20; −11, 16 | −22, 20; −23, 21; −10, 10 |
| $R(F^2)$ (obsd reflns) | 0.0630 | 0.0287 | 0.0613 |
| $wR(F^2)$ (all reflns) | 0.1601 | 0.0502 | 0.1792 |
| no. of variables | 731 | 325 | 372 |
| GOF | 1.083 | 0.929 | 1.097 |
| $\rho_{min}$, $\rho_{max}$/e Å$^{-3}$ | −0.834, 2.771 | −0.402, 0.526 | −0.755, 1.711 |

**X-ray Structure Determinations.** Data of compounds **2**·$CHCl_3$·$0.25H_2O$, **3**, and **9**·$2H_2O$ were collected on a Bruker APEX CCD diffractometer (XDIFRACT service of the University of Almería) using graphite monochromated Mo Kα radiation ($\lambda = 0.7107$ Å) at room temperature (295 K). The crystal parameters and other experimental details of the data collections are summarized in Table 1. The structures were solved by direct methods SIR92[19] and refined by full-matrix least-squares methods with SHELXTL.[20] The solvent molecules $CHCl_3$ and $H_2O$ for **2**·$CHCl_3$·$0.25H_2O$, and the $OSO_2$-$CF_3$ anion and $H_2O$ for **9**·$2H_2O$, were found to be disordered and refined isotropically. All the non-hydrogen non-disordered atoms for the compounds were refined with anisotropic atomic displacement parameters. All hydrogen atoms, except for disordered water solvate molecules, for all crystal structures were included in calculated positions and refined using a riding model. The **2**·$CHCl_3$·$0.25H_2O$ crystal was found to be a twin and was refined generating the indices of the twin components from the input reflection indices. All calculations were performed using SHELXTL. Crystallographic data (excluding structure factors) for the structures in this paper and have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC 272750−272752. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, +44 1223 336033; e-mail, deposit@ccdc.cam.ac.uk).

## Results and Discussions

**Synthesis and Characterization of New Hydrosoluble Ruthenium PTA Complexes (1, 2, and 3).** Complex [$RuCpI(PTA)_2$] (**1**) was straightforwardly obtained by metathetical reaction of [$RuClCp(PTA)_2$][9] with KI in refluxing MeOH by a slight modification of the method previously published by us.[20] As a consequence of the chloride substitution by iodide, the singlet of the PTA ligand in the $^{31}P\{^1H\}$ NMR moves ca. 5 ppm highfield (**1** $\delta_{PTA} = -30.11$ ppm; [$RuClCp(PTA)_2$] $\delta_{PTA} = -25.65$ ppm). This resonance is a lot affected by the solvent and shifts downfield in polar solvents [i.e., $\delta_{PTA} = -28.51$ ($D_2O$); −30.11 ($CDCl_3$)]. The $^1H$ and $^{13}C\{^1H\}$ NMR of **1** (see Experimental Section) do not significantly differ from those reported for [$RuClCp(PTA)_2$].[9]

**Scheme 1**




**2** **3**

Complex **2** was obtained by replacing one $PPh_3$ molecule in [$RuClCp(PPh_3)_2$] with the water-soluble phosphine PTA (Scheme 1) in refluxing toluene. Metathesis of chloride from **2** with excess KI in refluxing MeOH afforded **3** in high yield after workup.

The selective substitution of a single molecule of $PPh_3$ by one of PTA in the starting complex [$RuClCp(PPh_3)_2$] giving **2** was clearly confirmed by the appearance in the $^{31}P\{^1H\}$ NMR of two doublets at 48.16 ($PPh_3$, $^1J_{PP} = 34.7$ Hz) and −34.96 (PTA, $^1J_{PP} = 34.7$). No trace of the disubstituted PTA derivative [$CpRuCl(PTA)_2$] was detected by NMR analysis. Remarkably, the ruthenium atom in **2** is chiral, being coordinated by four different ligands (Cp, Cl, $PPh_3$, and PTA) and is a racemate of two chiral complexes. This situation was clearly confirmed by the analysis of the crystal structure by X-ray diffractometry (see Figure 1).

On going from **2** to **3**, the substitution of the chloride with the iodide ligand shifts both doublets in the $^{31}P\{^1H\}$ NMR to high field, the PTA resonance being more susceptible to the Cl/I substitution ($\Delta\delta_{PTA} = |\delta_{PTA}(\mathbf{3}) - \delta_{PTA}(\mathbf{2})|$ ppm = $|-39.50 - (-34.96)|$ ppm = 4.54 ppm; $\Delta\delta_{PPh3} = |\delta_{PPh3}(\mathbf{3}) - \delta_{PPh3}(\mathbf{2})| = |47.88 - 48.16|$ ppm = 0.28 ppm) and parallels (ca. 5 ppm) that observed for **1** in comparison to [RuClCp-

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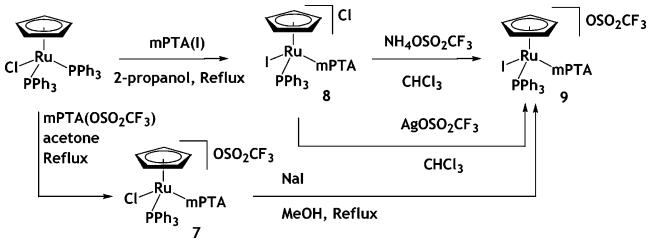
(20) Sheldrick, G. M. *SHELXTL* version 6.14; Bruker-AXS: Madison, WI, 2003.

**Scheme 2**




$(PTA)_2$] (see above). Both $^1$H and $^{13}$C{$^1$H} NMR completely support the proposed formula of **3** which was also confirmed by X-ray diffraction analysis (Figure 3).

**Synthesis and Characterization of New Hydrosoluble Ruthenium mPTA$^+$ Complexes (5, 6, 7, 8, and 9).** Interestingly, only single $PPh_3$ replacement in [RuClCp-$(PPh_3)_2$] was achieved by reaction with mPTA (**I**) in refluxing 2-propanol. Forcing the reaction conditions and increasing the ratio of mPTA (**I**) with respect to the parent chloride derivative did not afford the disubstituted mPTA complex but yielded the iodine-coordinated salt [RuCpI(mPTA)-$(PPh_3)$]Cl (**8**) via metathetical reaction of the coordinated chloride with the iodide counteranion of the *N*-methylated phosphadamantane ligand. Scheme 2 illustrates this behavior. The $^{31}$P{$^1$H} NMR of **8** agrees with the substitution of one $PPh_3$ by one mPTA, showing a behavior similar to that observed for the Cl/I pair **2**/**3**. In the case at hand the signal assigned to $PPh_3$ exhibits a chemical shift (46.37 ppm, $^1J_{PP}$ = 40.7 Hz) similar to that found for **2** and **3** whereas the doublet due to the mPTA falls at a lower field (−18.32 ppm, $^1J_{PP}$ = 40.7 Hz) in comparison with the chemical shift of the PTA ligand in **2** and **3**. Significant differences affect the $^1$H NMR spectrum of **8** in comparison with that of **2** and **3**. In particular, in **2** and **3** the $NCH_2N_{(PTA)}$ protons show almost identical $\delta$ values (**2**: 4.23−4.46 ppm; **3**: 4.24−4.46 ppm), whereas they move downfield (4.71−5.56 ppm) for **8**. In contrast, the Cp signal for **8** is shifted to lower field (4.77 ppm) than **2** and **3** (4.41 and 4.46 ppm).

Crystallization of **8** in $CHCl_3$ in the presence of $NH_4OSO_2$-$CF_3$ gave crystals of [RuCpI(mPTA)$(PPh_3)$]$(OSO_2CF_3)$ (**9**) suitable for an X-ray diffraction study (see below). Complex **9** was also obtained by reaction of **7** with NaI in MeOH at refluxing temperature but the best synthetic method was the plane reaction of **8** with $AgOSO_2CF_3$ in $CHCl_3$. The NMR and IR spectra for **8** and **9** are essentially the same, the only differences being due to the $OSO_2CF_3^-$ absorptions in the IR spectrum and the presence of the $CF_3$ quartet in the $^{13}$C-{$^1$H} NMR spectrum.

The crystal structure of the triflate salt **9** is in perfect agreement with the formula proposed for **8** (Figure 4). Inspection of the metrical data points out that the distances and angles are similar to that observed for the series of Ru−$PPh_3$−PTA complexes described above, which in turn suggests that both PTA and alkylated-PTA have similar cone angles and induce comparable electronic effects to the metal.

The synthesis of the complexes [RuClCp(mPTA)$(PPh_3)$]$^+$, [RuClCp$(mPTA)_2$]$^{2+}$, and [RuCpI$(mPTA)_2$]$^{2+}$ were successfully attempted in order to have in stock related hydrosoluble ruthenium complexes to obtain comparable information on their reactivity toward DNA. To synthesize these compounds, we required an mPTA salt, a soft and poorly coordinating anion like triflate. *N*-Methylation of PTA by $MeOSO_2CF_3$ was straightforwardly accomplished in $CHCl_3$, giving the ammonium triflate salt mPTA$(OSO_2CF_3)$ (**4**). The chemical shift for the signals observed in the $^1$H and $^{13}$C{$^1$H} NMR spectrum in $CDCl_3$ does not differ from those of mPTA (**I**), apart from the $OSO_2CF_3^-$ quadruplet in the $^{13}$C{$^1$H} NMR spectrum. However, **4** is more water-soluble than mPTA (**I**) ($S_{25°C}$ = 240 mg/mL).

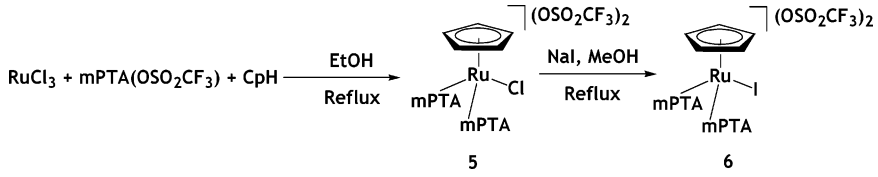
A synthetic procedure similar to that used for [RuClCp-$(PPh_3)_2$][17] was used to prepare [RuClCp$(mPTA)_2$] (**5**). Thus, freshly cracked dicyclopentadiene was directly reacted with $RuCl_3 \cdot xH_2O$ and mPTA$(OSO_2CF_3)$ in EtOH to yield **5**, although in very poor yield (Scheme 3). Chloride substitution in **5** by iodide via reaction with NaI in refluxing MeOH/$H_2O$ leads to complex **6** in very good yield.

The formula of complex **5** with two mPTA ligands is clearly supported by $^{31}$P{$^1$H} NMR in which a singlet at −10.74 ppm ($D_2O$) is observed. This chemical shift is ca. 5 ppm downfield shifted with respect to **7** ($\delta_{mPTA}$ ($CD_3OD$) = −15.38 ppm). The $^1$H NMR ($D_2O$) agrees with the proposed formula, showing the $CH_3N_{(mPTA)}$ signal ($\delta$ = 2.82 ppm) slightly downfield shifted compared to that of **7** ($\delta(CD_3OD)$ = 2.58 ppm). A similar downfield shift is exhibited by the Cp signal ($\delta(D_2O)$ = 4.85 ppm) in comparison to that of **7** (4.59 ppm). Metathesis of the chloride ligand with iodide gives **6**, which was characterized by NMR and IR spectroscopy and elemental analysis.

Finally, the 1:1 reaction of **4** with [RuClCp$(PPh_3)_2$] in acetone (Scheme 2) leads to the monosubstituted complex [RuClCp$(PPh_3)$(mPTA)]$(OSO_2CF_3)$ (**7**), which is practically insoluble in organic solvents, such as $CHCl_3$, scarcely soluble in water ($S_{25°C}$ = 1.1 mg/cm$^3$), but soluble enough in acetone, EtOH, and MeOH to allow for its NMR characterization. As good quality crystals could not be obtained, complex **7** was characterized only by spectroscopic techniques and elemental analysis. The $^{31}$P{$^1$H} NMR recorded in $CD_3OD$ shows a doublet at 46.31 ppm practically unchanged with respect to **8** (46.37 ppm) and a second doublet at −15.38 ppm assigned to mPTA. The latter is ca. 3 ppm low field shifted respective to the mPTA signal in **8** (−18.32 ppm). This NMR behavior is in agreement with the general tendency observed for these complexes: the substitution of the chloride bonded to the metal by iodide causes $PPh_3$ and mPTA resonances to move to higher field. The coupling constant between the phosphorus atoms for both compounds **8** (40.7 Hz) and **7** (43.3 Hz) are comparable, which further supports the proposed structure for **7**. The $^1$H NMR displays the signals expected for mPTA, Cp, and $PPh_3$ ligands in a 1:1:1 ratio. These resonances are similar to those found for **8** with only minimal differences observed in the *N*-methyl (**7** $\delta$: 2.58 ppm; **8** $\delta$: 3.00 ppm) and Cp singlets (**7** $\delta$: 4.59 ppm; **8** $\delta$: 4.77 ppm) groups.

**Solubility in Water and Stability toward Oxygen of the [RuCpX(L)(L′)]Y Complexes.** The chemico-physical properties exhibited by the new ruthenium complexes described

**Scheme 3**

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in this article, particularly their marked solubility in water and the $^{31}P\{^1H\}$ NMR data, agree with the proposed formulas and confirm that the solid state structures are maintained in water without any ligand replacement. As a common $^{31}P\{^1H\}$ NMR feature, the complexes show negative chemical shifts for the PTA ligands which anyway fall always at higher field than the mPTA. Coordinated $PPh_3$ ligands resonate over 40 ppm in the expected region. The water solubility of the complexes is predictable from the known hydrosolubility of the PTA and mPTA phosphines,[12] the number of water-soluble phosphines (1 or 2) bonded to the metal, the type of halogen (Cl or I) linked to the ruthenium, and last but not least, the nature of the counteranion in charged complexes. Generally, the water solubility of the complexes containing two PTA ligands is higher than that including one PTA and one $PPh_3$ which, in turn, is higher than that of the complexes with one mPTA and one $PPh_3$. When iodide replaces chloride, the solubility in water drops down. Finally, the solubility of the cationic mPTA complexes increases by replacing the chloride anion with triflate.

All the complexes are air-stable in water under aerobic conditions within 1 day at both room temperature and 40 °C. The air stability of these complexes is in agreement with previous observations by Sadler et al., suggesting that the presence of arene molecules bonded to ruthenium favors the stabilization of the Ru(II) species with respect to oxidized Ru(III) derivatives.[21] Therefore, for the complexes described in this paper, the Cp ligand not only provides a lipophilic side to the metal complex but also contributes to stabilization of the ruthenium center in the +2 oxidation state. In addition, no evidence for halide (Cl and I) replacement by water (aquation) is observed. As mentioned above, the decomposition of these compounds likely affords unidentified green-colored paramagnetic Ru(III) species which are silent by NMR spectroscopy.

**Crystal Structure of [RuClCp($PPh_3$)(PTA)]·$CHCl_3$·0.25$H_2O$ (2·$CHCl_3$·0.25$H_2O$).** An ORTEP[22] view of **2**·$CHCl_3$·0.25$H_2O$ is displayed in Figure 1 and the crystallographic data are given in Table 1. Crystals were obtained by slow evaporation from a solution of **2** in $CHCl_3$/*n*-hexane (1:1).

The asymmetric unit in the cell contains one disordered $CHCl_3$, 0.25 water molecules, and two [RuClCp($PPh_3$)(PTA)] neutral molecules which form enantiomeric pairs (Figure 1). In both complex molecules the metal is coordinated with a pseudo-octahedral geometry to one $\eta^5$-Cp, formally occupying three contiguous coordination positions, one Cl, one $PPh_3$, and one PTA. The coordination polyhedron about the metal atom adopts a highly distorted pseudo-octahedral geometry (P1−Ru−P1P = 99.05(8)°; P2−Ru−P2P = 98.92(9)°) likely due to steric repulsion between the two phosphines. The two independent molecules found in the asymmetric unit do not show 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 [$MCpXL_2$] such as [RuClCp($PPh_3$)$_2$].[23] The Cp rings for the two enantiomeric molecules are essentially planar, the biggest separation being 0.0120 Å (C1) from the overall plan for the Cp bonded to Ru1 and 0.0262 (C10) for the Cp bonded to Ru2. The Ru−$Cp_{(centroid)}$ distances are for the two molecules quite similar (Ru1−$Cp_{(centroid)}$ = 1.845 Å; Ru2−$Cp_{(centroid)}$ = 1.837 Å) and comparable with that for [CpRuCl(PTA)$_2$][24] (Ru−$Cp_{(centroid)}$ = 1.844 Å) but somewhat shorter than that in [RuClCp*(PTA)$_2$] (1.861 Å).[9] The Ru−$P_{(PTA)}$ separations (Ru1−P1P = 2.277(2) Å; Ru2−P2P = 2.280(2) Å) are somewhat larger than those of [RuClCp(PTA)$_2$] (average Ru−P = 2.252 Å) and match the values found for the few other X-ray authenticated Ru−PTA derivatives.[12,25] The Ru−Cl distances (Ru1−Cl1 = 2.448(2) Å, Ru2−Cl2 = 2.443(3) Å) for the two enantiomeric molecules are in line with that of [RuClCp(PTA)$_2$] (Ru−Cl = 2.445 Å). Despite the cone angle of $PPh_3$ (ca. 147°) being greater than

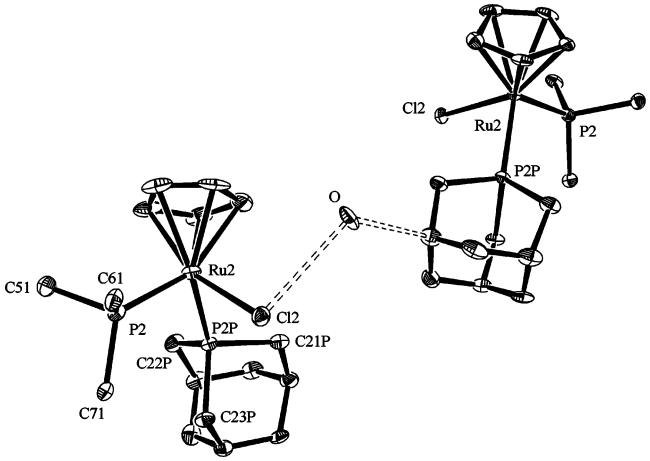


**Figure 1.** ORTEP view and atom numbering of compound **2**. Only the *ipso* carbons of the phenyl rings of $PPh_3$ are shown. Hydrogen atoms have been omitted for the sake of clarity.

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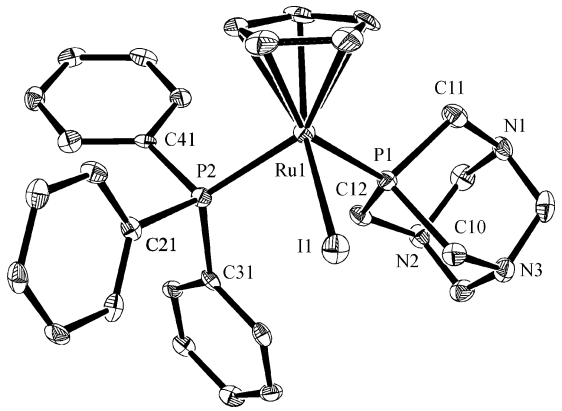


**Figure 2.** ORTEP view and atom numbering of compound **3**. Hydrogen atoms have been omitted for the sake of clarity.

that of the PTA (ca. 102 °),[26] the P−Ru−$P_{(PTA)}$ angle (99.05(8)°) is quite similar to that for [RuClCp$(PTA)_2$] ($P_{(PTA)}$−Ru−$P_{(PTA)}$ = 96.85°).

A disordered water molecule has been found interspersed in the lattice (Figure 1), clearly located between the N2P and Cl2 atoms. Both N2P−O1W (2.748(2) Å) and Cl2−O1W (3.144(2) Å) distances are shorter than those consider to be hydrogen-bond interactions among these kinds of atoms.[26]

The rest of the bond distances and angles are similar to those found in the known Ru−PTA complexes and do not deserve particular comments.[12,27,28]

**Crystal Structure of [RuCpI($PPh_3$)(PTA)] (3).** Solution of **3** separated good quality crystals by slow crystallization from $CHCl_3$ solution. An ORTEP[25] view of complex **3** is displayed in Figure 2; the crystallographic data are provided in Table 1.

The crystal structure is again constituted by a chiral molecule with the metal coordinated to Cp, $PPh_3$, PTA, and one iodide ligand. The geometry of the complex is quite similar to that of **2**, discussed above. The Ru−$Cp_{(centroid)}$ distance, 1.852 Å, is somewhat longer than those in both **2** (average Ru−$Cp_{(centroid)}$ = 1.841 Å) and [RuClCp$(PTA)_2$] (Ru−$Cp_{(centroid)}$ = 1.844 Å).[27] The Ru−$P_{(PTA)}$ distance (2.2979(11) Å) is much larger than those in **2** (Ru−$P_{ave}$ = 2.278 Å). The Ru1−I1 separation (2.7514(4) Å) is larger than the average value (2.711 Å) determined for the known [$RuCpIL_2$] complex structures.[27] The coordination P1−Ru1−P2 angle for **3** (97.31(4)°) is slightly shorter than that in **2** (average value P−Ru−$P_{(PTA)}$ = 99.48°), which suggests similar steric interactions in both complexes.

**Crystal Structure of [RuCpI(mPTA)($PPh_3$)][$OSO_2CF_3$)·$2H_2O$(9·$2H_2O$).** Crystals of **4** satisfactory for X-ray diffraction analysis were obtained by slow evaporation from $CHCl_3$ in the presence of $NH_4OSO_2CF_3$. An ORTEP[25] view is shown in Figure 3; the crystallographic data are given in Table 1.

The asymmetric unit is constituted by one $OSO_2CF_3$ anion, disordered by rotation around the C−S bond, two disordered water molecules, and one enantiomeric [RuCpI(mPTA)($PPh_3$)]$^+$ cation. The complex cation exhibits a pseudo-octahedral geometry with Cp, iodide, $PPh_3$, and mPTA ligands coordinated to ruthenium. By actuation of the spatial group symmetry ($P2_1/c$), the other enantiomeric cation is generated (Figure 3) and, therefore, **4** is a racemate of the two possible enantiomers obtained by distribution of the four different ligands around the Ru atom. The octahedral distortion around the metal (P1−Ru−P2 angle = 100.12(8)°) is more pronounced than that in **2**, likely due to the larger size of iodide which increases the repulsion between the halide ligand and the other ruthenium coordinated ligands, This result is intriguing as the cone angle for PTA and mPTA is practically the same,[12] which should have anticipated similar intramolecular repulsions in related piano-stool complexes.

The overall geometry of **4** is similar to that found for [RuClCp*$(PTA)_2$],[9] [RuClCp$(PTA)_2$],[27] and complex **2**. The most important metrical characteristics are as follows: The Cp ring is practically planar with the larger separation from the overall Cp plane of only 0.0115 Å. The Ru−$Cp_{(centroid)}$ distance (1.8563(7) Å) is similar to **3** (Ru−$Cp_{(centroid)}$ distance = 1.852 Å), shorter than in [RuClCp*$(PTA)_2$] (1.861 Å),[9] and somewhat longer than in [RuClCp$(PTA)_2$] (1.846 Å)[27] and in **2** (Ru1−$Cp_{(centroid)}$ = 1.845 Å; Ru2−$Cp_{(centroid)}$ = 1.837 Å). The Ru−$P_{(PTA)}$ separation (Ru1−P1 = 2.263(2) Å) is shorter than that for **3** (Ru1−P1 = 2.298(2) Å) but in line with other Ru−PTA complexes.[12,28] The Ru−I distance (2.724 Å), slightly shorter than in **3** (Ru1−I1 distance = 2.751 (1) Å), is similar to the average value (2.711 Å) found for the known [$RuCpIL_2$] complex structures.[27]

**Interaction of the Ru Complexes with DNA.** Modification of the electrophoretic mobility of plasmid DNA on agarose gels is commonly taken as evidence for direct DNA−metal interaction as has been shown in previous studies on Pt and Ru compounds.[28] Alteration of DNA structure, leading to unwinding of the plasmid molecule, causes retardation in the migration of supercoiled DNA (SC) and a slight increase in the mobility of open circular DNA (OC) to a point (coalescence point, CP) where both forms comigrate. We have investigated the interaction of the new water-soluble ruthenium complexes discussed above with SC DNA using the shift mobility assay. The reactions between the ruthenium complexes and SC plasmid DNA were performed in water-containing phosphate buffer at pH 7.0 for 14 h at 37 °C in darkness and then samples were analyzed by electrophoresis in agarose−TAE gels. The reaction was performed in the dark as a precaution against possible photochemical activation of the interaction process such as was observed for other ruthenium complexes.[29]

Retardation of SC DNA was observed for the chloro complexes [RuClCp$(PTA)_2$] (CP at Ri = 13.3; Figure 4 panel

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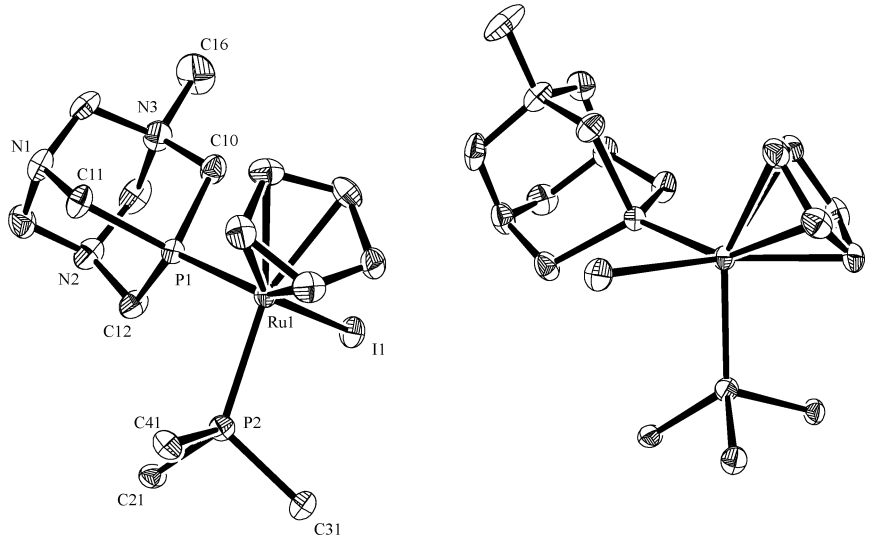


**Figure 3.** ORTEP view and atom numbering of compound **9**. Hydrogen atoms have been omitted for the sake of clarity.

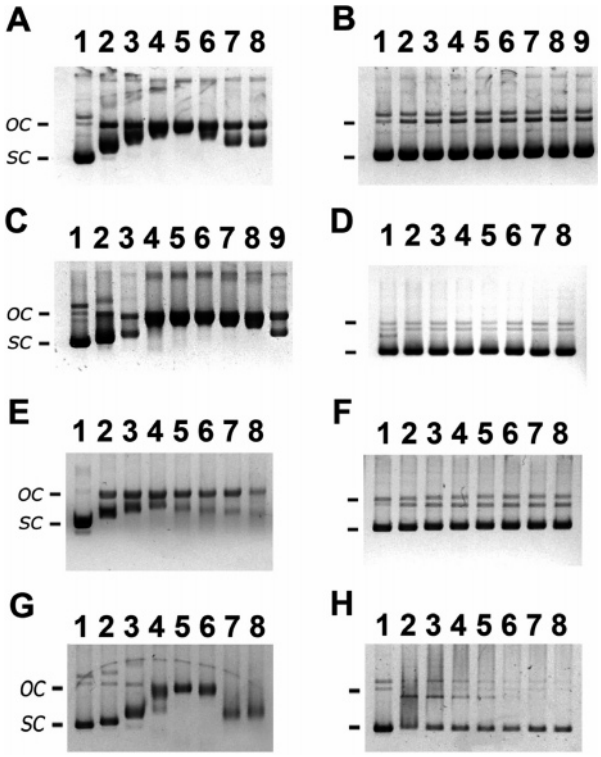


**Figure 4.** DNA mobility shift assay for the water-soluble ruthenium complexes. Plasmid DNA was incubated with $[RuClCp(PTA)_2]$ (panel A), $[RuCpI(PTA)_2]$ (**1**) (panel B), $[RuClCp(PPh_3)(PTA)]$ (**2**) (panel C), $[RuCpI(PPh_3)(PTA)]$ (**3**) (panel D), $[RuClCp(mPTA)_2](OSO_2CF_3)_2$ (**5**) (panel E), $[RuCpI(mPTA)_2](OSO_2CF_3)_2$ (**6**) (panel F), $[RuClCp(mPTA)(PPh_3)](OSO_2CF_3)$ (**7**) (panel G), and $[RuCpI(mPTA)(PPh_3)](OSO_2CF_3)_2$ (**9**) (panel H). Ri values (Ru/base molar ratio) in the different assays were as follows: 0, 5.3, 8.0, 10.7, 13.3, 16.0, 21.3, 26.7 (lanes 1−8 of panel A); 0, 5.3, 8.0, 10.7, 13.3, 16.0, 21.3, 26.7, 32.0 (1−9 panel B); 0, 2, 4, 5, 6, 7, 8, 10, 11 (1−9 panel C); 0, 2, 4, 6, 8, 10, 12, 15 (1−9 panels D and F); 0, 0.4, 0.8, 1.2, 1.6, 2, 2.4, 3 (1−8 panel E); 0, 0.33, 0.66, 1.0, 1.3, 1.7, 2.0, 2.5 (1−8 panels G and H).

A), $[RuClCp(PPh_3)(PTA)]$ (**2**) (CP at Ri = 5.0; Figure 4 panel C), $[RuClCp(mPTA)_2](OSO_2CF_3)_2$ (CP at Ri = 1.2; Figure 4, panel E), and $[RuClCp(mPTA)(PPh_3)](OSO_2CF_3)$ (CP at Ri = 1.3; Figure 4, panel G). No interaction between the iodide complexes (**1**, **3**, **6**, and **9**) and SC DNA was observed (Figures 4, panels B, D, F, and H).

As replacement of the halide ligand with water was not observed for any of the ruthenium complexes during 24 h at 40 °C and the reactions with SC DNA were performed in darkness, we are confident that the unchanged ruthenium complexes are the DNA active species. Remarkably, no DNA activity was observed with the iodide complexes **1**, **3**, and **9**, a fact indicating that the Ru−I bond is likely more robust than Ru−Cl and cannot be replaced by N-nucleophiles from DNA.

Although the N7 binding site of guanine, the most electron-rich site on DNA, is known to be the privileged target for both Ru(II) and Ru(III) metal complexes, many reported ruthenium derivatives do not selectively interact with nucleobases and act as intra- or interstrand cross-linking agents binding more than one reactive coordination site.[30] In the case at hand, it is reasonable that the interaction of the water-soluble ruthenium complexes here described takes place via removal of the coordinated chloride and coordination of the G nucleobase via N7. A similar situation was indeed observed by Sadler et al. during a study of the reaction of $[\{(\eta^6\text{-p-cymene})RuCl(\mu\text{-Cl})\}_2]$ with lysozime after chloride removal with silver triflate.[31] X-ray diffraction analysis showed that the three-legged piano-stool arene $[(\eta^6\text{-p-cymene})RuCl_2]^+$ unit binds the N$\epsilon$ of the imidazole ring of the unique histidine residue (His15) in the lysozyme protein. In the same paper, it was also reported that the interaction of $[(\eta^6\text{-p-cymene})RuCl(en)](PF_6)$ with DNA 14-mer d($A_1T_2A_3-C_4A_5T_6G_7G_8T_9A_{10}C_{11}A_{12}T_{13}A_{14}$) in aqueous solution occurs via chloride substitution and N7 coordination of guanine to ruthenium.

Complexes with anticancer activity of the type $[(\eta^6\text{-arene})RuCl(en)]^+$ are highly selective in their recognition of binding sites on nucleosides and nucleotides.[32] This arises not only from the differences in basicity between the possible binding

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sites but also from the demanding constraints imposed on the reactive monofunctional site in these pseudo-octahedral "piano-stool" Ru(II) arene complexes. By an appropriate choice of the arene coligand it has been possible to achieve a high degree of selectivity via kinetic effects due to $\pi-\pi$ arene-base stacking interactions (intercalation).

The interaction of the novel chloride ruthenium complexes **2**, **5**, **7**, and [CpRuCl(PTA)$_2$] with SC DNA is strictly dependent on the water-soluble phosphines bonded to the metal. The Ri values obtained at the coalescence point indicate that either methylation of the PTA or the substitution of PTA by $PPh_3$ increase the biological activity toward SC DNA. As the electronic and steric properties of PTA and mPTA are quite comparable,[12] it is hard to put down the observed differences in biological activity to only electronic and steric effects. A similar behavior was observed for Pt thiosalicylate complexes, [Pt($SC_6H_4COO$)(L)] (L = PTA or $PPh_3$), where the $PPh_3$ derivative exhibits higher antitumor activity toward leukemia P388 cells.[33] Similarly, complexes containing $PPh_3$ such as [Pt($PPh_3$)$_2$($\mu$-N,S-8-TT)]$_2$, *cis*-[PtCl(($PPh_3$)$_2$(8-MTT)], *cis*-[Pt($PPh_3$)$_2$(8-MTT)$_2$], and *cis*-[Pt($PPh_3$)$_2$(8-MTT)(8-TTH)] are stronger inhibitors of cisplatin-resistant SKOV3 cell line than analogous complexes containing PTA such as [Pt(PTA)$_2$($\mu$-S,N-8-TT)]$_2$, *cis*-[PtCl(PTA)$_2$(8-MTT)], and *cis*-[Pt(PTA)$_2$(8-MTT)$_2$] (8-$TTH_2$ = 8-thiotheophylline; 8-MTTH = 8-methylthiotheophylline).[2] Complex **9**, containing both $PPh_3$ and mPTA ligands, shows activity toward SC DNA similar to **7**, which contains two mPTA ligands, but higher than [RuClCp(PTA)$_2$] where only PTA are present. Therefore, we may conclude that coordination of either mPTA or $PPh_3$ to ruthenium increases the activity of the {RuClCp} unit toward SC DNA. All these results, taken altogether, suggest that the relatively modest DNA activity of the PTA complexes[7,9,10] could be interpreted with the basicity of the phosphadamantane cage which at the physiological pH value may be easily protonated at the nitrogen atom. The presence in transition metal PTA complexes of protonated PTA ligands may well account for the documented biological effects likely due to the formation of hydrogen-bonding interactions with different nucleophiles in biological systems.

## Conclusions

A family of new water-soluble ruthenium(II) chiral complexes [RuCpX(L)(L′)]Q (X = I, L, L′ = PTA, Q = 0, (**1**); X = Cl, L = $PPh_3$, L′ = PTA, Q = 0, (**2**); X = I, L = $PPh_3$, L′ = PTA, Q = 0 (**3**); X = Cl, L, L′ = mPTA, Q = ($OSO_2CF_3$)$_2$, (**5**); X = I, L, L′ = mPTA, Q = ($OSO_2CF_3$)$_2$, (**6**); X = Cl, L = $PPh_3$, L′ = mPTA, Q = $OSO_2CF_3$, (**7**); X = Cl, L = $PPh_3$, L′ = mPTA, Q = $Cl^-$, (**8**); X = I, L = $PPh_3$, L′ = mPTA, Q = $OSO_2CF_3$, (**9**)) (PTA = 1,3,5-triaza-7-phosphaadamantane; mPTA = methyl-1,3,5-triaza-7-phosphaadamantane) was synthesized and characterized. The X-ray crystal structures for **2**, **3**, and **9** have been determined, showing the expected piano-stool structures of a racemic mixture of the two possible enantiomers. The complexes are air-stable in both solid state and solution and maintain their solid state structure in water solution where no significant halide substitution is observed. The chloride derivatives actively destabilize the duplex SC DNA structure in the dark while the comparable iodides compounds are inactive. This result suggests that the interaction between the [RuClCp(L)(L′)]Q complexes and SC DNA occurs via chloride substitution by a DNA constituent, resulting in the formation of a chemical bond between ruthenium and a DNA base. The DNA activity further depends on the water-soluble phosphine coordinated to the metal, suggesting that modification of DNA by the water-soluble {RuClCp} species might be achieved by an adequate choice of the hydrosoluble phosphines bonded to the metal. Therefore, the study of the DNA activity of other components of this family of complexes could provide information good enough for the rational design of new hydrosoluble DNA-binding agents based on the {RuClCp} structural motif and capable of recognizing specific sequences or structures of DNA and/or modifying specific DNA functions. The final scope of this work is to better understand the interaction of water-soluble ruthenium species with DNA in view also of potential application of this chemistry in drug design.

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**Supporting Information Available:** X-ray crystallographic files in CIF format for the structure determination of compounds **2**·$CHCl_3$·0.25$H_2O$, **3**, and **9**·2$H_2O$. This material is available free of charge via the Internet at http://pubs.acs.org.

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