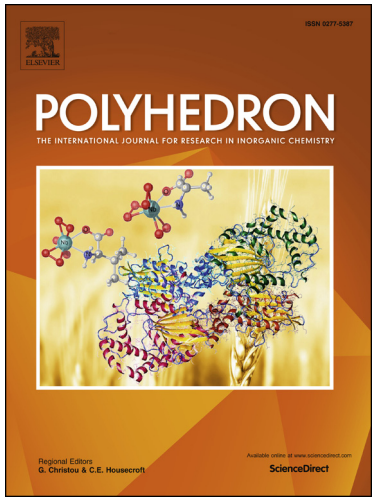

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Polyhedron

Clean oxidations by iodobenzene dichloride: platinum(IV) complexes containing triphenylphosphine

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Abstract: Neutral complexes with generic formula $[PtCl_2(PPh_3)(L)]$ were efficiently oxidized to $[PtCl_4(PPh_3)(L)]$ (L = dibenzylamine, p-toluidine, diethanolamine, pyridine and acetonitrile) using $PhICl_2$ The anionic complex $[TBA][PtCl_3(PPh_3)]$ (TBA = Tetrabutylammonium) was also oxidized to $[TBA][PtCl_5(PPh_3)]$ with this method. The obtained products were fully characterized by ^{1}H-, ^{13}C-, ^{31}P- and ^{195}Pt NMR, IR-ATR spectroscopy, elemental analysis and, for complexes *cis*-$([PtCl_4(PPh_3)(p\text{-toluidine})]\cdot CHCl_3$ and *trans*-$[PtCl_4(PPh_3)(NCCH_3)]\cdot CH_3CN$, also by single crystal X-Ray diffraction.

Keywords: platinum(IV); oxidation; iodobenzene dichloride; triphenylphosphine; *cis,trans* isomers.

1. Introduction

Platinum(IV) complexes have been gaining attention due to their possible use in the fields of catalysis,[1] and biochemistry.[2] Among the reported platinum(IV) complexes, those containing phosphine ligands are generally characterized by the presence of at least one strongly σ-donating, aryl or alkyl anionic ligand.[1d,e][3,4,5,6,7,8,9] For $[PtX_4(PR_3)(L)]$ and $[PtX_5(PR_3)]^-$ complexes (X= halogen, L= neutral ligand), data are scarcer, with only few cases structurally described.[10] Yet, the availability of $[PtX_4(PR_3)(L)]$ (L = Bz_2NH, p-toluidine, $(HOCH_2CH_2)_2NH$, Py, NCMe) and $[PtX_5(PR_3)]^-$ complexes and the study of their reactivity is an interesting target, in view of their potential applications as prodrugs.[2, 10a]. It is known, indeed, that analogous platinum(II) species possess good antiproliferative properties against some cancer cell lines.[11,12,13,14] The preparation of $[PtX_4(PR_3)(L)]$ complexes is not trivial, considering the redox features of the systems, with platinum(IV) species being quite easily reduced[15] and phosphines quite easily oxidized.[16] Phosphine oxidation can be assisted by the presence of water: as an example, in an electrochemical study [17] the anodic oxidation of a diluted solution of triphenylphosphine in nominally dry acetonitrile

afforded Ph_3PO. The oxidation proceeds with two one-electron steps, the former affording $PPh_3^{\cdot+}$. This intermediate reacts then with adventitious water present in the sample, with another one-electron step, affording the oxide.[17] Thus, synthetic routes to $[PtX_4(PR_3)(L)]$ systems carried out in non aqueous media have to be preferred. Pt(IV) species such as $[TBA]_2[PtCl_6]$ are well soluble in chlorinated solvents and can be easily prepared.[18] Although they could then be thought as useful precursors of $[PtCl_4(PR_3)(L)]$ systems, their strongly oxidant properties rule out synthetic approaches based on their direct interactions with phosphines. Thus, the synthesis of such compounds is generally achieved by oxidative addition of halogens to the corresponding Pt(II) complexes. While bromine and iodine can be easily dosed, the amount of chlorine is hard to control and a great excess of the reagent is usually added, often leading to formation of byproducts and low yields. Iodobenzene dichloride ($PhICl_2$) [24] is a convenient synthetic equivalent of gaseous chlorine and has already proven effective in oxidizing platinum(II) complexes, [2c,19] many of which bearing phosphino substituents.[6,7,8,9] We report here the clean oxidation of $[PtCl_2(PPh_3)(L)]$ (L = Bz_2NH, p-toluidine, $(HOCH_2CH_2)_2NH$, Py, NCMe) [20,11,12] by iodobenzene dichloride, together with the characterization of the corresponding platinum(IV) derivatives.

2. Experimental

2.1 General:

Reactions were performed in nitrogen atmosphere, if not otherwise stated. Unless otherwise specified all solvents were previously distilled in protected atmosphere and preserved with molecular sieves.[21] $[PtCl_2(NCCH_3)_2]$ was prepared from K_2PtCl_4 using a known procedure.[22] $[Pt_2Cl_4(PPh_3)_2]$ was prepared from $[PtCl_2(NCCH_3)_2]$ following procedures from literature.[20] $[PtCl_2(PPh_3)(L)]$ were prepared from $[Pt_2Cl_4(PPh_3)_2]$ adapting known literature synthesis.[11,12,23] Iodobenzene dichloride was prepared using a known literature procedure and stored at -20°C sheltered from light.[24] Elemental analyses were collected with an Elementar "vario MICRO CUBE" CHNOS elemental analyzer. Solid state IR spectra were collected with Perkin Elmer "Spectrum One" spectrometer outfitted with an Attenuated Total Reflectance (ATR) accessory. Abbreviations used to describe signal shape and intensity: w = weak; m = medium; s = strong; br = broad band. NMR spectra were collected with a Bruker "Avance DRX 400" spectrometer with a 400MHz ^1H frequency and with a Varian "Gemini 200" spectrometer with a 200MHz ^1H frequency. Spectra were recorded in $CDCl_3$, unless otherwise stated. ^{31}P- and ^{195}Pt NMR spectra were also acquired without deuterated solvents, using a capillary containing C_6D_6 to allow for locking by the spectrometer. Chemical Shifts (ppm) are

referenced to $Si(CH_3)_4$ for ^1H and ^{13}C, H_3PO_4 (85% in D_2O) and H_2PtCl_6 were employed for ^{31}P and for ^{195}Pt, respectively. Abbreviations used to describe signal multiplicity: s = singlet; d = doublet; t=triplet; td= triple doublet; m= multiplet.

2.2 Synthesis of [TBA][$PtCl_5(PPh_3)$] (**1**). *Step 1*: [$Pt_2Cl_4(PPh_3)_2$] (300.0 mg, 0.284 mmol) was suspended in chloroform under vigorous agitation, and TBACl (Tetrabutylammonium chloride) was added to the mixture (0.568 mmol, TBACl/Pt = 1.0 molar ratio). The reaction mixture rapidly changed from murky orange to clear yellow in a couple of minutes. A ^{31}P NMR spectrum at this point showed a signal at 7.7 ($^1J_{P\text{-}Pt}$ 3961Hz). *Step 2*: While still in the original Schlenk tube, $PhICl_2$ (275.6 mg, 0.570 mmol) was added. No apparent color change was observed. Progress was monitored by ^{31}P NMR and was found to be complete after an hour. The product was recovered adding heptane. Yield: 89% (referred to the amount of $Pt_2Cl_4(PPh_3)_2$ used in *Step 1*). *Anal*. calcd. for $C_{34}H_{51}Cl_5NPPt$: C=46.56, H=5.86, N=1.60. Found: C=47.06, H=6.08, N=2.19%. IR (ATR, cm^{-1}): 3064 w, 2960 s, 2871 m, 1588 w, 1574 w, 1471 s, 1436 s, 1381 m, 1091 s, 882 m, 738 s, 689 s. ^1H NMR: 8.04 (m, 6H, phosphine H_{arom}), 7.44 (m, 9H, phosphine H_{arom}), 3.29 (m, NCH_2, 8H), 1.64 (m, 8H, $NCH_2C\underline{H}_2$,), 1.43 (m, 8H, $C\underline{H}_2CH_3$), 0.98 (m, CH_3, 12H). ^{13}C NMR: 136.3 (d, $J_{C\text{-}P}$=8Hz), 131.4; 127.3 (d, $J_{C\text{-}P}$=13Hz), 126.1 (d, $^1J_{C\text{-}P}$=66Hz), 59.1, 24.4, 19.8, 13.8. ^{31}P NMR: 1.2 ($^1J_{P\text{-}Pt}$=2208Hz). ^{195}Pt NMR: -1361 (d, $^1J_{P\text{-}Pt}$=2208Hz).

2.3 Synthesis of platinum(IV) complexes [$PtCl_4(PPh_3)(L)$]-general description:

The procedure was adapted from a literature source.[19] The Pt(II) precursor complex (1.0 mmol) was dissolved in a solvent, usually $CHCl_3$ and placed within a Schlenk tube under magnetic stirring at room temperature. After dissolving the precursor, a stoichiometric amount of $PhICl_2$ (1.0 mmol, 1:1 molar ratio) was dissolved in the same solvent and added to the solution in the Schlenk tube. Reaction progress was monitored by using ^{31}P NMR spectroscopy. When full conversion was observed, most of the solvent was removed under reduced pressure. Heptane was subsequently added at 0°C to force precipitation of the Pt(IV) complex. After a few minutes, the system was filtered under nitrogen to separate the precipitate and the mother liquor. The precipitate collected on the filter was washed with a few mL of heptane, dried under reduced pressure for 6 -7 hours and then collected in sealed glass vials, under nitrogen. Characterization of the product was performed with IR/ATR, ^{31}P-, ^1H-, ^{13}C- and ^{195}Pt NMR analysis.

2.3.1 *Trans*-[$PtCl_4(PPh_3)(NHBz_2)$] (**2**). Only one product was observed. Both the precursor and the product are yellow, the reaction was complete after 90 minutes. Yield: 46%. *Anal*. calcd. for $C_{32}H_{30}Cl_4NPPt \cdot ½CHCl_3$: C=45.59, H=3.59, N=1.64. Found: C=46.27, H=3.88, N=2.36 %. IR data (ATR, cm^{-1}): 3256 w, 3064 w, 3028 w, 2963 w, 1604 w, 1588 w, 1571 w, 1487 m, 1436 s, 1260 m, 1097 s, 1026 m, 996 m, 917, m, 858 m, 796 m, 744 s, 690 s. ^1H NMR: 8.05 (m, 6H, phosphine H_{arom}), 7.51 (m, 9H, phosphine H_{arom}), 6.99 (mult, 10H, amine H_{arom}), 5.10 (m, 2H, NHC<u>H</u>H), 4.94 (m, 1H, NH), 3.97 (m, 2H, amine NHCH<u>H</u>). ^{13}C NMR: 136.9, 135.9 (d, J_{C-P} =9Hz), 132.2 (d, J_{C-P} 3Hz), 128.9, 128.2, 127.8 (d, J_{C-P} 12Hz),127.4, 125.84 (d, $^1J_{C-P}$ =69Hz), 57.4. ^{31}P NMR: 4.13 ($^1J_{P-Pt}$=2144Hz). ^{195}Pt NMR: -1498 (d, $^1J_{P-Pt}$=2144Hz).

2.3.2 [$PtCl_4(PPh_3)$(p-toluidine)] (**3**). The reaction was complete (^{31}P NMR) in 20 minutes. The product was obtained as a mixture of isomers. An isomerization equilibrium was reached (24h) in chloroform solution (60/40 molar ratio). The mixture was crystallized after slow diffusion of pentane vapors into a chloroform solution. Suitable crystals were selected for the X-ray structure determination, showing a *cis* stereochemistry. A freshly prepared $CDCl_3$ solution of crystals of *cis*-[$PtCl_4(PPh_3)$(p-toluidine)]·$CHCl_3$ showed both sets of signals for the two isomers. Yield: 84% *Anal*. calcd. for $C_{25}H_{24}NCl_4PPt$: C=42.51, H=3.42, N=1.98. Found: C=42.97, H=3.35, N=2.38%. IR data (ATR, cm^{-1}): 3286 w, 3213 m, 3112 w, 3053 w, 2963 w, 1600 m, 1509 m, 1482 m, 1436 s, 1088 s, 803 s, 750, s, 689 s.

Isomer A (selected signals from mixture). ^1H NMR: 7.93 (m, 6H, phosphine H_{arom}), 7.61 (m, 3H, phosphine H_{arom}), 7.43 (m, 6H, phosphine H_{arom}), 7,29 (m, partially covered by solvent peak, amine H_{arom}), 7.62 (m, 2H, amine H_{arom}), 6.22 (br s, 2H, NH_2), 2.32 (s, 3H, CH_3). ^{31}P NMR: 3.83 ($^1J_{P-Pt}$=2265Hz). ^{195}Pt NMR: -1600 (d, $^1J_{P-Pt}$=2265Hz).

Isomer B (selected signals from mixture). ^1H NMR: 8.07 (m, 6H, phosphine H_{arom}), 7.53 (m, 3H, phosphine H_{arom}), 7.43 (m, 6H, phosphine H_{arom}), 6.97 (m, 2H, amine H_{arom}), 6.54 (m, 2H, amine H_{arom}), 5.56 (br s, 2H, NH_2), 2.24 (s, 3H, CH_3). ^{31}P NMR: -0.91 ($^1J_{P-Pt}$=2142Hz).

2.3.3 [$PtCl_4(PPh_3)(NH(CH_2CH_2OH)_2)$] (**4**). The reaction was conducted at 0°C. Reaction was complete in the range of minutes and both the precursor and the product are yellow. Formation of two isomers was observed immediately and the mixture could not be resolved. (78% isomer A, 22% isomer B). Yield: 60%. *Anal*. calcd. for $C_{22}H_{26}Cl_4NO_2PPt$: C=37.52, H=3.72, N=1.99. Found: C=37.52, H=3.73, N=2.29%. IR data (ATR, cm^{-1}): 3056 w, 2958 w, 1726 w, 1585 w, 1569 w, 1482 m, 1436 s,

1096 s, 1034 m, 752 s, 689 s. ^{31}P NMR: 4.98 ($^{1}J_{P\text{-}Pt}$=2200Hz), -0.82 ($^{1}J_{P\text{-}Pt}$=2328Hz). ^{195}Pt NMR: -1183 (d, $^{1}J_{P\text{-}Pt}$=2328Hz), -1379 (d, $^{1}J_{P\text{-}Pt}$=2200Hz).

2.3.4 [$PtCl_4(PPh_3)(Py)$] (**5**). The reaction was complete in 30min. The product was less soluble than the precursor in chloroform and precipitated spontaneously out of the reaction mixture. Two ^{31}P NMR signals were observed and ascribed to *cis*/*trans* isomers of the oxidation product: 1.1 ($^{1}J_{P\text{-}Pt}$=2083Hz); -2.5 ($^{1}J_{P\text{-}Pt}$=2176Hz). In this case both geometrical isomers of the precursor were present. The precipitate is composed mainly of one isomer (isomer A), for which spectroscopic characterization was collected. After equilibrium was reached the composition was 70% isomer A, 30% isomer B. Yield: 94%. *Anal*. calcd. for $C_{23}H_{20}Cl_4NPPt\cdot\frac{1}{2}CHCl_3$: C=38.25, H=2.80, N=1.90. Found: C=38.14, H=2.74, N=2.27%. IR (ATR, cm^{-1}):3112 w, 3050 w, 1607 w, 1582 w, 1566 w, 1482 m, 1449 s, 1433 s, 1094 m, 1069 m, 746 s, 687 s.

Isomer A: ^{31}P NMR: -2.5 ($^{1}J_{P\text{-}Pt}$=2176Hz).^{195}Pt NMR: -1484 (d, $^{1}J_{P\text{-}Pt}$=2176Hz).

Isomer B: ^{31}P NMR: 1.1 ($^{1}J_{P\text{-}Pt}$=2082Hz).

2.3.5 [$PtCl_4(PPh_3)(NCCH_3)$] (**6**):. The reaction was carried out in CH_3CN at 60-70°C. Once the reaction was complete (3 hours) most of the solvent was removed, diethyl ether was added to precipitate the product. Formation of two isomers was observed by ^{31}P NMR [5.32 ($^{1}J_{P\text{-}Pt}$ 1937Hz), 1.28 ($^{1}J_{P\text{-}Pt}$ 2560Hz)], with the former slowly converting into the latter. When the reaction was performed over a longer time the dominant product was the isomer showing the signal at 1.28 ($^{1}J_{P\text{-}Pt}$ 2560Hz). In another experiment, a sample containing both isomers was heated at 70°C for a temperature controlled NMR acquisition. At this temperature, the equilibrium shifted in a few minutes in favor of the isomer showing the signal at 1.28 ($^{1}J_{P\text{-}Pt}$ 2560Hz), which was finally the only one detectable. When the NMR tube was removed from the instrument a portion of the product had crystallized after cooling down slowly. These crystals were analyzed by x-ray diffraction and found to be the *trans* isomer. By dissolving the crystals in CD_3CN and rapidly analyzing them at room temperature it was possible to correlate the NMR signals with the structure, since isomerization equilibrium occurred on a scale of hours. In an NMR test tube kept in protective atmosphere it was found that a pure *trans*-sample took approximately 9 days to reach the equilibrium composition at room temperature. Progress was monitored by ^{31}P NMR and the end solution showed an approximately 1:1 molar ratio of the two stereoisomers. Yield: 70%. *Anal*. calcd. for $C_{20}H_{18}Cl_4NPPt$: C=37.52, H=2.83, N= 2.19. Found: C=37.41, H=2.87, N=2.38 %. IR (ATR, cm^{-1}): 2963 m, 2328 w, 1585 w, 1571 w, 1482 w, 1436 m, 1088 s, 793 s, 752 s, 679, s.

Cis isomer (selected signals from a mixture of both isomers). ^{1}H NMR (CD_3CN): 8.03 (m, 6H, phosphine H_{arom}), 7.68 (m, 3H, phosphine H_{arom}), 7.57 (m, 6H, phosphine H_{arom}), 2.22 (s, $^{4}J_{H\text{-}Pt}$ 10Hz, 3H, CH_3). ^{31}P NMR: 5.32 ($^{1}J_{P\text{-}Pt}$=1937Hz). ^{195}Pt NMR: -1564 (d, $^{1}J_{P\text{-}Pt}$=1937Hz).

Trans isomer. ^{1}H NMR (CD_3CN):7.97 (m, 6H, phosphine H_{arom}), 7.66 (m, 3H, phosphine H_{arom}), 7.50 (m, 6H, phosphine H_{arom}). ^{31}P NMR: 0.49 ($^{1}J_{P\text{-}Pt}$=2560Hz). ^{195}Pt NMR: -1477 (d, $^{1}J_{P\text{-}Pt}$=2560Hz).

2.4 X-ray structure determination

Crystals were selected at room temperature (296 K), glued to glass fibers and analyzed with a Bruker Smart Breeze CCD diffractometer equipped with graphite monochromated Mo-$K\alpha$ radiation (λ = 0.71073 Å). Table 1 summarizes the lattice parameters and the respective space groups. Intensity data were collected in the ranges of 2θ angles reported in the table. After correction for Lorentz and polarization effects and for absorption, the structure solutions were obtained using the procedure contained in SHELXT program.[25] The asymmetric units of both crystals correspond to the respective molecules and a molecule of the solvent. The structure refinement was done using SHELXL program.[26] All the hydrogen atoms were introduced in calculated positions and included in the refinement process using riding model. Other control calculations were performed with the programs contained in the suite WINGX.[27]. Detailed structural parameters for *cis*-[$PtCl_4(PPh_3)$(p-toluidine)]·$CHCl_3$ (*cis*-**3**·$CHCl_3$) and *trans*-[$PtCl_4(PPh_3)(NCCH_3)$].CH_3CN (*trans*-**6**·CH_3CN).were deposited with the Cambridge Crystallographic Data Centre, see Table 1 for deposition numbers, and may be obtained free of charge by quoting this paper.

Table 1. Crystal data and structure refinement for *cis*-[$PtCl_4(PPh_3)$(p-toluidine)]·$CHCl_3$ (*cis*-**3**·$CHCl_3$) and *trans*-[$PtCl_4(PPh_3)(NCCH_3)$].CH_3CN (*trans*-**6**·CH_3CN).

Identification code	*cis*-**3**·$CHCl_3$	***trans*-6·CH_3CN**
CCDC number	1586904	1586905
Empirical formula	$C_{26}H_{25}Cl_7NPPt$	$C_{22}H_{21}Cl_4N_2PPt$
Formula weight	825.68	681.27
Crystal system	Monoclinic	Orthorhombic
Space group	$P\,2_1/c$	$P\,b\,c\,a$
a (Å)	10.2241(5)	10.6007(2)
b (Å)	17.2085(10)	16.0987(3)
c (Å)	17.8575(9)	29.2974(7)
β (°)	94.863(2)	-
Volume (Å^3)	3130.6(3)	4999.82(18)
Z	4	8

ρ_{calc} (g cm^{-1})	1.752	1.810
μ (mm^{-1})	5.148	6.117
F(000)	1600	2624
θ range (°)	3.1 to 32.5	2.7 to 32.0
Reflections collected	38871	40385
Independent reflections, R_{int}	11249, 0.0234	8652, 0.0216
Data / restraints / parameters	11249 / 0 / 326	8652 / 0 / 270
Goodness-of-fit (GOF) on F^2	1.002	1.055
Final R_1 [$I \geq 2\sigma(I)$]	0.0315	0.0267
Final wR_2 [$I \geq 2\sigma(I)$]	0.0778	0.0602
Final R_1 [all data]	0.0542	0.0373
Final wR_2 [all data]	0.0887	0.0641
Largest peak/hole (e Å^{-3})	1.776, –1.151	1.027, –1.633

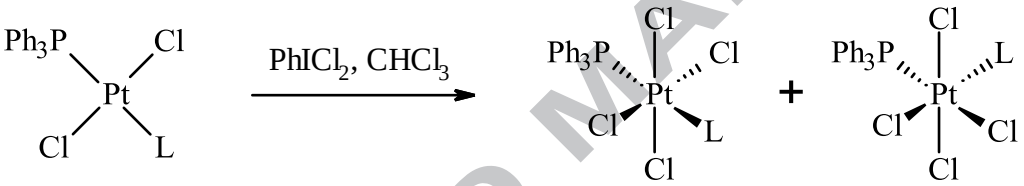
3. Results and discussion

Considering that phosphines are π-acid ligands and are stabilized by higher electron densities on the metal center,[28] this study started with the oxidation of anionic [TBA][$PtCl_3(PPh_3)$] (TBA=tetrabutylammonium). Dry solvents were used under nitrogen to avoid the presence of water and minimize the risk of phosphine oxidation.[17] The precursor was synthesized starting from [$Pt_2Cl_4(PPh_3)_2$][20] by mixing it, in chloroform, with tetrabutylammonium chloride (TBACl). The reaction was monitored with ^{31}P NMR spectroscopy and provided a reference point for the chemical shift and coupling constant of the Pt(II) anionic species. In the same Schlenk tube, $PhICl_2$ was added and the reaction progress was followed once again by ^{31}P NMR. A variation of both chemical shifts and Pt-P coupling constant of the coordinated phosphine [from 4.0ppm ($^1J_{Pt-P}$=3960Hz) to 1.1ppm ($^1J_{Pt-P}$=2208Hz)] was taken as preliminary proof of platinum oxidation, in good agreement with values reported [10b,29,30] for analogous Pt(IV) complexes. ^{195}Pt NMR spectrum was also in good agreement with the literature,[10b] affording a doublet at -1361 ppm ($^1J_{P-Pt}$=2208Hz). Finally, the complete NMR characterization (^{1}H, ^{13}C, ^{31}P, ^{195}Pt), IR (ATR) analysis and elemental analysis on the isolated complex could be used to determine conclusively that the derivative was indeed [TBA][$PtCl_5(PPh_3)$]. The ionic species, maintained in chloroform solution, was checked regularly (^{31}P NMR) and proved to be quite stable for a week before starting to show signs of degradation.

To investigate the procedure viability further, it was carried out on selected neutral complexes bearing, in addition to PPh_3, different types of N-coordinated ligands. The synthesis of these Pt(II) precursors, most of which possessing good antiproliferative properties, had been optimized previously.[20,11,12,13,31,32] *Trans*-[$PtCl_2(PPh_3)(NHBz_2)$] was chosen for the first experiment as

it can be cleanly prepared from reaction between $[Pt_2Cl_4(PPh_3)_2]$ and $NHBz_2$, in $CHCl_3$ solution, as the single, *trans* isomer (^{31}P NMR, 3.70 ppm, $^1J_{P-Pt}$ = 3633 Hz). To the resulting solution, a stoichiometric amount of $PhICl_2$ was added and the reaction was monitored spectroscopically (^{31}P NMR). After 90minutes, the signal of the precursor had disappeared and a new, single signal was observed at 4.13ppm ($^1J_{P-Pt}$=2144Hz), which was ascribed to the oxidation product $[PtCl_4(PPh_3)(NHBz_2)]$, in analogy with data collected for the anionic species $[TBA][PtCl_5(PPh_3)]$ (Scheme 1). The usual work-up procedure afforded a single product in good yield, which was completely characterized by spectroscopic and elemental analysis, confirming its nature. It seems reasonable to assign a *trans* configuration to the complex, considering the steric hindrance of phosphine and amine ligands.

The same procedure was followed to oxidize other Pt(II) neutral derivatives, the complete series of compounds can be found in Scheme 1.

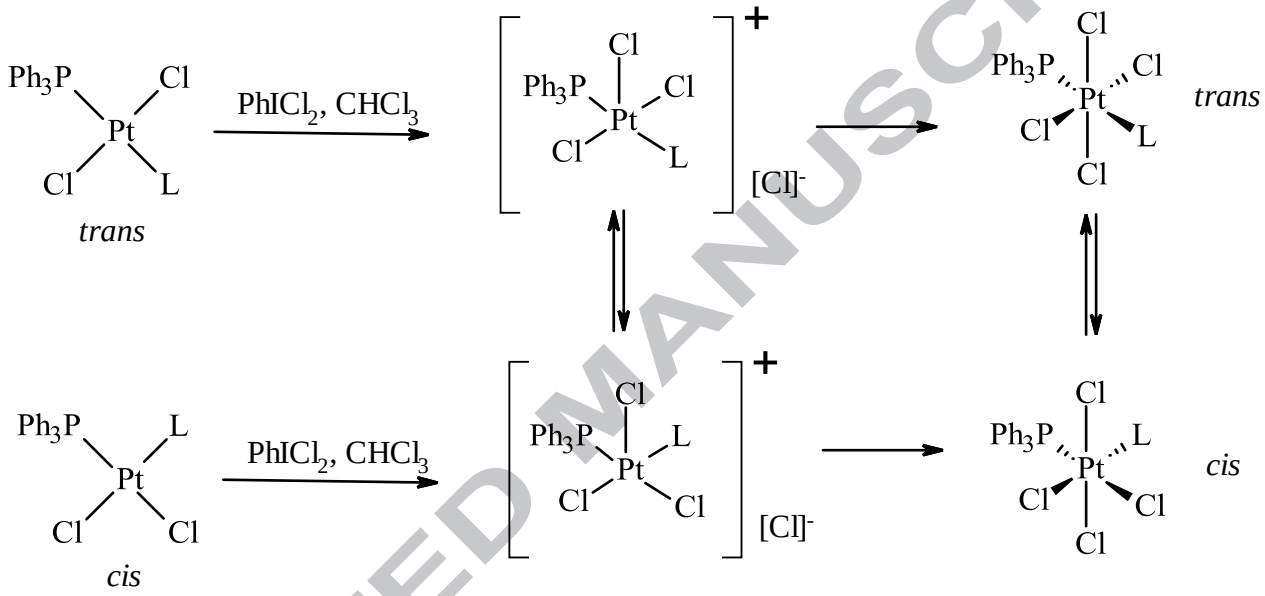


L = Bz_2NH^a, $H_3C\text{-}C_6H_4\text{-}NH_2{}^b$, $(HOCH_2CH_2)_2NH^c$, Py^d

Scheme 1: General reaction template with all the complexes studied: a) only *trans*-$[PtCl_4(PPh_3)(NHBz_2)]$ was obtained; b) 60/40 molar ratio of the two isomers; c) 78/22 molar ratio molar ratio of the two isomers; d) (*cis,trans)*-$[PtCl_2(PPh_3)(Py)]$ afforded a mixture containing the two isomers in 70/30 molar ratio.

Pyridine and p-Toluidine bearing platinum(II) complexes reacted in the same conditions of the first complex, while in the case of the complex $[PtCl_2(PPh_3)(NH(CH_2CH_2OH)_2)]$ the reaction mixture was kept a 0°C to avoid unwanted reactions of the hydroxyl functions. The reaction was complete in minutes and yielded in all cases a mixture containing two platinum(IV) species, which were identified as *cis* and *trans* isomers. Only the $[PtCl_2(PPh_3)(Py)]$ precursor was a mixture of both *cis* and *trans*-isomers,[32] while in all the other cases the platinum(II) starting compound was the stereochemically pure *trans* complex. The occurrence of both Pt(IV) isomers indicated, therefore,

an isomerization during the oxidation step. While it is known[33] that isomerization and substitution reactions in platinum(IV) complexes can be catalyzed by platinum(II) species, a long lived pentacoordinated intermediate seems also reasonable if the oxidant adds one chlorine moiety at a time. While in our systems the long lived intermediate species (Scheme 2) have not been observed even at low temperature, in a recent study these Pt(IV) intermediates have been isolated at low temperature using rigid chelating ligands on the equatorial plane and coordinating molecules such as DMSO and triphenylphosphine.[34]

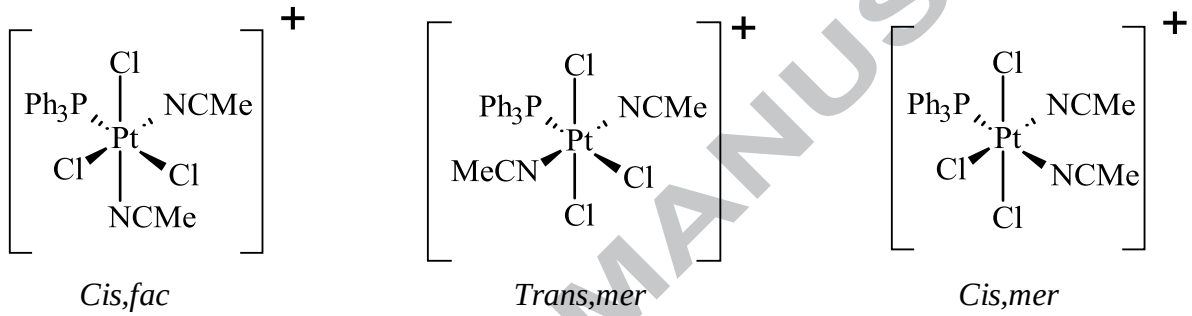


Scheme 2: Isomerization *via* a potential pentacoordinated Pt(IV) intermediate .

Most likely [$PtCl_2(PPh_3)(NHBz_2)$] does not isomerize since both PPh_3 and $NHBz_2$ are bulky ligands and steric hindrance would be much higher in the *cis* arrangement compared to the *trans* disposition. The most significant NMR data for the Pt(IV) complexes reported in Scheme 1 are summarized in Table SI-1, where the corresponding signals for the Pt(II) precursors in the same solvent ($CHCl_3$) have been included.

The oxidation of *cis*-[$PtCl_2(PPh_3)(NCCH_3)$] could not be carried out in chloroform, since this platinum(II) complex [20], is stable only in acetonitrile. Oxidation with $PhICl_2$ was then carried out in this solvent, monitoring the reaction by ^{31}P NMR.

This reaction proceeded slowly. In fact, 2 hours at 70°C were necessary for the disappearance of the precursor signal. Interestingly, ^{31}P NMR analysis (Figure SI-3) carried out on a sample of the reaction mixture after about 30 minutes evidenced, besides the precursor, the presence of four new signals (11.96 ppm, $^{1}J_{P\text{-}Pt}$ = 1681 Hz; 7.99 ppm, $^{1}J_{P\text{-}Pt}$ not determined; 5.37 ppm, $^{1}J_{P\text{-}Pt}$ = 1937 Hz; 1.25 ppm, $^{1}J_{P\text{-}Pt}$ = 2560 Hz), with the first two less abundant and slowly converting into the other ones. These last two signals were assigned to *cis*- and *trans*-$[PtCl_4(PPh_3)(NCCH_3)]$. In this case, the coordinating nature of the solvent could temporarily stabilize the intermediate Pt(IV) species (Scheme 2) as $[PtCl_3(PPh_3)(NCCH_3)_2][Cl]$. Although three isomers could form, (Figure 1) we detected only two of them in our spectra at 11.96 and 7.99 ppm (Figure SI-3).



Cis,fac *Trans,mer* *Cis,mer*

Figure 1: Possible intermediate Pt(IV) cationic species

The relatively long span life of such intermediates can account for the formation of both *cis* and *trans* isomers of the oxidation product $[PtCl_4(PPh_3)(NCCH_3)]$. Prolonged heating at 70°C yields a single product, showing the signal at 1.25 ppm. This complex has been crystallized by slowly cooling the concentrate solution. On this crystalline sample a single crystal X-ray diffraction study was carried out, showing the *trans* configuration (*trans*-$[PtCl_4(PPh_3)(NCMe)]\cdot CH_3CN$). A pure sample of this complex in acetonitrile slowly reached an isomerization equilibrium at 25 °C . (1/1 molar ratio), while at 70°C only the *trans* species was observed (^{31}P NMR). When ^{1}H NMR was carried out on a sample of *trans*-$[PtCl_4(PPh_3)(NCMe)]\cdot CH_3CN$ in CD_3CN, only the signals ascribed to phosphine hydrogen atoms were observed, while in the ^{1}H NMR spectrum registered on a sample containing both isomers a singlet signal was observed at 2.22 ppm ($^{4}J_{H\text{-}Pt}$ 10Hz), attributable to methyl group of coordinated acetonitrile in *cis*-$[PtCl_4(PPh_3)(NCMe)]\cdot CH_3CN$. Collected ^{1}H NMR data show that *trans* -$[PtCl_4(PPh_3)(NCMe)]\cdot CH_3CN$ quickly exchanges coordinated acetonitrile with the solvent, while *cis* isomer does not. This behavior is a clear indication of a different reactivity exhibited by the two geometric isomers towards nucleophilic substitution.

All the neutral species described so far have proven stable enough to be recovered as solid products in good yields. In solid state all of them have also proven to be stable over prolonged periods of time. However, in solution, any trace of water can degrade the complex with oxidation of phosphine to $OPPh_3$ and reduction of platinum(IV) to platinum(II). As an example, a chloroform solution containing *trans*-[$PtCl_4(PPh_3)(Bz_2NH)$] was monitored spectroscopically (^{31}P NMR): while no isomerization was detected, after some time the slow, but progressive decomposition of Pt(IV) species was observed. In the ^{31}P NMR spectrum two new signals were observed: a singlet, without satellites, at 30 ppm, which could be attributed to Ph_3PO for comparison with an authentic sample, and a signal at 3.7ppm, with satellites ($^1J_{P\text{-}Pt}$ = 3633Hz), which was identified with *trans*-[$PtCl_2(PPh_3)(Bz_2NH)$]. Repeatedly, multiple ^{31}P NMR signals related to $OPPh_3$ were detected which are likely caused by adducts between $OPPh_3$, HCl and/or water.[35] It is known [9] that platinum(IV) complexes containing phosphine ligands (PR_3) undergo photodegradation when irradiated with UV light (313 nm) to afford the corresponding platinum(II) reduction product. When the photoreduction is carried out in the presence of chlorine traps, chlorinated products are formed, while, in the absence of suitable traps, the formation of Cl_2PR_3 species is observed. In our case the mechanism of degradation was not investigated, but a reasonable hypothesis is that PPh_3 may initially assist the formal reductive elimination of chlorine from the platinum(IV) complex to form Cl_2PPh_3 which would then rapidly undergo hydrolysis with any available water molecule. No UV irradiation was used in these cases, but [$PtCl_4(PPh_3)(L)$] solutions were never shielded from natural light, thus photoreduction can not be excluded *a priori*.

4. *Structural data*

4.1 Cis-[$PtCl_4(PPh_3)$(*p*-Toluidine)]·$CHCl_3$ (*cis*-**3**·$CHCl_3$):

This complex crystallizes with a molecule of chloroform (Figure 2) and the most significant bond lengths and angles are listed in Table 2. The coordination around platinum is octahedral, with PPh_3 and *p*-toluidine in *cis* position relative to each other. This complex can be compared with c*is*{o-diphenylphosphino-[N-(2-methoxyethyl)-N-methyl]aniline}dichloroplatinum(II) [36], where the arylphosphino and the aniline ligands are in mutual *cis* position. Pt–N bond lengths are quite similar in the two complexes (2.135(3) against 2.111(2) Å) The angle N(1)–Pt(1)–P(1) is 97.92(8)° (against 90° for the ideal octahedral geometry) for the expected repulsion between the two bulky ligands.

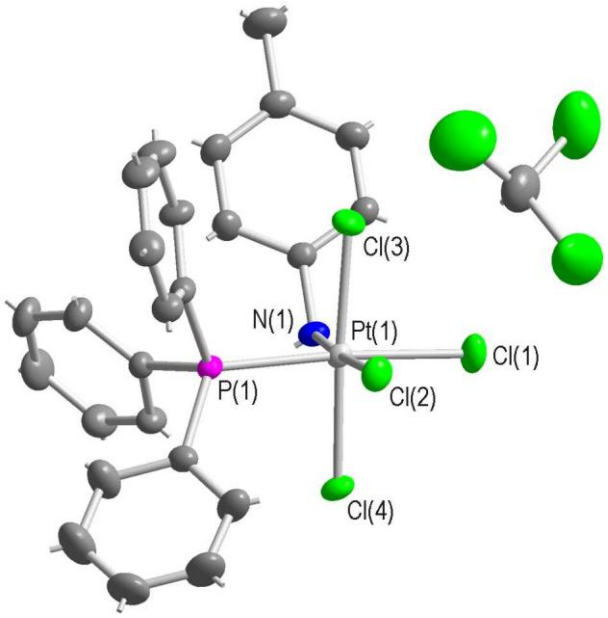


Figure 2: Structure of *cis*-[$PtCl_4(PPh_3)$(*p*-toluidine)]·$CHCl_3$ (cis-**3**·$CHCl_3$)

As shown by the other angles, all of the Pt–Cl bonds are bent away from the bulky ligands. The Pt–Cl bond *trans* to the phosphine (2.39 Å) is significantly longer than the average of the other three, 2.31 Å.

Table 2: Selected bond lengths (Å) and angles (°) for *cis*-[$PtCl_4(PPh_3)$(*p*-toluidine)]·$CHCl_3$ (*cis*-**3**·$CHCl_3$)

Pt(1)–Cl(1)	2.3944(9)	Pt(1)–Cl(2)	2.3085(8)
Pt(1)–Cl(3)	2.3045(9)	Pt(1)–Cl(4)	2.3254(8)
Pt(1)–P(1)	2.3476(8)	Pt(1)–N(1)	2.135(3)
Cl(1)–Pt(1)–Cl(2)	90.93(4)	Cl(1)–Pt(1)–Cl(3)	88.55(4)
Cl(1)–Pt(1)–Cl(4)	87.69(4)	Cl(1)–Pt(1)–N(1)	84.78(8)
Cl(1)–Pt(1)–P(1)	175.14(3)	Cl(2)–Pt(1)–Cl(3)	86.98(3)
Cl(2)–Pt(1)–Cl(4)	94.57(3)	Cl(2)–Pt(1)–P(1)	86.49(3)
Cl(2)–Pt(1)–N(1)	175.34(8)	Cl(3)–Pt(1)–Cl(4)	175.95(3)
Cl(3)–Pt(1)–P(1)	95.42(3)	Cl(3)–Pt(1)–N(1)	91.08(7)
Cl(4)–Pt(1)–P(1)	88.41(3)	Cl(4)–Pt(1)–N(1)	87.09(7)
N(1)–Pt(1)–P(1)	97.92(8)		

4.2 Trans-[$PtCl_4(PPh_3)$(NCMe)]·CH_3CN (*trans*-**6**·CH_3CN):

The molecular structure of *trans*-[$PtCl_4(PPh_3)(NCCH_3)$]·CH_3CN is shown in Figure 3, the most significant bond lengths and angles are listed in Table 3. The coordination around the metal is octahedral with the bond angles deviating very few from ideality. PPh_3 and N-coordinated acetonitrile occupy *trans* positions. The structure is reminiscent of that of *trans*-[$PtCl_4$(ipa)(PPh_3)] (ipa =

isopropylamine),[10a] where analogous Pt–P and Pt–N bond distances are reported: 2.310(7) and 2.148(5) Å vs. 2.3098(7) and 2.129(3) Å, respectively. Unlike cis-**3**·$CHCl_3$), it is more difficult to decide if any *trans*-influence of phosphine ligand is present. By comparing, however, our Pt–N distance with the mean value found in 24 nitrile complexes of Pt(IV) contained in the Cambridge Crystallographic Database,[37] 2.03(5) Å, we can notice that the distance we found is slightly longer, although with a low statistical significance.

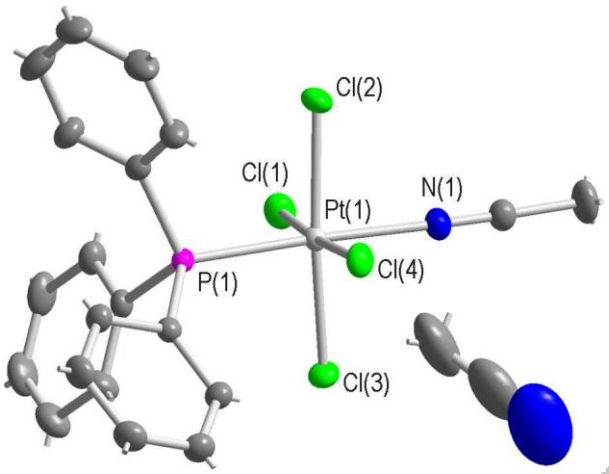


Figure 3: Structure of *trans*-[$PtCl_4(PPh_3)(NCCH_3)$] (*trans*-**6**·CH_3CN)

Table 3: Selected bond lengths (Å) and angles (°) for *trans*-[$PtCl_4(PPh_3)$(NCMe)] (*trans*-**6**·CH_3CN)

Pt(1)–Cl(1)	2.3160(8)	Pt(1)–Cl(2)	2.3202(8)
Pt(1)–Cl(3)	2.3143(7)	Pt(1)–Cl(4)	2.3190(7)
Pt(1)–P(1)	2.3098(7)	Pt(1)–N(1)	2.129(3)
Cl(1)–Pt(1)–Cl(2)	88.44(4)	Cl(1)–Pt(1)–Cl(3)	89.39(3)
Cl(1)–Pt(1)–Cl(4)	175.36(3)	Cl(1)–Pt(1)–N(1)	87.34(8)
Cl(1)–Pt(1)–P(1)	93.43(3)	Cl(2)–Pt(1)–Cl(3)	174.64(3)
Cl(2)–Pt(1)–Cl(4)	89.27(3)	Cl(2)–Pt(1)–P(1)	96.64(3)
Cl(2)–Pt(1)–N(1)	85.75(8)	Cl(3)–Pt(1)–Cl(4)	92.55(3)
Cl(3)–Pt(1)–P(1)	88.38(3)	Cl(3)–Pt(1)–N(1)	89.25(8)
Cl(4)–Pt(1)–P(1)	90.84(3)	Cl(4)–Pt(1)–N(1)	88.47(8)
N(1)–Pt(1)–P(1)	177.50(8)		

5. Conclusions

Iodobenzene dichloride ($PhICl_2$) was successfully used, in anhydrous solvents, to oxidize [TBA][$PtCl_3(PPh_3)$] and [$PtCl_2(PPh_3)(L)$] complexes (L = Bz_2NH, p-toluidine, $(HOCH_2CH_2)_2NH$, Py, NCMe) to their analogous tetrachloro Pt(IV) species (**1**-**6**), which were completely characterized. The oxidation appears to be of general applicability. It was fast for the anionic complex and for the pyridine and the amino derivatives and much slower for the acetonitrile

complex. Mixtures of geometric isomers were obtained, with the only exception of the hindered dibenzylamino derivative. For the species *cis*-$[PtCl_4(PPh_3)(p\text{-toluidine})]\cdot CHCl_3$ and *trans*-$[PtCl_4(PPh_3)(NCCH_3)]\cdot CH_3CN$ X-ray structures were determined. The complexes have proven to be stable over time in solid state, even when exposed to natural light, while in solution and in the presence of traces of water they undergo slow, but progressive degradation. This behavior makes these compounds unsuitable for the study of their antiproliferative properties. Isomerization was observed in dry solvents for $[PtCl_4(PPh_3)(L)]$ complexes. In particular, for L = MeCN a fast exchange with the solvent (acetonitrile) was observable (^{31}P NMR) at 70 °C, where only *trans* isomer is observed. At room temperature in CD_3CN, ^1H NMR data showed that *trans*-**6**, *trans*-$[PtCl_4(PPh_3)(NCCH_3)]$, exchanges rapidly coordinated MeCN with the solvent, while the *cis* isomer does not. This behavior suggests a different reactivity of the two isomers towards substitution and will be object of further investigation.

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Appendix A. Supplementary data CCDC 1586904-1586905 contain the supplementary crystallographic data for *cis*-$[PtCl_4(PPh_3)(p\text{-Toluidine})]\cdot CHCl_3$ and *trans*-$[PtCl_4(PPh_3)(NCCH_3)]\cdot CH_3CN$. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/retrieving. html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033 or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version.

Synopsis

Clean oxidations by iodobenzene dichloride: platinum(IV) complexes containing triphenylphosphine

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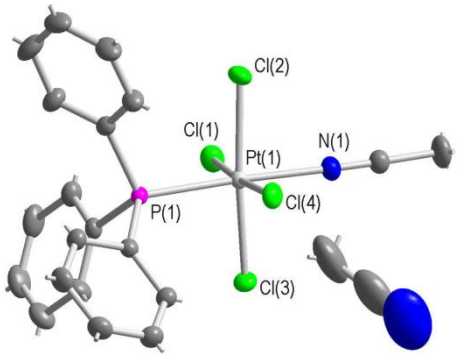

$[PtCl_2(PPh_3)(L)]$ complexes were oxidized to the corresponding Pt(IV) species by $PhICl_2$ in dry solvents. $[PtCl_4(PPh_3)(L)]$ complexes, fully characterized, are stable in the solid state, but decompose in solutions containing some water. The dynamic behavior shown by *trans*-$[PtCl_4(PPh_3)(NCMe)]$ in CD_3CN solution suggests its possible use as precursor in substitution reactions.

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