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Synthetic strategies for dinuclear platinum complexes containing inequivalent coordination spheres. Design of complexes capable of specific attack at one platinum center

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Abstract

Synthetic strategies to dinuclear bis(platinum) complexes with inequivalent Pt coordination spheres are outlined. The isomeric pair of complexes containing formally a $[PtCl_2(Me_2SO)(amine)]$ coordination sphere linked to a $[PtCl_2(amine)_2]$ moiety giving a bis(platinum) complex $[\{PtCl_2(NH_3)\}–NH_2(CH_2)_4H_2N–\{PtCl_2(Me_2SO)\}]$ (*cis*/*cis* complex **I**, *trans*/*trans* complex **II**) has been prepared. Displacement reactions using pyridine on the tetra-iodo derivative of **I** gives evidence of selective substitution on the $[PtI_2(H_2NR)(Me_2SO)]$ coordination sphere. Isomerisation of $[\{$*trans*-$PtCl_2(Me_2SO)\}_2NH_2(CH_2)_4NH_2]$ to the dinuclear *cis* derivative can occur initially in a reaction which is competitive with bridge cleavage.

Introduction

We are currently studying the chemistry and biology of dinuclear bis(platinum) complexes containing two platinum centers linked by a diamine bridge [1–4]. An interesting aspect of the chemistry of these species is their mode of substitution. Bis(platinum) complexes with two identical coordination spheres are equally likely to react at either metal center. In a substitution reaction this equivalence is broken upon reaction of the first Pt atom. There is now a competition between the two inequivalent platinum centers and the final products will therefore depend on the nature of the incoming group and the ligands bound to the platinum atoms. This aspect of substitution reactions on bis(platinum) complexes has been exemplified in the formation of the complex with two *trans*-$[PtCl_2(amine)_2]$ coordination spheres, $[\{$*trans*-$PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)]$, from doubly-bridged tetra-amines [5] and in the reactions of 5′-GMP with the tetra-aqua species derived from $[\{$*cis*-$PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)]$ [1].

The fact that the first substitution reaction in bis(platinum) complexes produces inequivalent coordination spheres and that this induced difference dictates further reactivity led us to examine the chemistry of dinuclear complexes containing inequivalent coordination spheres. This paper reports on the synthesis and characterisation of the isomeric pair of complexes containing formally a $[PtCl_2(Me_2SO)(amine)]$ coordination sphere linked to a $[PtCl_2(amine)_2]$ moiety of formula $[\{PtCl_2(NH_3)\}–NH_2(CH_2)_4H_2N–\{PtCl_2(Me_2SO)\}]$ and a study of their chemical properties.

Experimental

Starting materials and physical methods

The complexes $K[PtCl_3(NH_3)]$ [6], $K[PtCl_3(Me_2SO)]$ [7], *cis*-$[PtCl_2(Me_2SO)_2]$ [8] and $[PtCl(Me_2SO)(H_2N(CH_4)NH_2)]Cl$ [9] containing chelated 1,4-butanediamine and the dinuclear complex with bridging 1,4-butanediamine $[\{$*trans*-$PtCl_2(Me_2SO)\}_2(H_2N(CH_4)NH_2)]$ [9] were prepared by literature methods. IR spectra were obtained as KBr disks on a Perkin-Elmer 1430 spectrophotometer. NMR spectra were run on Bruker 250 and 270 MHz spectrometers. ^{195}Pt NMR spectra (on the 250 MHz instrument) were run in d_7-DMF or d_6-acetone with respect to a Na_2PtCl_6 solution in D_2O as external reference. ^1H NMR spectra were relative to TMS. Elemental analyses were performed by Robertson Laboratories, Madison, NJ 07940, USA.

Synthesis of precursors

The monomeric precursors *cis*-$[PtCl_2(Me_2SO)(NH_2(CH_2)_4NH_3)]Cl$ (**A**) and *trans*-$[PtCl_2(NH_3)(H_2N(CH_2)_4NH_3)]Cl$ (**B**) have been prepared previously [10, 5]. In the case of complex **A** we used MeOH (50 ml) rather than H_2O as solvent for the chelate complex

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$[PtCl(Me_2SO)(H_2N(CH_2)_4NH_2)]Cl$ (3.5 g, 8.1 mmol) which with 5 ml conc. HCl gave the desired precipitate upon stirring overnight and addition of Et_2O. The spectral properties were $\delta(Pt) = -3088$ ppm and $\delta(^1H) = 3.57$ (Me_2SO), 3.03, 2.90 (both NH_2CH_2–) and 1.77 (C2 and C3 protons of 1,4-diaminobutane) ppm in D_2O.

Preparation of [{cis-$PtCl_2(Me_2SO)$*}–*$(H_2N(CH_2)_4NH_2)$*–{cis-*$PtCl_2(NH_3$*}] (I)*

A solution of *cis*-$[PtCl_2(Me_2SO)(NH_2(CH_2)_4NH_3)]Cl$, precursor **A**, (0.469 g, 1 mmol) in MeOH (50 ml), was added to a solution of 1 equiv. of $K[PtCl_3(NH_3)]$ (0.357 g, 1 mmol) dissolved in warm MeOH (50 ml) in the presence of 0.2 ml Et_3N. After stirring overnight, the solution was filtered and evaporated to half volume when a yellow compound precipitated out. This product was filtered off, washed with H_2O and dried (yield 10%). *Anal.* Found: C, 10.1; H, 2.9; N, 6.0; Cl, 19.6. Calc. for $C_6H_{21}Cl_4N_3OSPt_2$: C, 10.1; H, 3.0; N, 5.9; Cl, 19.8%.

Preparation of [{trans-{$PtCl_2(NH_3)$*}–*$(H_2N(CH_2)_4NH_2)$*–{trans-*$PtCl_2(Me_2SO)$*}] (II)*

To precursor **B**, *trans*-$[PtCl_2(NH_3)(H_2N(CH_2)_4NH_3)]Cl$ (0.207 g, 0.51 mmol) dissolved in MeOH/H_2O (40/5), was added 1 equiv. of $K[PtCl_3(Me_2SO)]$ (0.209 g, 0.51 mmol) in MeOH (40 ml) in the presence of 0.1 ml Et_3N. After stirring overnight, the solution was filtered and evaporated to half volume when the yellow compound **II** precipitated out. The complex was filtered, washed with H_2O and dried (yield 60%). *Anal.* Found: C, 10.6; H, 2.9; N, 5.6; Cl, 20.4. Calc. for $C_6H_{21}Cl_4N_3OSPt_2$: C, 10.1; H, 3.0; N, 5.9; Cl, 19.8%.

Preparation of [{cis-$PtI_2(Me_2SO)$*}–*$(H_2N(CH_2)_4NH_2)$*–{cis-*$PtI_2(NH_3$*}] (IV)*

$K[PtCl_3(NH_3)]$ (0.357 g, 1 mmol) was dissolved in MeOH (50 ml) at 40 °C and 4 equiv. of KI (0.664 g) in MeOH (10 ml) containing 0.15 ml Et_3N were added dropwise. The solution colour changed to deep red and *cis*-$[PtCl_2(Me_2SO)(NH_2(CH_2)_4NH_3)]Cl$ (precursor **A**) (0.469 g, 1 mmol) dissolved in MeOH (50 ml) was then added. The reaction solution was stirred at room temperature overnight. The yellow product which is probably best described as a mixed chloro/iodo complex [{*cis*-$Pt(I)Cl_2(Me_2SO)$}–$(H_2N(CH_2)_4NH_2)$–{*cis*-$Pt(Cl)I_2(NH_3$}] (**III**) precipitated, was filtered off and washed with H_2O. This compound (0.9 g. 1 mmol) was then suspended in H_2O and 3.8 equiv. of $AgNO_3$ (0.65 g) dissolved in H_2O were added. Overnight stirring at room temperature, followed by filtering of AgCl and AgI gave a clear solution of the tetra-aqua species. Addition of KI (0.83 g) precipitated the deep yellow product, which was filtered off and washed with H_2O (yield 35%). This complex can be recrystallised from acetone. *Anal.* Found: C, 6.9; H, 1.8; N, 3.5. Calc. for $C_6H_{21}I_4N_3OSPt_2$: C, 6.7; H, 1.9; N, 3.9%. When either complex **III** or **IV** is treated as above with 4 equiv. of $AgNO_3$ in H_2O, addition of KCl to the filtered solution of the tetra-aqua species precipitated complex **I** (IR, ^{195}Pt NMR).

Results and discussion

In the most general sense dinuclear bis(platinum) complexes can be divided into two classes: (i) those containing equivalent coordination spheres or (ii) those with inequivalent coordination spheres. In the first category are complexes with important biological activity such as [{*cis*-$PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)]$ [3] and [{*trans*-$PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]Cl_2$ [2]. These complexes are usually prepared by reaction of two equivalents of a suitable monomeric platinum complex with the diamine, although the products are somewhat dependent on the nature of the diamine [11, 12]. In general

$$2K[PtCl_3(NH_3)] + NH_2(CH_2)_nNH_2 \longrightarrow$$

$$[\{cis\text{-}PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)] \qquad n > 4$$

$$2trans\text{-}[PtCl_2(NH_3)_2] + H_2N(CH_2)_nNH_2 \longrightarrow$$

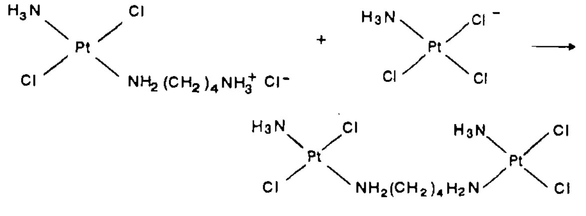
$$[\{trans\text{-}PtCl(NH_3)_2\}_2H_2N(CH_2)_nNH_2]Cl_2 \qquad n = 2\text{–}4$$

The synthesis of complexes containing inequivalent coordination spheres requires first the preparation of a precursor complex containing a diamine bound through only one end (a 'dangling' amine) and subsequent reaction of this precursor with a suitable target molecule to produce the bis(platinum) linkage. In its most general form

$$Pt(1)\text{–}H_2N\text{–}R\text{–}NH_3^+ + Pt(2) \longrightarrow$$

$$Pt(1)\text{–}H_2N\text{–}R\text{–}NH_2\text{–}Pt(2)$$

This approach has been exemplified in the preparation of the complex containing one *cis*-$[PtCl_2(amine)_2]$ and one *trans*-$[PtCl_2(amine)_2]$ group



This so-called 2,2/*c*, *t* complex is a unique example of coordination isomerism within one dinuclear structure as the ligands around each platinum atom are the same [3].

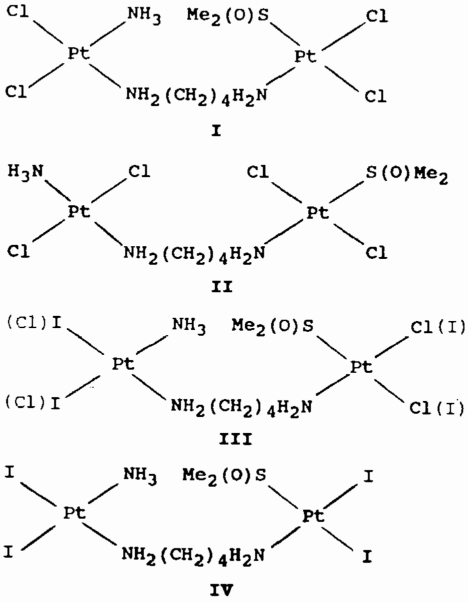
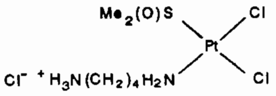


Fig. 1. Structures of dinuclear bis(platinum) complexes with inequivalent coordination spheres. Complex **III** is proposed as a mixed iodo/chloro species.

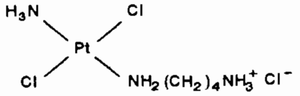
The rates of reaction of monomeric *cis*- and *trans*-$[PtCl_2(amine)_2]$ are different [13] and we would expect some selective reactivity between the two coordination spheres of the above complex. The individual reactions however may be hard to distinguish because of overlap of commonly monitored spectroscopic properties such as λ_{max} or $\delta(^1H$ or $^{195}Pt)$. To address the question of whether we could design dinuclear complexes capable of specific attack on one platinum atom we decided to prepare bis(platinum) complexes with two inequivalent coordination spheres, i.e. where the ligands around the platinum atom in the starting complex are not identical. Selective substitution may be favored by use of groups with strong *trans* influence. We reasoned therefore that a bis(platinum) complex where one coordination sphere contains a group such as Me_2SO *trans* to chloride and where the second coordination sphere contains groups such as amines with weak *trans* influence would be suitable complexes to study. Accordingly we prepared such species, Fig. 1. Characterisation data are given in Table 1.

Preparation of precursor complexes

The precursor complexes chosen were



A



B

The desired precursor **A** has been reported briefly [10] but no spectroscopic data were reported. The complex was prepared by acid cleavage of a chelate 1,4-butanediamine ring [9].

$$\textit{cis}\text{-}[PtCl(Me_2SO)(H_2N(CH_2)_4NH_2)]^+ + HCl \longrightarrow$$
$$\textit{cis}\text{-}[PtCl_2(Me_2SO)(H_2N(CH_2)_4NH_3)]Cl$$

A

Spectroscopic data (see 'Experimental') were fully consistent with the structure.

Precursor **B** is formed in the reaction of the doubly-bridged tetra-amine complexes with HCl to give the bis(platinum) complex with two *trans*-$[PtCl_2(amine)_2]$ units [5].

$$[\{Pt(NH_3)_2\}_2(H_2N(CH_2)_4NH_2)_2]Cl_4 + HCl \longrightarrow$$
$$[\{\textit{trans}\text{-}PtCl_2(NH_3)\}_2H_2N(CH_2)_4NH_2]$$
$$+\,\textit{trans}\text{-}[PtCl_2(NH_3)(H_2N(CH_2)_4NH_3)]Cl$$

B

Complexes of this type have been briefly reported by acid cleavage of the 1,4-butanediamine ring in $[PtCl(NH_3)(H_2N(CH_2)_4NH_2)]^+$ [14].

Although the desired precursor monomers may be prepared from chelated 1,4-butanediamine we note that a more general method for synthesis of precursors with dangling diamines of any length is to use the blocked diamines such as $H_2N\text{–}R\text{–}NH(t\text{-}Boc)$ (Boc = *N*-tert-butoxycarbonyl) [15]. Upon binding the blocking group is easily removed with weak acid such as HCl. Thus

$$Pt\text{–}Cl + NH_2\text{–}R\text{–}NH(t\text{-}Boc) \longrightarrow$$
$$Pt\text{–}NH_2\text{–}R\text{–}NH(t\text{-}Boc)^+Cl^-$$
$$Pt\text{–}NH_2\text{–}R\text{–}NH(t\text{-}Boc) + HCl \longrightarrow$$
$$Pt\text{–}NH_2\text{–}R\text{–}NH_3{}^+Cl^-$$

Preparation of dinuclear platinum complexes with inequivalent coordination spheres

Incorporation of two different coordination spheres occurs upon reaction of the precursors with suitable target monomers. In our experience it is best to choose as target a complex with only one reactive site (Pt–Cl or Pt–I bond in these examples). In this way side reactions such as displacement of more than one ligand can be minimised. For the synthesis of the bis(platinum) complex, use of the *trans* effect gives the correct isomer.

$$\textit{cis}\text{-}[PtCl_2(Me_2SO)(H_2N(CH_2)_4NH_3)]Cl + K[PtCl_3(NH_3)] \longrightarrow$$
$$[\{\textit{cis}\text{-}PtCl_2(Me_2SO)\}(H_2N(CH_2)_4NH_2)\{\textit{cis}\text{-}PtCl_2(NH_3)\}]$$

I

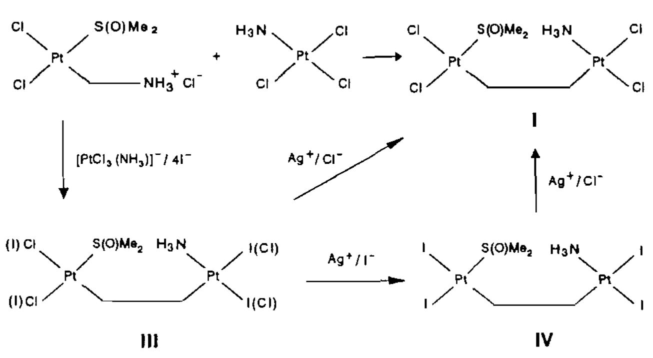
The yield in this instance is rather low and a study of the reaction by ^{195}Pt NMR in d_7-DMF showed that a competitive reaction is ring closure of the 1,4-butane-

TABLE 1. Spectroscopic data for dinuclear bis(platinum) complexes containing inequivalent coordination spheres

Complex	IR (cm^{-1})[a]			NMR, δ (ppm)[b]		
	ν(Pt–Cl)/ν(Pt–S)	ν(SO)	ν(NH)	^1H		^{195}Pt
				diamine	Me_2SO	
I	310	1110	3200, 3115	2.83, 1.82	3.49	−2188, −3125
II	330	1115	3260, 3200, 3110	2.74, 1.84	3.42	−2172, −3131
IV		1110	3200, 3120	3.00, 1.81	3.75	−3374, −4230
V	347	1130	3280, 3220 3140	2.57, 1.65	3.31	−3120

[a] KBr discs. [b] $\delta(^1H)$ relative to TMS, $\delta(^{195}Pt)$ relative to external solution of Na_2PtCl_6 in D_2O. Complexes **I**, **II** and **V** in d_7-DMF, complex **III** in d_6-acetone.

diamine ring. This side reaction would be minimised for longer chain diamines. In attempts to increase the yield we used a modification of Dhara's method for the preparation of cisplatin [16]. The scheme developed is shown below. Addition of I^- to the solution of the $K[PtCl_3(NH_3)]$ anion resulted in formation of complex **III** which in principle would be a mixed chloro/iodo complex [{*cis*-$PtCl_2(Me_2SO)$}$(H_2N(CH_2)_4NH_2)$-{*cis*-$PtI_2(NH_3)$}]. The complex gave an elemental analysis consistent with this formulation but both ^1H and ^{195}Pt NMR spectra were complicated with a greater number of peaks than predicted. It is possible that rapid scrambling between the iodo and chloro ligands produce in



(Note that the bridging symbol in the schemes refers to $H_2N(CH_2)_4NH_2$ for clarity)

solution rapid scrambling between the iodo and chloro ligands produce in solution a number of different species complicating the spectra. Nevertheless, complex **III** could be converted to both **I** and the iodo derivative **IV** in slightly higher yields than the direct method. The method was not, however, as clean as we had hoped presumably due to the mixed nature of the intermediate **III**.

To obtain the isomeric complex with both *trans* coordination spheres the precursor **B** is allowed to react with the $[PtCl_3(Me_2SO)]$ anion. In this case substitution must occur *trans* to the Me_2SO ligand

$$\textit{trans}\text{-}[PtCl_2(NH_3)(H_2N(CH_2)_4NH_3]Cl + K[PtCl_3(Me_2SO)] \longrightarrow$$
$$[\{\textit{trans}\text{-}\{PtCl_2(NH_3)\}(H_2N(CH_2)_4NH_2)\{\textit{trans}\text{-}PtCl_2(Me_2SO)\}]$$
$$\mathbf{II}$$

In contrast to the formation of **I**, this reaction is quite clean – the *trans* influence of Me_2SO facilitates the displacement of one unique chloride and the absence of Me_2SO in the precursor appears to retard the competitive chelation of the 1,4-butanediamine ligand.

The spectral data are consistent with the presence of two inequivalent coordination spheres for complexes **I**, **II** and **IV**, Table 1. The ^{195}Pt NMR spectrum of complex **I** (Fig. 2) clearly shows the presence of two peaks at −2188 and −3125 ppm which correspond to a $PtCl_2N_2$ and $PtCl_2SN$ coordination sphere, respectively [17]. Likewise **II** shows two peaks at −2172 and −3131 ppm. The difference in linewidth is presumably because of the different number of ^{14}N nuclei bound to the independent Pt atoms. The integration is approximately

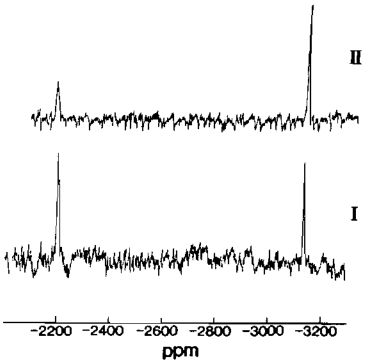


Fig. 2. ^{195}Pt NMR spectra for complex **I**, [{*cis*-$PtCl_2$-(NH_3)}–$NH_2(CH_2)_4H_2N$–{*cis*-$PtCl_2(Me_2SO)$}] and complex **II**, [{*trans*-$PtCl_2(NH_3)$}–$NH_2(CH_2)_4H_2N$–{*trans*-$PtCl_2(Me_2SO)$}].

1:1 in both cases. The ^{1}H NMR spectrum of both complexes is simple with the expected integral of one Me_2SO to one diamine (in d_7-DMF the protons of the amine-bound carbons are obscured by solvent). The IR spectra are also consistent with the structures and we note that the *trans*-geometry gives three bands in the ν(NH) region as previously noted [5].

The ^{195}Pt NMR chemical shifts for **IV** are assigned as -3374 ($[PtI_2(amine)_2]$) and -4230 ($[PtI_2(Me_2SO)(amine)]$). There is some discrepancy in the literature assignments of the species *cis*-$[PtI_2(NH_3)_2]$ – assigned as -3198 ppm in H_2O [18] and -3636 ppm in Me_2SO [19]. Both of these values were obtained in studies of hydrolysis and solvolysis of Pt–amine complexes. Allowing for discrepancies due to concentration, solvent and temperature effects [17] this difference is still large. Stepwise substitution of one ligand by another can produce systematic chemical shifts in a well defined series of complexes. In Pt–amine complexes ^{195}Pt chemical shifts are usually shifted -500 to -600 ppm upon replacement of Cl^- by I^- [18]. Therefore a value of approximately -3200 ppm for *cis*-$[PtI_2(NH_3)_2]$ is expected. The value of -3636 ppm for *cis*-$[PtI_2(NH_3)_2]$ in Me_2SO may better be assigned to a species such as $[PtI(NH_3)_2(Me_2SO)]^+$. The chemical shift found for the *cis*-$[PtI_2(NH_2R)(Me_2SO)]$ moiety of **IV** is consistent with literature values [19] and our studies. We have measured the ^{195}Pt NMR chemical shift of *cis*-$[PtI_2(NH_3)(Me_2SO)]$ (prepared from *cis*-$[PtCl_2(NH_3)(Me_2SO)]$ [20] as -4421 ppm in d_6-acetone.

Substitution reactions of bis(platinum) complexes with inequivalent coordination spheres

Complexes **I** and **II** are only sparingly soluble in solvents such as DMF. We therefore chose to study complex **IV** because the presence of iodo ligands renders this complex readily soluble in acetone. Pyridine was chosen as incoming nucleophile because its reactions have been much studied in monomeric compounds [21–23] and because the donor properties are somewhat similar to the purine and pyrimidine bases of biological interest.

The reactions with complex **IV** were followed by ^{195}Pt NMR spectroscopy, Fig. 3. When 1 equiv. of pyridine was added to **IV** in d_6-acetone the peak corresponding to the $[PtI_2(Me_2SO)(NH_2R)]$ coordination sphere, spectrum I, changes cleanly to a peak at -3982 ppm assigned as due to $[PtI(py)(Me_2SO)(NH_2R)]$ unit, spectrum II. The peak corresponding to $[PtI_2(NH_3)(NH_2R)]$ is unchanged. Over time the system becomes unfortunately complicated by side reactions including isomerisation of the initially formed $[PtCl(Me_2SO)(pyridine)(amine)]$ species. This is evidenced by the appearance of new peaks in the -3900 to -4100 ppm region of the spectrum. The assignment of the peak at -3982 ppm as due to $[PtI(py)(Me_2SO)(amine)]$ is based on the trends in known monomer complexes [17, 23]. To confirm the isomerisation reaction we studied the monomer *cis*-$[PtI_2(Me_2SO)(NH_3)]$. Treatment with 1 equiv. of pyridine gave again a number of peaks associated with isomerisation (data not shown). Interestingly, the reaction of the monomer appears slower than the dinuclear species.

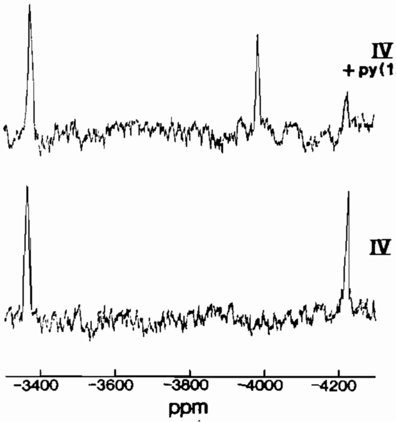


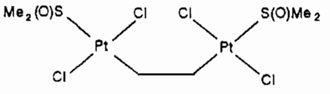
Fig. 3. ^{195}Pt NMR spectral changes for complex **IV**, $[\{cis\text{-}PtI_2(NH_3)\}\text{–}NH_2(CH_2)_4H_2N\text{–}\{cis\text{-}PtI_2(Me_2SO)\}]$ upon addition of pyridine in acetone. The reaction spectrum was recorded within 10 min of addition of the pyridine ligand.

The reactions of complex **IV** with excess of pyridine also proved to be complicated. In the presence of 1:4 pyridine the $[PtI_2(Me_2SO)(amine)]$ species immediately disappears and after 30 min only two peaks are observed at -3169 and -3370 ppm. No evidence for a coordination sphere such as $[Pt(amine)_2(pyridine)_2]^{2+}$ in the -2500 to -3000 ppm region was found. A large excess of pyridine (1:10) resulted in loss of Me_2SO.

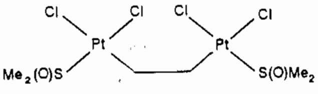
In summary, the reactivity of the $[PtI_2(Me_2SO)(amine)]$ unit prevented us from studying the stepwise substitution of pyridine and the reaction was further complicated by isomerisation of the $[PtCl(Me_2SO)(amine)(pyridine)]^+$ intermediate but nevertheless it is clear that the initial substitution reaction occurred specifically at the $[PtI_2(Me_2SO)(amine)]$ center.

Isomerisation reactions of bis(platinum) complexes

The isomerisation reaction noted in bis(platinum) complexes is interesting because isomerisation appeared to occur without bridge cleavage. The reaction is a further example of the capability of bis(platinum) complexes to undergo specific reactions at only one center. To examine this aspect further we examined the *trans*/*cis* isomerisation for



V



VI

The known *trans* isomer, **V**, is prepared from the reaction [9]

$$cis\text{-}[PtCl_2(Me_2SO)_2] + 1{,}4\text{-}H_2N(CH_2)_4NH_2 \longrightarrow \underset{\mathbf{V}}{[trans\text{-}\{PtCl_2(Me_2SO)\}_2H_2N(CH_2)_4NH_2]}$$

Monomeric species of this type are known to undergo isomerisation in various solvents, including Me_2SO [23–26]. The rate of isomerisation is dependent on solvent and ligand (e.g. Cl, Br, I). In dinuclear complexes, if bridge cleavage was to occur immediately two species would be produced – $[PtCl_2(Me_2SO)(amine)]$ and a chloro-dimethyl sulfoxide species such as $[PtCl_2(Me_2SO)_2]$. These two products are easily recognisable by their different ^{195}Pt NMR chemical shifts. In d_7-DMF no change is observed in the ^{195}Pt NMR spectrum of **V** but in d_6-Me_2SO the initial reaction is isomerisation and a *cis/trans* mixture is attained within a few hours, Fig. 4:

$$\underset{\mathbf{V}}{[trans\text{-}\{PtCl_2(Me_2SO)\}_2H_2N(CH_2)_4NH_2]} \longrightarrow \underset{\mathbf{VI}}{[cis\text{-}\{PtCl_2(Me_2SO)\}_2H_2N(CH_2)_4NH_2]}$$

Over a period of time a peak corresponding to *cis*-$[PtCl_2(Me_2SO)_2]$ appears indicating bridge cleavage. However, the initial reaction is clearly that of isomerisation. In the ^1H NMR spectrum a new set of Me_2SO resonances corresponding to the *cis* isomer at δ 3.52 ppm appears on the same time scale as the ^{195}Pt NMR spectral changes. The bridging diamine protons are indistinguishable.

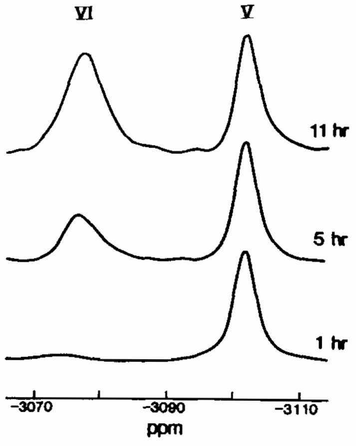


Fig. 4. Isomerisation of complex **V**, $[trans\text{-}\{PtCl_2(Me_2SO)\}_2\text{-}H_2N(CH_2)_4NH_2]$ in d_6-Me_2SO followed by ^{195}Pt NMR spectroscopy.

Conclusions

Dinuclear platinum complexes with inequivalent coordination spheres can be designed which are capable of selective substitution reactions on one platinum center. Further, isomerisation reactions can occur competitive with cleavage of the diamine bridge. While our principal interest so far has been in the biological activity of bis(platinum) species these fundamental features of their chemistry have implications not only in DNA binding but also indeed in the possible use of bis(platinum) complexes in catalysis. With respect to DNA binding, bis(platinum) complexes produce a variety of adducts. In the specific case of bis(platinum) complexes with bidentate coordination spheres such as $[\{cis\text{-}PtCl_2(NH_3)\}_2(NH_2(CH_2)_nNH_2)]$, adducts similar to cisplatin are formed as well as structurally unique interstrand crosslinks by binding of one Pt atom to each strand of DNA [27]. A critical hypothesis under investigation is that the array of 'non-cisplatin' like adducts dictates the pattern of antitumor activity and its similarity or otherwise to the parent cisplatin. The ability to produce selective attack on one platinum center shows that it is possible to design complexes capable of producing unique DNA-binding profiles, even in the presence of one *cis*-$[PtCl_2(amine)_2]$ unit.

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