A Rapid Method for the Synthesis of Water-soluble Platinum(II) Amine and Pyridine Complexes

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Seventeen *cis*-$[Pt(am)_2(ONO_2)_2]$ complexes (am = methylamine, cycloalkylamines, substituted pyridines, aniline, or benzylamine; 2am = 2,2'-bipyridyl) were synthesized by reaction of *cis*-$[Pt(am)_2I_2]$ with silver nitrate in acetone. The reaction was rapid (5—20 min at room temperature) with a yield of about 85%. The complexes appear to be stable in acetone with respect to isomerization. Thus, after 1 h at 25 °C acetone solutions of *cis*-$[Pt(am)_2X_2]$ (am = cyclohexylamine or 4-methylpyridine; X = I or ONO_2) showed no isomerization judging by ^1H n.m.r. spectroscopy of these compounds and their corresponding *trans* isomers.

Since the discovery of the cytotoxic properties of *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin) by Rosenberg in 1967,[1] the nitrato derivatives *cis*-$[Pt(am)_2(ONO_2)_2]$ (am = amine) have been used in various pharmacological studies because of their improved solubility over the dichloro complexes.[2—4] These compounds are usually obtained by the reaction of chloro complexes, *cis*-$[Pt(am)_2Cl_2]$, with silver nitrate in aqueous solution. These solutions are often used directly without isolating the product. The method was first described by King[5] in 1938 for the synthesis of *cis*-$[Pt(NH_3)_2(ONO_2)_2]$. There are however some disadvantages. The complexes *cis*-$[Pt(am)_2Cl_2]$ frequently contain significant amounts of the Magnus salt. This can be overcome by synthesizing the dichloro complex from *cis*-$[Pt(am)_2I_2]$ according to the methods of Dhara[6] and Gil'dengershel.[7] Moreover the reaction time is often long because of the insolubility of the dichloro complex in water.

We describe in this paper a more rapid and general method, using acetone as solvent, for the synthesis, isolation, and purification of *cis*-diaminedinitratoplatinum(II) complexes using acetone as solvent. Since isomerization of *cis*-$[Pt(am)_2Cl_2]$ (am = cyclobutylamine) to the *trans* isomer has been reported in this solvent,[8] we investigated the isomeric stability of these compounds in acetone.

Results and Discussion

The ligands used in this work were NH_2R [R = Me, Ph, CH_2Ph, cyclopropyl (C_3H_5), cyclobutyl (C_4H_9),† cyclopentyl (C_5H_9), cyclohexyl (C_6H_{11}), 4-hydroxycyclohexyl ($C_6H_{10}OH$-4),† or cycloheptyl (C_7H_{13})], pyridine (py), 4-methylpyridine (mpy), 4-hydroxymethylpyridine (hmpy), 4-chloropyridine (cpy),† 4-acetylpyridine (apy), 4-dimethylaminopyridine (dmapy), 4-cyanopyridine (cypy), methyl isonicotinate (mina), or 2,2'-bipyridine (bipy). The amines marked † were obtained as the hydrochlorides; they were dissolved in an aqueous solution containing 2 mol of sodium hydroxide per mol of amine.

Synthesis.—The *cis*-di-iodo complexes were prepared by a slight modification of the methods of Dhara[6] and Gil'dengershel[7] as shown in equations (1) and (2).

$$[PtCl_4]^{2-} \xrightarrow[\text{excess}]{I^-} [PtI_4]^{2-} \qquad (1)$$

$$[PtI_4]^{2-} \xrightarrow[\text{excess}]{am} cis\text{-}[Pt(am)_2I_2] \qquad (2)$$

The synthesis of $[PtI_4]^{2-}$ from $[PtCl_4]^{2-}$ with a stoicheiometric amount of KI produced a shiny brown impurity on the surface of the solution. The use of 8 mol of KI per mol of Pt avoided the formation of this impurity. The use of an excess of iodide to stabilize the $[PtI_4]^{2-}$ ion has been mentioned by Baer *et al.*[9] and other workers.[10,11] Moreover an excess of amine (2.5 mol per mol of Pt) allowed the *cis*-$[Pt(am)_2I_2]$ complex to precipitate more rapidly[9] without the formation of a brown by-product which contaminated the reaction product when stoicheiometric amounts were used. The formation of this by-product could not be avoided for ammonia and cyclopropylamine.

Addition of silver nitrate to a solution of *cis*- or *trans*-$[Pt(am)_2I_2]$ in acetone results in a rapid metathesis [equation (3)]. It is easy to visualize the end of the reaction which is marked by a clear change in colour from yellow before the reaction started to colourless when the reaction is finished. The yield was about 85% and the purity of the products was satisfactory (Table 1).

$$cis\text{-}[Pt(am)_2I_2] + 2\,AgNO_3 \xrightarrow{\text{Acetone}} cis\text{-}[Pt(am)_2(ONO_2)_2] + 2\,AgI \qquad (3)$$

Although silver nitrate is practically insoluble in acetone, the precipitation of silver iodide is very rapid. The reaction time depended on the solubility of the di-iodo complexes in acetone and varied from 5 to 20 min at room temperature. The corresponding reaction using the method of King,[5] *viz.* $[Pt(am)_2Cl_2]$ plus $AgNO_3$ in water, is much slower.

The slight excess of $AgNO_3$ (2.2 mol per mol of Pt) results in a rapid reaction with a good yield. Trace amounts of the relatively insoluble $AgNO_3$ are eliminated by redissolution of crude *cis*-$[Pt(am)_2(ONO_2)_2]$ in a minimum of acetone, and filtration. The second filtration also eliminated micrograins of AgI which escaped the first filtration.

This general method was used for the synthesis of seventeen *cis*-dinitrato complexes of Pt^{II} with a variety of amines and pyridines. However we encountered some limitations in this approach. At room temperature the method failed for aniline, benzylamine, cyclopropylamine, and ammonia. Solutions of *cis*-bis(cyclopropylamine)di-iodoplatinum(II) and *cis*-bis(aniline)-di-iodoplatinum(II) in acetone are unstable although the products of this reaction have not been identified. For benzylamine the dinitrato complex was obtained as an oil which

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Table 1. Elemental analyses (%) for the complexes [$Pt(am)_2(ONO_2)_2$]

	C		H		N	
	Found	Calc.	Found	Calc.	Found	Calc.
cis isomers						
[$Pt(NH_2Me)_2(ONO_2)_2$]	6.4	6.3	2.6	2.6	14.6	14.7
[$Pt\{NH_2(C_4H_7)\}_2(ONO_2)_2$]	20.7	20.8	3.9	3.9	12.1	12.1
[$Pt\{NH_2(C_5H_9)\}_2(ONO_2)_2$]	24.5	24.5	4.5	4.5	11.4	11.4
[$Pt\{NH_2(C_6H_{11})\}_2(ONO_2)_2$][a]	27.6	27.8	5.0	5.1	10.8	10.8
[$Pt\{NH_2(C_7H_{13})\}_2(ONO_2)_2$]	30.8	30.8	5.5	5.5	10.2	10.3
[$Pt\{NH_2(C_6H_{10}OH\text{-}4)\}_2(ONO_2)_2$]$\cdot$1.8 H_2O	24.7	24.7	4.9	5.1	9.4	9.6
[$Pt(py)_2(ONO_2)_2$]	25.1	25.2	2.1	2.1	11.7	11.7
[$Pt(mpy)_2(ONO_2)_2$]	28.4	28.5	2.8	2.8	10.9	11.1
[$Pt(hmpy)_2(ONO_2)_2$][b]	26.4	26.8	2.8	2.6	9.9	10.4
[$Pt(apy)_2(ONO_2)_2$]	29.7	29.9	2.5	2.5	9.8	10.0
[$Pt(cpy)_2(ONO_2)_2$]	22.0	22.0	1.4	1.5	10.3	10.3
[$Pt(dmapy)_2(ONO_2)_2$]	29.6	29.8	3.5	3.6	14.9	14.9
[$Pt(mina)_2(ONO_2)_2$]$\cdot$0.32Me_2CO	29.4	29.4	2.6	2.6	9.0	9.1
[$Pt(cypy)_2(ONO_2)_2$]	27.5	27.3	1.7	1.5	15.4	15.9
[$Pt(bipy)(ONO_2)_2$]	25.1	25.3	1.7	1.7	11.5	11.7
[$Pt\{NH_2(CH_2Ph)\}_2(ONO_2)_2$]	31.7	31.5	3.5	3.4	10.2	10.5
[$Pt(NH_2Ph)_2(ONO_2)_2$]	28.4	28.5	2.8	2.8	10.6	11.1
trans isomers						
[$Pt(mpy)_2(ONO_2)_2$]	28.4	28.5	2.8	2.8	10.9	11.1
[$Pt\{NH_2(C_6H_{11})\}_2(ONO_2)_2$]	27.9	27.8	5.1	5.1	10.8	10.8

[a] Crystallization *via* toluene gave 0.17 mol of toluene of crystallization. [b] This compound is deliquescent.

Table 2. Selected i.r. bands (cm^{-1}) for *cis*-[$Pt(am)_2(ONO_2)_2$] *

am	Nitrato bands *					ν(Pt–O)
	ν_4	ν_1	ν_2	ν_6	ν_5	
NH_2Me	1 505	1 280	995	790m	720w	332wm
	1 490	1 260	975	780w	708w	
$NH_2(C_6H_{11})$	1 500	1 285	985	800w		340vw
	1 483	1 270	978			334vw
hmpy	1 510	1 288	970	792w	715(sh)	346w
	1 500	1 270			710w	338w
mpy	1 510	1 284	975	794w	720w	338w
	1 500	1 268	960	788w		
bipy	1 552	1 284	961	795m	719w	350m
	1 520	1 265	950		705w	340m
$NH_2(CH_2Ph)$	1 510	1 270	950	782m	710w	360w
	1 500	1 265	945	768w		350w

* m = Medium, w = weak, and sh = shoulder; other bands are strong or very strong.

Table 3. Selected i.r. bands (cm^{-1}) for *trans*-[$Pt(am)_2(ONO_2)_2$]

am	Nitrato bands					ν(Pt–O)
	ν_4	ν_1	ν_2	ν_6	ν_5	
$NH_2(C_6H_{11})$	1 502	1 300	972	783wm	695w	345w
mpy	1 515	1 268	955	782wm	712vw	350w

decomposed on standing. These problems can be overcome by working at 0 °C. The insolubility of *cis*-bis(ammine)dinitratoplatinum(II) in acetone makes the use of this method unsatisfactory for its preparation.

For the ligands 4-aminocyclohexanol and 4-(hydroxymethyl)pyridine, evaporation of the acetone solution to dryness gave an unstable oil, which slowly darkened even at 0 °C. The nitrato complex was precipitated by addition to an excess of diethyl ether. Although evaporation of ether gave an oil, a stable white powder was recovered after the supernatant was removed with a Pasteur pipette, and drying the product under vacuum.

Characterization of the Compounds.—The i.r. spectra of the *cis*-dinitrato complexes showed six bands characteristic[12] of nitrate co-ordinated to platinum, *i.e. ca.* 1 500, 1 280, 980, 800, 700, and 350 cm^{-1} (Table 2). The bands were split suggesting a *cis* structure for these compounds.[13] The i.r. spectra of the *trans* complexes are simpler with no splitting of the nitrato bands (Table 3).

The ^1H n.m.r. spectrum of *cis*-[$Pt(mpy)_2(ONO_2)_2$] showed two doublets of doublets at δ 8.710 and 7.549 and a singlet at 2.610. The doublets were assigned to α- and β-protons of the pyridine ring and the singlet to the methyl group in the

Table 4. Proton n.m.r. data (δ) in $(CD_3)_2CO$

		X			
		ONO_2^-		I^-	
Complex	Proton	*trans*	*cis*[a]	*trans*	*cis*[a]
$[Pt(mpy)_2X_2]$[b]	CH_3	2.650	2.610	2.567	2.500
	H_α	8.631	8.710	8.857	8.876
	H_β	7.655	7.549	7.387	7.436
		(29.0)	(43.0)	(31.0)	(41.0)
$[Pt\{NH_2(C_6H_{11})\}_2X_2]$[c]	NH_2	4.859	5.521	4.023	4.521
		(56.0)	(64.0)	(56.0)	(64.0)

[a] The spectra were recorded immediately after dissolution and after 1 h at 25 °C; no change was observed. [b] Chemical shift of α- and β-protons of pyridine and protons of methyl group in 4 position, $J(Pt-H_\alpha)$/Hz in parentheses. [c] Chemical shift of the amine protons, with coupling constants (Hz) between platinum and these protons in parentheses.

4 position. The spectrum of *trans*-$[Pt(mpy)_2(ONO_2)_2]$ was similar but with the doublets at δ 8.631 p.p.m. and 7.655 and the singlet at 2.650. The Pt–H_α coupling constants depended on the isomer and were 43 and 29 Hz for the *cis* and *trans* isomer respectively.

The proton n.m.r. spectra of *cis*- and *trans*-$[Pt\{NH_2(C_6H_{11})\}_2(ONO_2)_2]$ were more difficult to assign because of the overlapping resonances of the cyclohexyl ring. Nevertheless the amine protons were obvious with chemical shifts of δ 5.521 and 4.859 for the *cis* and *trans* isomer respectively. The Pt–NH coupling constants were 64 and 56 Hz for the *cis* and the *trans* isomer respectively.

Similar differences were observed for the *cis* and *trans* isomers of the di-iodo complexes (Table 4).

Although platinum complexes are generally considered to be stable to isomerization, Lock and Zvagulis[8] have described a facile isomerization of *cis*-$[Pt\{NH_2(C_4H_7)\}_2Cl_2]$ during slow crystallization from acetone. The presence of the *trans* isomer in our complexes could not be ruled out by the i.r. spectrum. To determine unambiguously their isometric purity we compared the ^1H n.m.r. spectra of *trans*-$[Pt(mpy)_2(ONO_2)_2]$ and *trans*-$[Pt\{NH_2(C_6H_{11})\}_2(ONO_2)_2]$ in deuteriated acetone with the corresponding *cis* isomers (Table 4). There is sufficient difference between the spectra of the two isomers to be able to determine whether a complex is isomerically pure. The n.m.r. spectra of the isolated *cis* complexes, both iodo and nitrato, for all ligands used in this study indicated the absence of any *trans* isomer.

However the absence of the *trans* isomer in the solid *cis* complex does not prove its non-existence in the reaction medium. If the *trans* isomer is formed in solution it may not be precipitated during the crystallization process. Furthermore the amount of acetone used as well as the time of contact of di-iodo or dinitrato complexes with the solvent varied with the ligands and might influence the amount of isomerization.

In order to investigate any possible isomerization of the complexes during their synthesis in acetone, the ^1H n.m.r. spectra of *cis*-$[Pt(am)_2I_2]$ and *cis*-$[Pt(am)_2(ONO_2)_2]$ (am = cyclohexylamine or 4-methylpyridine) were checked immediately after dissolution in acetone and after 1 h at 25 °C. The peaks corresponding to different protons had the same chemical shifts at both times, and no trace of the *trans* complex was observed.

Thus isomerization of these *cis* complexes to their *trans* isomers in acetone is negligible after 1 h. In contrast solutions of *cis*-$[Pt(NH_2Ph)_2I_2]$ in acetone rapidly became orange-red at room temperature. The ^1H n.m.r. spectrum indicated a mixture of products, but the spectrum was not analysed in detail.

In summary, we report a rapid method for the synthesis of *cis*-$[Pt(am)_2(ONO_2)_2]$. The successful synthesis of 17 complexes and some limitations of the method are presented. The dinitrato complexes are 100—1 000 times more water soluble than their dichloro analogues and as such have been used for pharmacological studies.[4]

Experimental

The salt $K_2[PtCl_4]$ was obtained from Johnson Matthey, the amines and pyridines from Aldrich or Merck.

Infrared spectra were run as Nujol mulls (CsI plates) using a Perkin-Elmer 597 spectrophotometer, proton n.m.r. spectra at 250.01 MHz in deuterioacetone at 25 °C on a Bruker 250 FT spectrometer. Chemical shifts were calculated relative to the acetone peak at δ 2.17.

Carbon, H, and N analyses were carried out by the Interuniversity Microanalytical Services, Ecole Nationale Superieure de Chimie de Toulouse.

Isonicotinic Acid Methyl Ester.—Isonicotinic acid (0.040 mol) was dissolved in concentrated sulphuric acid–methanol (6 cm^3:80 cm^3). The colourless solution was heated under reflux at 70—75 °C for 6 h whereupon it had turned pale yellow. After removal of the methanol with a Rotavapor, addition of water, and neutralization with sodium hydrogencarbonate, the solution was reduced by rotavaporation until the appearance of a gel formed by sodium sulphate and the oily ester, methyl isonicotinate. The latter was extracted with diethyl ether. After removal of the ether, a brown-yellow oil was obtained which was distilled under vacuum (*ca.* 15 mmHg, *ca.* 1995 Pa) at 86 °C.

Iodo Complexes.—*cis*-$[Pt(am)_2I_2]$ (am = NH_2Me, *cycloalkylamine, or a pyridine*). A concentrated solution of potassium iodide (8 mmol) in water was added to a solution of $K_2[PtCl_4]$ (1 mmol) in a minimum quantity of water and the mixture was stirred for 20 min. The deep brown solution was filtered with stirring into a dilute aqueous solution of the ligand (2.5 mmol). After several minutes a deep yellow precipitate formed. If the solid contained a trace of brown, stirring was continued for 30—40 min. The yellow precipitate was filtered off, washed liberally with water, then ethanol and ether, and dried *in vacuo* (yield >90%).

The products were generally yellow, except *cis*-$[Pt\{NH_2(C_3H_5)\}_2I_2]$ which was yellow-brown. The complexes were recrystallized from dimethylformamide (dmf)–water at room temperature.

cis-$[Pt(NH_3)_2I_2]$. The solution obtained by mixing $K_2[PtCl_4]$ and KI was filtered into concentrated ammonia solution according to Dhara.[6] This gave a yellow solid with a trace of brown which was recrystallized from dmf–water.

The complex $[Pt(bipy)I_2]$ was prepared as described previously.[14]

trans-$[Pt(am)_2I_2]$ [am = $NH_2(C_6H_{11})$ *or* mpy]. The salt $K_2[PtCl_4]$ was boiled in water with an excess of ligand to give a colourless solution. After cooling to room temperature a solution of potassium iodide in water was added to precipitate $[Pt(am)_4]I_2$ as white crystals in near-quantitative yield. These were filtered off, washed with water, and dried *in vacuo*. This salt suspended in ethanol was heated to boiling for several minutes. After cooling to room temperature, the yellow needles of *trans*-$[Pt(am)_2I_2]$ were filtered off, washed with ethanol and ether, and dried *in vacuo*. The complex *trans*-$[Pt\{NH_2(C_6H_{11})\}_2I_2]$ is somewhat soluble in ethanol.

Nitrato Complexes.—*cis*-$[Pt(am)_2(ONO_2)_2]$ (am = *cyclo-*

alkylamine or a pyridine, 2am = bipy). A yellow solution was obtained by dissolving *cis*-[Pt(am)$_2$I$_2$] (1 mmol) in a minimum of acetone. Finely powdered silver nitrate (2.2 mmol) was added and the solution was stirred for 5—20 min until it became colourless and the silver iodide settled rapidly. The solution was filtered through cellulose and evaporated to dryness. The whitish powder of *cis*-[Pt(am)$_2$(ONO$_2$)$_2$] was redissolved in a minimum of acetone and refiltered through cellulose. Toluene or ether was added to the solution until turbidity appeared. The solution was cooled to 3 °C for several hours. The white fine microcrystals which precipitated were filtered off, washed with ether, and dried under vacuum over silica gel.

The complexes were stable if stored in the dark. Nonetheless some (mainly am = NH$_2$Me) are slightly photosensitive, and developed a grey colour after several months, necessitating a further recrystallization in acetone.

cis-[Pt(am)$_2$(ONO$_2$)$_2$] [am = NH$_2$Ph *or* NH$_2$(CH$_2$Ph)]. These complexes were obtained by the preceding method, but the reaction was carried at 0 °C in order to avoid the formation of a dark brown impurity. They were stored at 0 °C; *cis*-[Pt(NH$_2$Ph)$_2$(ONO$_2$)$_2$] decomposed over a few days to give a black solid.

cis-[Pt(am)$_2$(ONO$_2$)$_2$] [am = NH$_2$(C$_6$H$_{10}$OH-4) *or* hmpy]. The complex *cis*-[Pt(am)$_2$I$_2$] (1 mmol) was dissolved in a minimum of acetone and powdered AgNO$_3$ (2.2 mmol) was added. The mixture was stirred until the solution was colourless. Silver iodide was removed by filtration and the filtrate was concentrated to half volume and refiltered. The filtrate was poured into 10 volumes of ether. A fine white suspension was immediately visible. The mixture was cooled to 5 °C until flocculation of the precipitate was complete. The supernatant was removed with a Pasteur pipette and the precipitate was dried using a vacuum pump.

The pale yellow hmpy complex was kept under vacuum at 4 °C, while that of NH$_2$(C$_6$H$_{10}$OH-4) was stored at room temperature in a desiccator over P$_2$O$_5$.

trans-[Pt(am)$_2$(ONO$_2$)$_2$] [am = NH$_2$(C$_6$H$_{11}$) *or* mpy]. Powdered AgNO$_3$ (2.2 mmol) was added to a solution of *trans*-[Pt(am)$_2$I$_2$] (1 mmol) in acetone. When the pale yellow solution became colourless the reaction was complete. After filtration through cellulose and evaporation to dryness, the whitish powder of *trans*-[Pt(am)$_2$(ONO$_2$)$_2$] was dissolved in a minimum of acetone and the solution was refiltered. Ether was added until the solution turned slightly cloudy. It was left overnight in a refrigerator. White microcrystals of *trans*-[Pt(am)$_2$(ONO$_2$)$_2$] were filtered off and dried under vacuum over silica gel.

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