Inorganica Chimica Acta, 8 (1974) 105–127

Monodentate Amine Complexes of Platinum(II)

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Received August 30, 1973

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1. Introduction

Complexes of platinum(II) have a d^8 electronic configuration and, as in the case of other d^8 systems show considerable thermodynamic stability and inertness to reaction. The most prevalent stereochemistry in this system is square-planar and the factors favouring this configuration are outlined elsewhere.[1]

Monodentate amines are of the general formula NR_3 where R is either H or an alkyl or aryl group and these molecules, having N (a first row element) as their donor atom, do not take part in out-of-plane π-bonding as do phosphines.

Neutral, anionic and cationic complexes of platinum(II) with monodentate amines (primary, secondary and tertiary) are known and are of the general types: *cis*- and *trans*-$[PtL_2X_2]$, $[PtLX_3]^-$, $[PtL_3X]^+$ and $[PtL_4]^{2+}$ where L = monodentate amine and X = singly charged anionic ligand. Also known are complexes of mixed monodentate amines with bi- or tri-dentate amines. These may be formulated as e.g. $[PtL'LX]^+$ and $[PtL''L]^{2+}$ where L′ = bidentate and L″ = tridentate amine.

This survey sets out to review the literature relating to these complexes from 1960 to the beginning of 1973. It is pertinent to do this at this time. The recent discoveries that some simple amine complexes of platinum(II) possess potent antitumour activity makes a review of the chemistry of these compounds timely.

Because of the way in which the chemistry of these simple compounds has diversified it has been found that a number of papers do not readily fit into the scheme of this review; we have thus added an appendix in order to include such papers.

2. Preparations

Several methods are available for the preparation of *cis*-dichlorodiammineplatinum(II), and are outlined below:

(i) $$K_2PtCl_4 + \underset{\text{equimolar amounts}}{\text{aq.}(\text{conc.}\,HCl + NH_4Cl)} + \underset{\text{slight excess}}{NH_4OH} \xrightarrow{\text{store at } 0^\circ\text{C for 48 h}} 60\%\ \text{yield}$$ [2]

(ii) $$K_2PtCl_4 + NH_4Cl + \text{conc.}\ NH_3 \xrightarrow{\text{stir at room temp. for 3–4 h}} 90\%\ \text{yield}$$ [3]

(iii) $$\begin{tikzcd} K_2PtCl_4 \arrow[r, "KI"] & K_2PtI_4 \arrow[r, "NH_4OH/KI"] & cis\text{-}[Pt(NH_3)_2I_2] \arrow[d, "AgNO_3\ (\text{ref. }4)"] \\ & cis\text{-}[Pt(NH_3)_2Cl_2] & cis\text{-}[Pt(NH_3)_2(H_2O)_2]^{2+} \arrow[l, "KCl"'] \end{tikzcd}$$

The corresponding *trans* complex is usually prepared by dissolving K_2PtCl_4 in an aqueous solution of conc. $HCl + NH_4OH$ and subsequently evaporating nearly to dryness. A large excess of 6*M* HCl is added and the solution evaporated to 20 ml. The solid formed is filtered off.[2]

Both *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ are recrystallised from dilute HCl, and thin-layer[5,6] and paper[7,8] chromatographic techniques have been used to separate mixtures of the geometric isomers and as purity checks.

These complexes are useful starting materials in the preparation of many other platinum amine compounds, and some of these preparations are summarised in Figures 1 and 2.

Another common and readily available starting material is K_2PtCl_4 and some preparations starting from this material are presented in Figure 3.

Complexes containing amines and many other ligands may be prepared by substitution reactions as in Figures 1 and 2 and also as:

(iv) $[Pt(dien)Br]^+ + \text{excess aq. } RNH_3{}^+NO_3{}^- \rightarrow [Pt(dien)(RNH_2)]^{2+}$ [25]

(v) $\text{boiling}[Pt(MeNH_2)_2Cl_2] + \text{aq. AcOH} + KNO_2 \rightarrow [Pt(MeNH_2)_2(NO_2)_2]$[26]

(vi) $\text{cold}[Pt(MeNH_2)_2Cl_2] + KCN \xrightarrow{\text{constant stirring}} [Pt(MeNH_2)_2(CN)_2]$[26]

(vii) $\text{cold}[Pt(MeNH_2)_2Cl_2] + KSCN \xrightarrow{\text{constant stirring}} [Pt(MeNH_2)_2(SCN)_2]$[26]

(vii) $trans\text{-}[PtCl_2(NH_3)(3\text{-pic})] + \underset{5\%}{\text{aq. } NH_3} \xrightarrow[\text{30–40 min}]{\text{water bath}} [Pt(NH_3)_3(3\text{-pic})]Cl_2$[11]

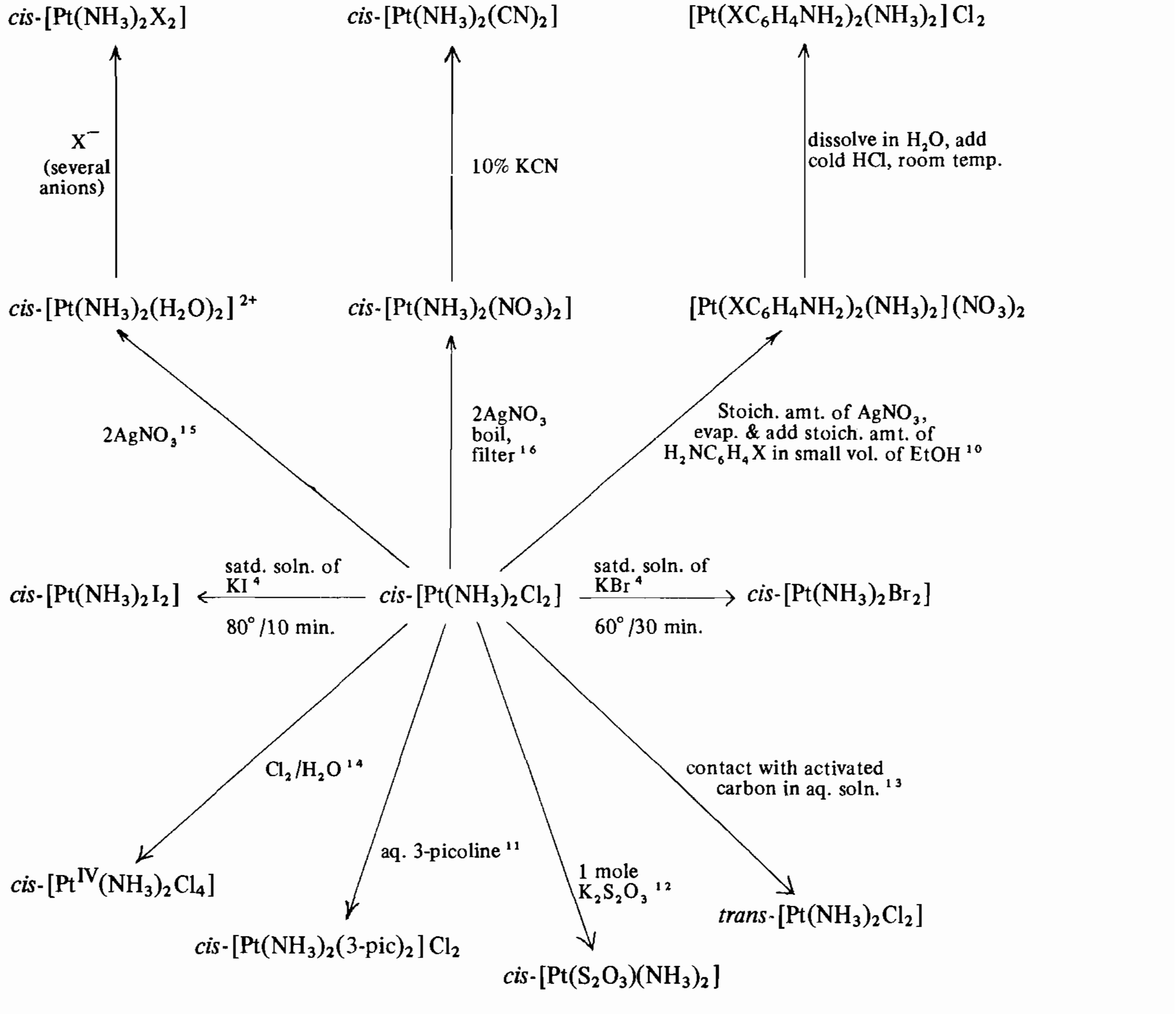
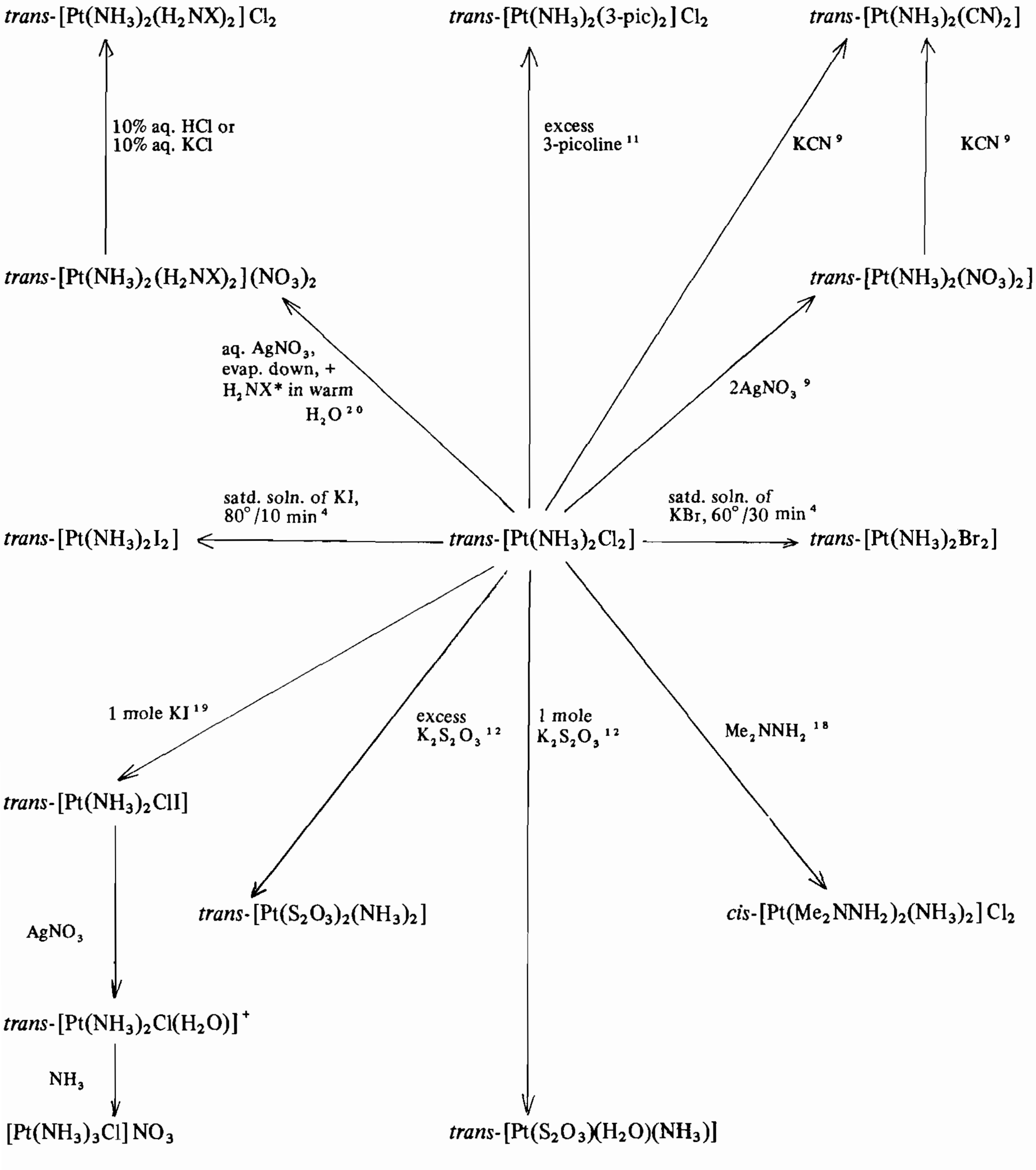


Figure 1. Some complexes prepared from *cis*-$[Pt(NH_3)_2Cl_2]$.

Russian workers[27–31] have used dimethyl sulphoxide in the preparation of compounds containing amines. The advantage of using this ligand is its high *trans*-directing influence. Some reactions are illustrated:

(ix) $K_2PtBr_4 + Me_2SO \rightarrow K[Pt(Me_2SO)Br_3]$[27]

(x) $K[Pt(Me_2SO)Br_3]$ + equimolar amount of amine → *trans*-$[Pt(am)(Me_2SO)Br_2]$ (am = NH_3, py, $MeNH_2$, $EtNH_2$)[27]



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*X = phenyl or substituted phenyl group.

Figure 2. Some complexes prepared from *trans*-$[Pt(NH_3)_2Cl_2]$.

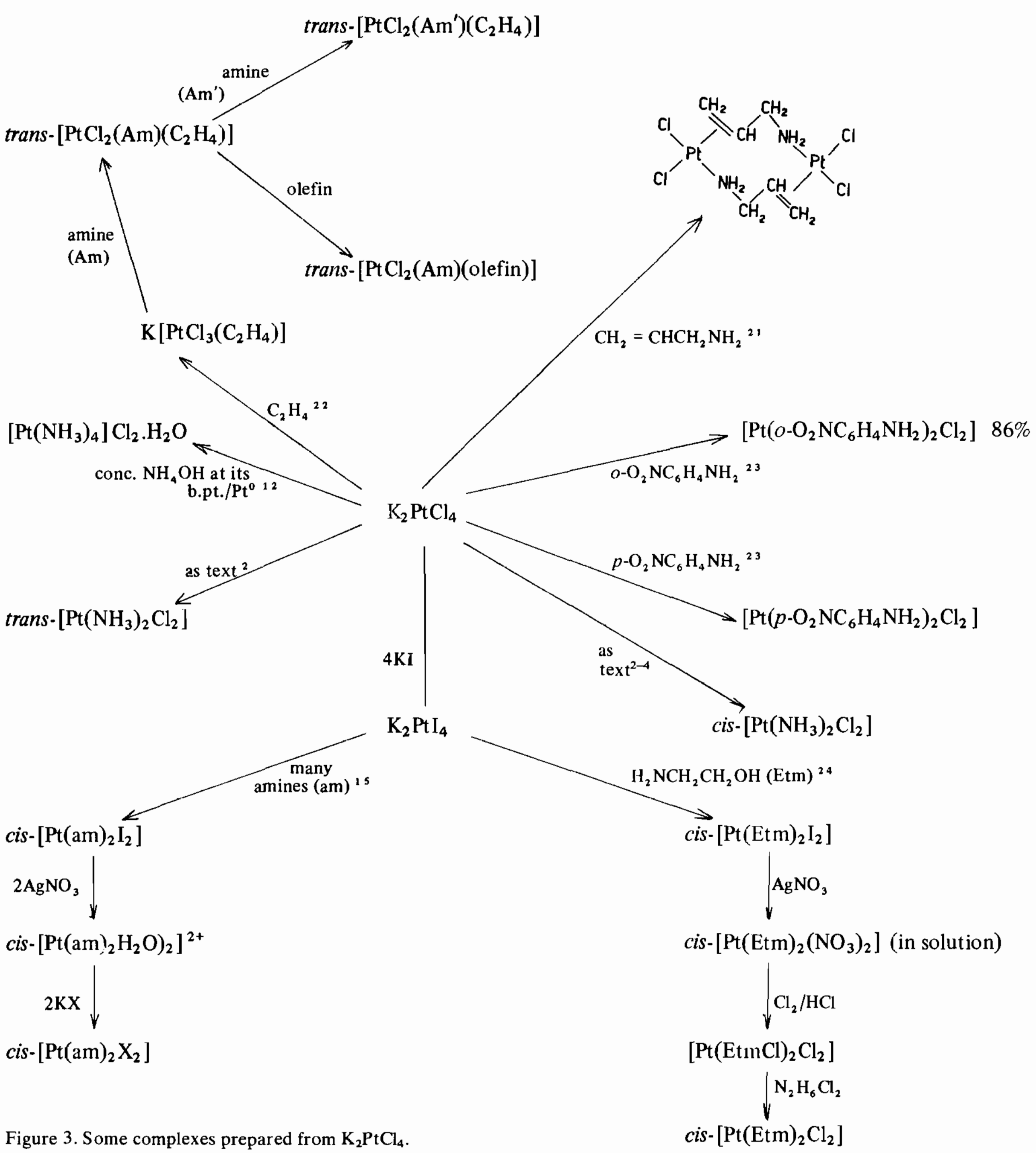


Figure 3. Some complexes prepared from K_2PtCl_4.

Similar reactions occur starting from K_2PtCl_4[28,29]. These compounds with $MeNH_2$ and $EtNH_2$ isomerise to the *cis* form on heating[27] as does the pyridine complex *trans*-$[Pt(py)(Me_2SO)Cl_2]$ when heated at 145° C for three hours.[28]

Compounds containing Me_2SO in the *cis* position to an amine can be prepared by reaction of monoamine complexes with Me_2SO as in:[27,30]

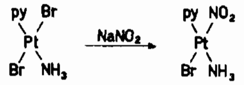
(xi) $K[Pt(py)Cl_3] + Me_2SO \rightarrow$ *cis*-$[Pt(py)(Me_2SO)Cl_2]$

(xii) $K[Pt(NH_3)Cl_3] + Me_2SO \rightarrow$ *trans*-$[Pt(NH_3)(Me_2SO)Cl_2]$

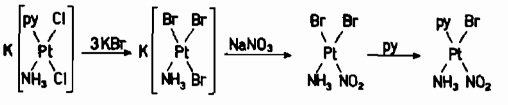
Attempts to prepare analogous compounds containing I^- and NO failed. The coordinated Me_2SO may be reduced by HCl to Me_2S.[30]

Essen and Bukhtiyarova[30] have reported the preparation of the three isomers of [PtBr(NO$_2$)(py)(NH$_3$)] by the following reactions.

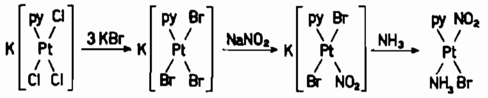
(xiii)



(xiv)

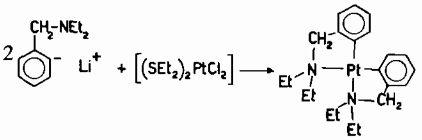


(xv)



The complex *cis*-[2-(diethylaminomethyl)phenyl]-platinum(II) has been prepared.[32] The ligand is coordinated to the platinum atom by the amino group and also by the carbon atoms ortho to the amine substituent. N,N-diethylbenzylamine (DEBA) is first metallated in the ortho position by treatment with ^{n}BuLi or magnesium metal. The reaction of this product with [(SEt$_2$)$_2$PtCl$_2$] (as below) forms the product:

(xvi)



Only the *cis* form is produced.

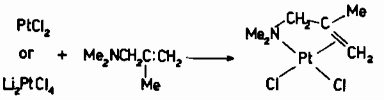
Simultaneous crystallisation of the complexes *trans*-[Pt(NH$_3$)$_2$(CN)$_2$] and *trans*-[Pt(NH$_3$)$_2$(NO$_2$)$_2$], after heating them in boiling water for four hours, leads to scrambling of the two acido ligands to form *trans*-[Pt(NH$_3$)$_2$(CN)(NO$_2$)]. The preparations of *trans*-[Pt(NH$_3$)$_2$(CN)X] where X = Cl or Br are similar.[33]

A carbon monoxide adduct, *trans*-[(CO)PtCl$_2$L] has been prepared as follows,[34] (L = NH$_2$R where R = CHMePh or CH$_2$CH$_2$Me).

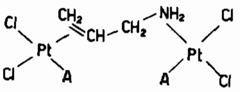
$$\text{(xvii)}\ [(C_2H_4)PtCl_3]^- + L \rightarrow trans\text{-}[(C_2H_4)PtCl_2L] \xrightarrow{CO} trans\text{-}[(CO)PtCl_2L].$$

Allylamine complexes of platinum(II) may be coordinated through both the double bond and amine group[21,35] or through the double bond only.[36] Reaction of either PtCl$_2$ or Li$_2$PtCl$_4$ with N,N-dimethyl-2-methylallylamine leads to the formation of 2-methyl-3-(dimethylamino)propenylplatinum(II) chloride in 46% yield.[37]

(xviii)



Reaction of chloroplatinites(II) with allylamine itself forms the binuclear [PtCl$_2$(CH$_2$:CHCH$_2$NH$_2$)]$_2$,[21] the structure of which is shown in Figure 3. A binuclear complex [Pt$_2$A$_2$(CH$_2$:CHCH$_2$NH$_2$)Cl$_4$] is also formed by reaction of allylamine with M[PtACl$_3$](M = K$^+$, pyridinium, or NH$_4^+$; A = py or NH$_3$),[21] but here there is only one allylamine bridging group:



Venanzi and co-workers[38] have studied a number of platinum(II) complexes with unsaturated amines. Allylamine complexes, PtCl$_2$L.HCl (L = CH$_2$:CHCH$_2$NR$_2$), have been shown to be olefin complexes of the cationic species LH$^+$, with structures analogous to Zeise's salt; corresponding complexes of 2° bases, CH$_2$:CHCH$_2$NHR, are probably polymeric. Similar PtCl$_2$.LHCl complexes were obtained with butenylamines and pentylamines, which, upon neutralisation, produced dimeric complexes [PtLCl$_2$]$_2$. The thermodynamics of formation of some platinum(II) and silver(I) complexes with these ligands, and their ultraviolet spectra have also been studied by Venanzi's group.

The Magnus type salts [Pt(NH$_3$)$_4$][PtX$_4$] where X = CN or SCN have been prepared.[17,37] The first complex, [Pt(NH$_3$)$_4$][Pt(CN)$_4$], has been the product of several attempts to prepare *cis*-[Pt(NH$_3$)$_2$(CN)$_2$]. Chernyaev and co-workers[9] have reported the preparation of the *cis* compound but Evstaf'eva *et al.*[17] contest this since all their attempts produced the Magnus type salt. The preparation of the salt, [Pt(NH$_3$)$_4$][Pt(SCN)$_4$], which is pink is by a route similar to the appearance of Magnus' green salt during the preparation of *cis*- and *trans*-[Pt(NH$_3$)$_2$Cl$_2$], i.e.:

$$\text{(xix)}\ [Pt(NH_3)_4]Cl_2 + K_2[Pt(SCN)_4] \rightarrow [Pt(NH_3)_4][Pt(SCN)_4]$$

Stability and Instability Constants

Grinberg and his co-workers have studied the instability constants of several ammine and amine complexes.[38–43] Some of their results are included in Table I.

These results show that the bromo complexes are more stable than the corresponding chloro complexes and that the *trans* complexes are more stable than the corresponding *cis* complexes.

K^c is the overall stability constant for the complexes. For the complexes [PtA$_2$X$_2$] it is a measure of the equilibrium constant for the reaction:

$$\text{(xx)}\ PtA_2X_2 \rightleftharpoons Pt^{2+} + 2A + 2X^-$$

and is represented by the relation:

TABLE I. Instability Constants for the Removal of the First X^- Ion (X = Cl, Br).

Complex or Complex Ion	Instability Constant	Reference
$[PtBr_4]^{2-}$	2.4×10^{-3}	38
	3.0×10^{-3}	43
$[Pt(NH_3)Br_3]^-$	4.0×10^{-3}	38
cis-$[Pt(NH_3)_2Br_2]$	1.4×10^{-3}	38
trans-$[Pt(NH_3)_2Br_2]$	1.0×10^{-3}	38
$[Pt(NH_3)_3Cl]^+$	0.3×10^{-4}	40
$[PtCl_4]^{2-}$	1.7×10^{-2}	43
$[Pt(NH_3)Cl_3]^-$	8.0×10^{-3}	43
cis-$[Pt(NH_3)_2Cl_2]$	4.0×10^{-3}	43
trans-$[Pt(NH_3)_2Cl_2]$	0.8×10^{-3}	43

$$\text{(xxi)}\quad K^c = [Pt^{2+}][A]^2[X^-]^2 \Big/ [PtA_2X_2]$$

Some values of pK^c are given in Table II.[39]

Grinberg and Gel'fman[44] report an extremely large increase in the compound stability of $\Delta pK^c = 7.5$ on introduction of one NH_3 molecule into the $[PtCl_4]^{2-}$ ion. On passing from monoammine to a *trans* diammine complex the increase is not so great and $\Delta pK^c = 4.3$. On introduction of the third ammine molecule ΔpK^c increases by about the same amount again ($\Delta pK^c = 4.5$).

3. Spectroscopic Studies

A. Infrared Studies

(i) Amine complexes with simple mono- and bidentate acido ligands

Infrared studies of platinum(II) ammine complexes have been carried out for complexes with the acido ligands X^- (halide)[45–49] and SO_3^{2-},[50,51] while with allylamine complexes the acido ligands X^- [52–59] and DMSO[30] have been studied. The double Magnus type salts of formula $[Pt(amine)_4][PtX_4]$ have also been investigated for NH_3[45,46] and $MeNH_2$[126] with X = Cl or Br.

TABLE II. Values of pK^c for some Amine Complexes of Platinum(II).

Complex or Complex Ion	pK^c
$[Pt(NH_3)Cl_3]^-$	24.1
cis-$[Pt(NH_3)_2Cl_2]$	29.5
trans-$[Pt(NH_3)_2Cl_2]$	28.4
$[Pt(NH_3)_3Cl]^+$	32.8
cis-$[Pt(MeNH_2)_2Cl_2]$	30.5
trans-$[Pt(MeNH_2)_2Cl_2]$	30.7
cis-$[Pt(NH_3)_2I_2]$	32.3
trans-$[Pt(NH_3)_2I_2]$	32.7
cis-$[Pt(MeNH_2)_2I_2]$	34.7
trans-$[Pt(MeNH_2)_2I_2]$	34.2

Table III summarises the ammonia deformation and rocking frequencies and the asymmetric metal–nitrogen and metal–halogen vibrations for a series of diacidodiammineplatinum(II) complexes.

According to Babaeva and Evstaf'eva,[60] the *cis*-diacidodiammine complexes all show two bands in the region of the rocking and symmetrical deformations of NH_3 but the assignments given by both Clark and Williams[46] and Nakamoto *et al.*[4] give only one band in the rocking region of NH_3 in *cis*-$[Pt(NH_3)_2X_2]$, X = Cl, Br, I. Nakamoto assigns a weak band at 806 cm^{-1} to the symmetrical deformation of NH_3 while Babaeva and Evstaf'eva suggest a band at 807 cm^{-1} of strong intensity to be the NH_3 rocking deformation.

Nakamoto and his co-workers[4] have drawn attention to the bands at around 1580 cm^{-1}, the NH_3 degenerate deformation bands, which are split into two or three peaks in the dihalogenodiammineplatinum(II) complexes. The magnitude of the splitting is between 140 and 65 cm^{-1} for all the compounds including the deuterated analogues. The splitting seems to be a characteristic feature of square-planar platinum(II) complexes containing at least two ammine groups, but there is no evident correlation between the number of bands and the structure of the complex, or the nature of the ligands involved. The splitting is explained by postulating that one hydrogen atom from each of the NH_3 groups in the yz plane interacts with one of the filled platinum d orbitals, the d_{yz}. Any bending of the H–N–H angle would result in a slight weakening or strengthening of this hydrogen–electron interaction, which might in turn cause some local variation in electron density within the d orbital. Transmission of this effect through the orbital would affect the strength of the other hydrogen–electron interaction. By normal coordinate analysis, such an interaction leads to two different frequencies for the ammonia deformation. Further evidence is provided in the palladium(II) ammine complexes which do not show a similar splitting since the 4d orbital of the palladium atom is spacially less extensive than the 5d orbitals of the platinum atom.

From the data of Table III it can be seen that on comparing the changes in the symmetrical vibration frequencies of ammonia when going along the series Cl^- to I^-, the change is insignificant in the *trans*-dihalogenodiammines but in the corresponding *cis* complexes the observed frequencies decrease noticeably.

The Pt–X (X = halogen) stretching vibration decreases in frequency going along the same series as the halogen increases in weight, due to the decrease in the Pt–X force constants.[49]

The *cis* isomers, having symmetry C_{2v}, are expected to show two infrared active Pt–X stretchings (A_1 and B_2), whereas the *trans* isomers, having symmetry C_{2h},

TABLE III. Spectroscopic Data of some Diacidodiammineplatinum(II) Complexes $[Pt(NH_3)_2X_2]^a$.

Complex X	NH_3 deformations						NH_3 rock		ν(Pt–N)		ν(Pt–X)		Ref.
	degenerate			symmetric					asym.		asym.	sym.	
cis Cl	1625w		1544w	1316s	1301m		765s			510w	330s	323s	46
	1625		1544	1316	1301		795		517	508	(324)	317	4
							807	787m					60
cis Br	1630s		1530s	1308s	1294s		798m	774m					60
	1623		1523	1307	1288		774		513	499		226	4
cis I	1620s		1525s	1290s	1276s		762m	750w					60
	1604		1532	1293	1278	806	752		491	477			4
trans Cl	1627w		1530w		1290vw		825mw	804mw	509w		330s		46
	1635	1597	1538	(1307)	1294		819		509		330	322	4
trans Br	1639s	1594s	1541s		1288s		820m		504				60
	1627	1587	1537		1289		813		502			237	4
trans I	1630s		1536s		1290s		815m						60
	1620	1579	1534		1290		806		498				4
cis CN	1642	1598		1332	1325	1312	859	813	430		441		133
							784	768i					
cis SCN	1630mw	1579w			1289w		822w	760s	485vw		299s		46
	1644s	1560s		1541s	1522s	1321s	964vw	937vw					60
				1285s			878vw	859w					
							805m	775m					
cis NO_2	1651s			1300s	1280s		832s	801m					60
							775m						
trans CN	1670	1595			1328		835		458		407		65
trans SCN	1655w	1560w		1328m	1312s		863w	838mw	508vw		268s		46
	1659s			1542s	1526s	1316s		833m					60
trans NO_2	1659s				1294s			830s					60

[a] All assignments in cm^{-1}. Assignments in parentheses are tentative.

are expected to give only one (B_u). In general the antisymmetric M–X stretching band is stronger and is found at higher frequency than the symmetrical M–X stretch.[61]

Hirashi *et al.*[45] assign two bands at 236 and 221 cm^{-1} in *cis*-$[Pt(NH_3)_2Br_2]$ to the Pt–Br stretching vibrations. Other workers' results[46,48] agree with this but Nakamoto *et al.*[4] and Poulet and co-workers[48] assign two bands in the spectrum of *trans*-$[Pt(NH_3)_2Cl_2]$ at 330 and 322 cm^{-1} as Pt–Cl stretching bands, Nakamoto pointing out the band at 322 cm^{-1} as a shoulder.

It is dangerous, therefore, to undertake configurational assignments on the basis of this type of far infrared data alone. Tobe[62] says that the far infrared test is grossly overrated, and both his results and those of Beaumont and McAuliffe[63] show that in the series of complexes *cis*-$[Pt(cycloamine)_2Cl_2]$ where cycloamine = cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclohexylamine, cycloheptylamine or cyclooctylamine, the *cis* isomer shows a broad absorption in the region 290 to 340 cm^{-1}, centred at 312–320 cm^{-1}.[63] It is possible that this can be explained by some form of hydrogen bonded interaction.

Hirashi and co-workers[45] have studied the far infrared spectra of $[Pt(NH_3)_4]Cl_2.H_2O$ and $K[Pt(NH_3)Cl_3]$. In the former complex they assign the band at 510 cm^{-1} to the asymmetric Pt–N stretching vibration, which is about the same region as that reported by Clark and Williams[46] and Nakamoto *et al.*[4] for *trans*-$[Pt(NH_3)_2Cl_2]$, as might be expected; and the Pt–N in plane and out of plane bending modes in the regions 300–200 cm^{-1} and 250–180 cm^{-1}, respectively. Thus, for $[Pt(NH_3)_4]Cl_2.H_2O$, these modes are assigned to the bands at 297 cm^{-1} (in plane) and 235 cm^{-1} (out of plane). Poulet *et al.*[48] assign the band at 236 cm^{-1} to the in plane mode and a band at 150 cm^{-1} to the out of plane mode and their calculation of the fundamental frequencies by a modified Urey-Bradley model support their assignments.

In $K[Pt(NH_3)Cl_3]$, three M–Cl stretching frequencies are expected[45] at 329 (symmetric $PtCl_2$ stretch), 316 (*trans* PtCl stretch) and 324 cm^{-1} (antisymmetric $PtCl_2$ stretch), whereas only two bands, at 325 and 315 cm^{-1} are observed.

Kharitonov *et al.* have discussed the spectra of the series of complexes *cis*- and *trans*-$[Pt(RNH_2)_2Cl_2]$ where R = Me, Et or ^nPr in a number of papers.[53,55,56,58] They report the spectra of the *cis* isomer to be more complicated than the *trans* isomer in each case, in accordance with the lower symmetry of the *cis*-complex. The values of the N–H stretching frequencies are not altered significantly in the series but the Pt–N stretching frequencies increase by ~100 cm^{-1} in going from the methylamine to the ethylamine complex. The increase on going to the n-propylamine derivative from the ethylamine derivative is only ~3 cm^{-1}. These increases are due to the increase in the force constant of the Pt–N bond and apply to both the *cis* and *trans* isomers. The frequencies and assignments for the methylamine complex have been confirmed by Watt *et al.*,[57] who have also studied the spectra of *cis*- and *trans*-$[Pt(MeNH_2)_2Br_2]$. From the force constants it is concluded that the introduction of the first methylene group into the hydrocarbon radical of the amine leads to a considerable increase in the Pt–N bond strength, but introduction of the second methylene group has little effect, that is, 'quenching' of the inductive effect is observed. A comparison of the force constants of the Pt–N bond in the complexes [Pt (amine)$_2$Cl$_2$] shows that the Pt–N bond strength increases in the series:

$$NH_3 < MeNH_2 < EtNH_2 \sim {}^{n}PrNH_2$$

It is interesting to note that these changes in the Pt–N bonds have almost no outward influence on the stretching vibrations of the N–H bonds.

There is little infrared data on secondary and tertiary amine complexes of platinum(II). One such study by Goggin *et al.*[59] has involved the investigation of the complexes *trans*-$[Pt(NMe_3)_2X_2]$ and $(Pr_4N)[Pt(NMe_3)X_3]$, where X = Cl and Br. For the *trans* complex the values of the asymmetric Pt–X stretch and the asymmetric Pt–N stretch are 342 and 560 cm^{-1} and 216 and 556 cm^{-1}, respectively, for the chloro and bromo complexes. Thus in the tertiary amine complexes these assignments are at higher frequency than for the corresponding *trans*-$[Pt(NH_3)_2X_2]$ complex[4] except for the assignment of the Pt–Br stretch, which is lower (the Pt–Br stretch is at 237 cm^{-1} in the ammine complex). Similarly, in the anionic platinum complex, the asymmetric Pt–N stretch is reported at 549 cm^{-1} which is higher than the 510 cm^{-1} reported for $[Pt(NH_3)Cl_3]^-$.[45]

Hirashi and co-workers[45] have assigned bands at ~200 cm^{-1} in the spectrum of $[Pt(NH_3)_4][PtX_4]$, where X = Cl or Br, to the A_{2u} lattice vibration, which appears at high frequency due to the strong metal-metal interaction. On cooling to liquid nitrogen temperatures these bands shift to ~208 cm^{-1} and become stronger which suggests that they are due to the antisymmetric stretching vibration of the –Pt–Pt–Pt–Pt– chain in the salts. This behaviour only occurs for salts of the Magnus type.

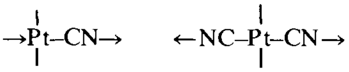
The study by Babaeva *et al.*[51] of complexes with an inner sphere sulphito group indicates the existence of a coordinate Pt–S bond which is in keeping with the results of other Pt–SO_3 complexes.[50]

(ii) Amine complexes with π-acceptor ligands

The infrared spectra of platinum(II) amine compounds with the ligands CN^-,[33,64–66] SCN^-,[46,60] NO_2^-,[60,67] CO,[68] olefins[69] and nitrile[70] have been studied.

Kharitonov and co-workers,[64] in a study of more than sixty complexes of platinum(II) and platinum(IV) found that for platinum(II) complexes the non-bridging C–N stretch occurs at ~2118–2140 cm^{-1}, whereas bridging C–N stretch occurs between ~2150–2210 cm^{-1}. Evidence for the former range is given for *cis*- and *trans*-$[Pt(NH_3)_2(CN)_2]$ which show C–N stretching bands at 2123 cm^{-1} for the *cis* and 2123 and 2138 cm^{-1} for the *trans* isomer. The force constant k_{CN} for the *trans* compound is 16.35 mdyn A^{-1}. The C–N stretching vibration of free CN^- is also reported as 2080 cm^{-1}. The bands of the degenerate and symmetric NH_3 deformations and NH_3 rocking are all at higher frequency in the *cis*- and *trans*-dicyanodiammine complexes as shown in Table III. In contrast the asymmetric Pt–N stretching vibrations are at lower frequency in the cyano complexes than in the halogeno complexes.

Baranovskii[33] has investigated the joint crystallisation of *trans*-$[Pt(NH_3)_2(CN)_2]$ and *trans*-$[Pt(NH_3)_2X_2]$ where X = NO_2, Cl, or Br. This leads to the formation of the complexes $[Pt(NH_3)_2(CN)X]$. From a study of the infrared spectra it was possible to decide the ratio of monomer to polymeric species. For X = NO_2 there is very little polymer present, for X = Cl the ratio is 5 : 1, the polymer chains being short, and when X = Br chiefly polymer is present. The polymer chains are of the two types:



$$\rightarrow \underset{|}{\overset{|}{Pt}}{-}CN\rightarrow \qquad \leftarrow NC{-}\underset{|}{\overset{|}{Pt}}{-}CN\rightarrow$$

of which the former are more prevalent, and are identified in respect of C–N stretching bands at 2198 (weak), 2189 (strong) and 2198 (strong) cm^{-1} in the three compounds respectively.

Clark and Williams[46] have studied the spectra of *cis*- and *trans*-$[Pt(NH_3)_2(SCN)_2]$ and $[Pt(NH_3)_4][Pt(SCN)_4]$. Babaeva and Evstaf'eva[60] have also studied the spectra of the *cis*- and *trans*-dithiocyanatodiammine complexes but the assignments are not in close agreement with Clark and Williams. The two sets of spectra are recorded in Table III.

Studies of the infrared spectra of amine complexes containing an NO_2^- group have been undertaken by Muraveiskaya and Orlova[67] and Babaeva and Evstaf'eva.[60] The spectra of the two complexes studied, *cis*- and *trans*-$[Pt(NH_3)_2(NO_2)_2]$, are outlined in Table III. In addition to the bands indicated (due to NH_3), the NO_2^- group exhibits asymmetric stretching vibrations at 1478(m), 1460(m), 1417(s) cm^{-1} and at 1464(s) and 1419(m) cm^{-1} in the *cis*- and *trans*-complexes, respectively. The symmetric stretching vibrations are at 1387(s), 1349(s) cm^{-1} and at 1387(s) and 1339(s) cm^{-1}.[60] The lower symmetry of the *cis* isomers is reflected in the spectra as there are two NO_2^- rocking vibrations in the *cis* and one in the *trans* and three NO_2^- deformations in the *cis* with none in the *trans*. On substitution of one of the NO_2^- groups by Cl^- to give *cis*-$[Pt(NH_3)_2(NO_2)Cl]$ the number of bands due to the NO_2^- group is reduced in all cases except the two NO_2^- rocking vibrations. The bands move to lower frequency in general, except for these NO_2^- rocking bands. Similarly, when substitution of NO_2^- by Br^- takes place in the *trans* complex the number of bands in the spectrum remains the same or decreases in all cases.[60]

In the spectra of the complexes *cis*- and *trans*-$[Pt(NH_3)(CO)Cl_2]$ which have been studied by Gribov and co-workers[68] the vibrations due to the CO group have been monitored. Both isomers have bands which are assigned to free CO in the crystalline product at 2144, 2136, and 2116 cm^{-1} in the *trans*- and 2144 and 2114 cm^{-1} in the *cis*-isomer. Each isomer has a band due to the 'valency vibration' of CO at 2062 and 2060 cm^{-1} respectively and two bands due to the bending vibration of OCPt at 532 and 477 cm^{-1} and 534 and 483 cm^{-1}, repsectively. The authors conclude that in this case there is some interaction of the free d electrons in platinum with the lone pair of electrons in CO which therefore points to a linear Pt–C–O bond.

The infrared spectra of the nitrile complexes $[Pt(NH_3)_2(RCN)_2][PtCl_4]$ where R = Me, Pr or Ph and $[Pt(NH_3)(PrCN)Cl_2]$ have been determined.[70]

(iii) Pyridine and related complexes

Three sets of workers[69,71,72] have studied the infrared spectra of simple dihalogenodipyridineplatinum(II) complexes and the results are in good agreement in most cases. However the medium strong band at 240 cm^{-1} in *trans*-$[Pt(py)_2Br_2]$ reported by Adams *et al.*[72] was not found by Clark and Williams,[71] and the same workers[72] also found a band at 297 cm^{-1} of weak intensity instead of the strong band reported previously. Allen and Theophanides[69] report the Pt–N stretching vibrations for the pyridine ligand to be at 474(m) cm^{-1} in $[Pt(py)_4]Cl_2 . 3H_2O$, 480(m) cm^{-1} in *trans*-$[Pt(py)_2Cl_2]$ and at 467(m) and 454(m) cm^{-1} in the *cis* isomer, while Clark and Williams[71] remark on the uncertainty to be attached to these vibration assignments and tentatively assign the Pt–pyridine vibrations to 282 cm^{-1} in the *trans* complex and 260(s) and 234(s) cm^{-1} in the *cis* isomer, remarking on how high this value seems. The same workers[71] assign the bands at 479 and 656 cm^{-1} to the pyridine ring vibrations. They alter only slightly (to 476 and 656 cm^{-1}, respectively) when Cl^- is replaced by Br^- in the *trans* complex, while the *cis*-dibromodiammineplatinum(II) complex shows these vibrations at 448 cm^{-1} and a doublet at 644 and 659 cm^{-1}, respectively. The spectra are listed in Table IV.

Aniline complexes of platinum(II) have been prepared by Jungbauer and Curran[73] and their spectra studied, although not enough evidence has been collected to decide whether or not the complexes $[Pt(aniline)_2X_2]$ (X = Cl or I) have the *cis* or *trans* configuration. The Pt–Cl stretch is assigned to the band at 331(s) cm^{-1}. The two complexes show NH_2 wagging vibrations at 1172 and 1185 cm^{-1} when X = Cl and I, respectively, a difference of 30 cm^{-1} which the authors suggest is attributable to a conformational effect.

The N–H stretching vibrations of 2-methylthioaniline (mta) are lowered in frequency from the free ligand to the complexes $[Pt(mta)_2X_2]$ (X = Cl or Br), which indicates coordination through the nitrogen rather than the sulphur atom.[74] These compounds show Pt–X stretching vibrations at 325(s) and 240 cm^{-1} for the chloro and bromo complexes, respectively. Once again there is insufficient evidence to point to either a *cis* or *trans* configuration, but a shoulder at 335 cm^{-1} could be due to the symmetric Pt–Cl stretching vibration and indicate the *cis* complex. It is interesting to note that under the same preparation conditions, palladium produces the complex $[Pd(mta)_2X_2]$ where the 2-methylthioaniline is coordinated through both the sulphur and nitrogen atoms.

(iv) Hydroxylamine and amino acid complexes

Kharitonov and co-workers[75–77] have been active in the study of hydroxylamine complexes of platinum(II). They have carried out a full coordinate analysis study

TABLE IV. Infrared Spectra Assignments for some Pyridine Complexes of Platinum(II).[a]

Complex	Pyridine ring vibrations		Pt–X stretch	Pt–N stretch	Reference
trans-$[Pt(py)_2Cl_2]$	656	479	341 vs	(282 s)	71
			343 vs	480 m	69
trans-$[Pt(py)_2Br_2]$	656	476	249 s	(297 w)	71
cis-$[Pt(py)_2Cl_2]$			344 s	467 m	69
			330 ms	454 m	
cis-$[Pt(py)_2Br_2]$	659	448	218 s	(260 s)	71
	644		209 s	234 s	

[a] All assignments given in cm^{-1}. Tentative assignments are in parentheses.

of the *cis*- and *trans*-[Pt(NH_2OH)$_2$$Cl_2$] isomers and their deuterated analogues and report that a satisfactory interpretation of the spectra is obtained if the NH_2OH molecule is considered to be coordinated through the nitrogen atom.[76] The band profiles are preserved in various complexes in the regions of 910–1035, 1170–1350, 1500–1650 and 2200–3650 cm^{-1}, and are attributed to NO stretching, NH or OH bending, NH bending, and NH and OH stretching vibrations, respectively. The value of the NO stretching frequency is highly characteristic of the complexes and occurs at ~480–545 cm^{-1}.

The spectra of amino acid complexes are complicated and few complexes have been studied since 1960. A study of platinum complexes of methionine[78] shows that the functional groups (NH_2, MeS^-, CO_2^-) can take part in the bonding in different ways in various complexes. Thus, in the complexes [Pt(MtH)$_2$]Cl_2.2H_2O and [PtMt(NH_3)Cl], MtH = methionine, methionine acts as a bidentate ligand bonded *via* both the nitrogen and sulphur atoms. In [Pt(MtH)$_2$(NH_3)$_2$]Cl_2 the dipolar MtH ion behaves as a monodentate ligand. whereas in [Pt(MtH)$_2$(NH_3)]Cl_2 one molecule functions as a bidentate and the other as a monodentate ligand (bonded *via* the sulphur atom).[78] For a more detailed discussion of amino acid complexes of platinum there are a number of recent review articles.[78b]

B. Electronic Spectra

The electronic absorption spectra of platinum(II) amine complexes have been studied very little since 1960. Thomson, Williams and Reslova,[15] in a review of the chemistry of *cis*-[Pt(NH_3)$_2$$Cl_2$], discuss the origins of these spectra which will be summarised here.

The $[PtCl_4]^{2-}$ ions in solution exhibit an electronic absorption spectrum which can be divided into two regions; the first containing weak absorption bands at energies below 35,000 cm^{-1} due to d–d transitions, and the second due to charge transfer bands (in this case L→M) at higher energy. The weak bands are formally forbidden, but gain intensity through vibrational perturbations and through borrowing from the intense allowed bands. This intensity borrowing becomes more pronounced the lower the symmetry of the complex ion.

Upon successive replacement of the chloride ligands of $[PtCl_4]^{2-}$ by NH_3, the d–d bands move progressively to higher energy since ammonia is higher in the spectrochemical series than chloride. A complex containing a mixture of ligands will have a d–d spectrum at energies close to the mean of the spectra of complexes with only one type of ligand.[15]

These spectra also supply information about the geometry of the complex ion. The spectra of *cis*- and *trans*-[Pt(NH_3)$_2$$Cl_2$] are shown in Figure 4. The splitting between prominent bands is rather different and the intensity of the *cis* spectrum is markedly higher. Thus, the d–d splitting depends on the symmetry of the field of ligands and the lower symmetry complex, the *cis* isomer in this case, has the more intense spectrum.

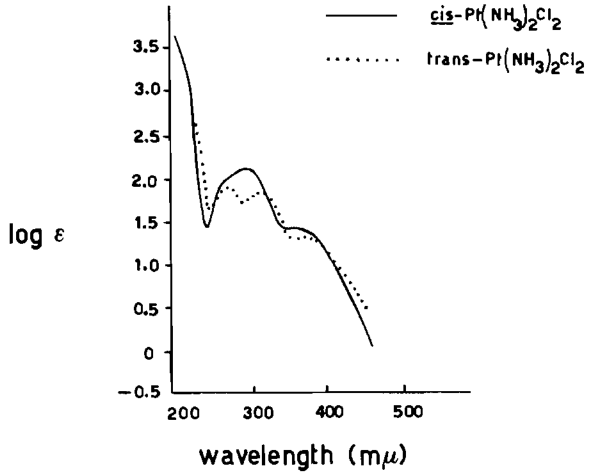


Figure 4. The spectra of *cis*- and *trans*-[Pt(NH_3)$_2$$Cl_2$].

Charge transfer bands, which characteristically have intensities ~10^4 l.mol^{-1}, are found at energies determined mainly by the oxidising power of the metal relative to the reducing power of the ligand if the transition is L→M and vice versa for M→L transitions. As the reducing power of the ligand increases, as in moving from chloride to bromide, the charge transfer band moves to lower energy.

König and Schläfer[79] have studied the electronic spectra of [Pt(py)$_2$$X_2$] X = Cl, Br, I, and assign a new band of high intensity (log ε ~4) to a charge transfer process. In the short wave u.v. spectral range the band of the pyridine ligand appears and is but insignificantly altered compared to that of free pyridine.

Franke[80] has studied the polarised electronic spectra of [Pt(NH_3)$_4$]Cl_2.H_2O single crystals at 15° and 300° K, and the magnetic circular dichroism spectrum of the $[Pt(NH_3)_4]^{2+}$ ions as [Pt(NH_3)$_4$](ClO_4)$_2$.$^1/_2$$H_2O$ has also been investigated.[81] The highest occupied energy levels in this ion are b_{2g}(xy) and e_g(xz, yz).

4. Reaction Kinetics and Mechanism Studies

A. Substitution and Exchange Reactions

A general ligand substitution reaction for a coordination complex may be described by the equation:

(xxii) $MX + Y \rightarrow MY + X$

when an entering group Y from the solution replaces a leaving group X on the metal atom M to which several other ligands are also bonded. There is a wide variety in the rates of these reactions from extremely fast to kinetically inert.

Many substitution reactions of platinum(II) complexes lie between these two extremes and a normal pattern of behaviour has emerged which fits a fairly simple mechanistic model for these reactions. These developments have been traced by a series of review articles.[82–85] The replacement of a ligand by a chemically identical group, often studied by using a tagged radioactive or stable isotope, commonly called an exchange reaction, may be considered as a special type of ligand substitution reaction. Studies of the isotopic exchange of halide ligands with free halide ions have recently uncovered several instances which do not fit into the accepted 'normal' pattern of behaviour.[86]

A large amount of data from kinetic studies of substitution reactions of platinum(II) complexes appears to be consistent with a nucleophilic replacement which involves an associative process. Such a process is illustrated in Figure 5 in which a nucleophile Y attacks along an axis normal to the square. Y may replace a solvent molecule or may form a weak interaction in a site perpendicular to the plane. The group Y moves closer to displacing X, and the coordination figure is approximately a trigonal bipyramid with X, Y, and L in the equatorial plane. When Y finally moves into the square, the group X is bonded to a labile axial position and then is quickly lost.

There is considerable experimental evidence to support this mechanism. In these reactions the geometric configuration is always retained: that is the group *trans* to the leaving group is *trans* to the replaced group in the product. Haake[87] has reported the presence of a transient intermediate, the five coordinate $[Pt(NH_3)_2(NO_2)_2Cl]^-$, formed in the reaction of nitrite with *cis*-$[Pt(NH_3)_2(NO_2)Cl]$ causing immediate enhancement of the optical density of the solution on addition of the nitrite. Haake proposes that the rate determining step may be the rearrangement from structure (I) to structure (II) with the trigonal bipyramid probably a stable configuration during it.

Further evidence is provided by studies such as those of Odell and Raethal[88,89] who studied reactions of the type shown in (xxiii).

$$\text{(xxiii)}\quad [(R_3{}^1P)PtX_2(NHR_2{}^2\text{–}{}^{14}C)] + \text{amine} \rightleftharpoons [(R_3{}^1P)PtX_2(\text{amine})] + NHR_2{}^2\text{–}{}^{14}C$$

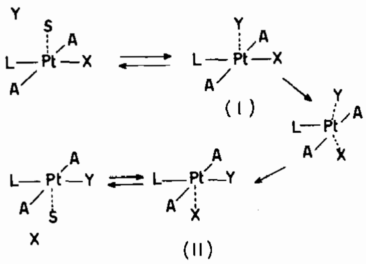
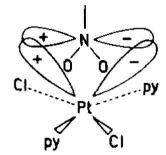


Figure 5.

(where R_2 = Me, Et, Pr; X = I or Cl; and amine = Me_2NH, Et_2NH, and several aromatic amines and their heterocyclic analogues). Both complexes have the *trans* configuration and the reactions were carried out in methanol or hexane at 25° C. The rates were followed by measuring the loss of ^{14}C activity from the complex. With shorter R^2 chains of the coordinated amine molecule, a significantly greater increase in the substitution rate resulted than did a comparable or even greater reduction in the size of R^1, indicating that the amine attack occurred at an angle acute to the leaving group, with the formation of a trigonal bipyramidal transition state. Tertiary amines gave no reaction, aromatic heterocyclic amines reacted faster than their alicyclic analogues and primary amines reacted faster than secondary amines.

The importance of the solvent in substitution reactions has been shown by Pearson, Gray and Basolo.[90] The reaction studied was the exchange of radioactive chloride ions with *trans*-$[Pt(py)_2Cl_2]$. Two groups of solvents emerged, those in which the rate of reaction was first order in both complex and $[{}^*Cl^-]$ e.g. CCl_4, C_6H_6, $(CH_2Cl)_2$, Me_2CO; and those first order in complex but zero order in $[{}^*Cl^-]$ e.g. H_2O, Me_2SO, $MeNO_2$, EtOH. The 'fast' solvents (those in the second group), have available potentially vacant orbitals of a type capable of bonding with the filled d_{yz} or d_{xz} orbitals of the platinum atom. These orbitals are those which project above and below the plane of the complex e.g.



This model shows π-bonding of the M→L type and how such π-bonding may permit these solvent molecules to approach so that their basic O atoms are very close to Pt and in a good position to displace Cl^- from the complex. Alternatively, one may say the transition state is stabilised by π-bonding.

When the axial positions in these complexes are blocked by bulky groups in the plane the rates of substitution are considerably slower. The rates of reaction of *cis*-$[Pt(2\text{-picoline})_2Cl_2]$ is 1/25 of that of *cis*-$[Pt(4\text{-amylpyridine})_2Cl_2]$ in ethanol. It is believed the methyl groups of the picoline partially block the access of the solvent to the metal atom.[90]

The rate law for this associative mechanism is often simplified by using a large excess of the nucleophilic reagent Y in the experiments so that the reversibility of the substitution is suppressed almost completely. The concentration of Y will be effectively constant and pseudo first order conditions may apply. If the rate for replacement of a solvent ligand by Y is sufficiently high, the concentration of the solvent containing species may be held to inappreciable levels. Then if the pseudo first order rate constant is plotted against the concentration of Y, a straight line is obtained. The rate expression resulting under these conditions is shown in (xxiv) and is usually considered as normal behaviour for ligand substitution reaction of platinum(II).

(xxiv) Rate = [Pt complex]$(k_1 + k_Y[Y])$

The constant k_Y characterises the direct replacement of X by the process of Figure 5, and k_1 is the rate constant for the replacement of X by solvent which is in turn rapidly replaced by Y.

Experimental confirmation of the rate equation has been demonstrated by Basolo, Gray and Pearson[91] in a study of the reaction of pyridine with the complex $[Pt(dien)X].NO_3$ where X = various anions. They list the relative reactivities of replacable ligands in square-planar complexes of platinum(II). The ease of replacement of the ligands X follows the order:

$NO_3^- > Cl^- > Br^- > I^- > SCN^- > NO_2^-$

Peshchevitskii and Shchenkochikhina[92,93] and Shul'man[94,95] have studied spectrophotometrically the reaction

(xxv) $Pt(Hx)_2X_2 + 2Y^- \rightleftarrows Pt(Hx)_2Y_2 + 2X^-$
(Hx = hydroxylamine)

where X_2, Y = Cl_2, Br; ClBr, Cl; Br_2, Cl; Br_2, I; Cl_2, I; and shown the reaction to obey the 'normal' rate law.

Complexes containing both phosphines and amines have been shown to obey the above rate law (xxiv).[96] These authors report that replacement of one PEt_3 molecule in *trans*-$[Pt(PEt_3)_2X_2]$, X = Cl, Br, by NH_3 produces no systematic difference in the rate law.

Panasyuk and Malashok[97] and Makashev *et al.*[98] have studied the kinetics of aquation of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$, $[Pt(en)Cl_2]$ and *trans*-$[Pt(NH_3)_2X_2]$ where X = Br, I, in aqueous solution. The aquation reaction is found to be first order with respect to the complex and in the case of *trans*-$[Pt(NH_3)_2X_2]$ the rate of aquation decreases with X in the order I > Br > Cl. Shchekochikhina[99] confirms this order for the aquation of *trans*-$[Pt(Hx)_2X_2]$ on standing. The precipitate formed in this reaction is assumed to be *trans*-$[Pt(Hx)_2(H_2O)_2]^{2+}.2X^-$ which subsequently dimerises with a simultaneous dissociation of H^+.

Panasyuk *et al.*[100] report that the aquation reaction of *cis*-$[Pt(EtNH_2)_2Cl_2]$ in several aqueous-organic solvents proceeds by a two step mechanism, the first step involving a significant polarisation of the Pt–X bond and the second step involving insertion of a water molecule from the outer into the inner coordination sphere of the platinum(II).

Panasyuk and Malashok[101] report that in all substitution reactions both S_N1 and S_N2 reaction routes are possible. In the S_N1 route the slowest stage is represented by:

(xxvi) *trans*-$[PtCl_2(NH_3)_2] \rightarrow$ [*trans*-$PtCl(NH_3)_2...Cl]$

in the reaction

(xxvii) *trans*-$[PtCl_2(NH_3)_2] + H_2O \rightleftarrows$ *trans*-$[PtCl(H_2O)(NH_3)_2]^+ + Cl^-$

The say that both S_N1 and S_N2 reactions are possible in all substitution reactions but the S_N2 mechanism predominates only in those platinum(II) complexes for which the transition state is characterised by the formation of π-bonds.

Table V gives data relating to chloride exchange reactions in several complexes and complex ions. The exchange conditions employed to obtain the data range from high chloride concentrations, where only negligible solvation existed to situations in which sometimes the concentration of the aquo species exceeded that of the unsolvated complex.

The $[Pt(NH_3)Cl_3]^-$ species contains non-equivalent chlorides and it has been found that one type exchanges nine times faster than the other.[102] The aquo species formed more slowly is more thermodynamically stable and eventually achieved a concentration ten times that of the one formed more rapidly. Tucker, Colvin and Martin[102] have assigned the larger rate constant to the displacement of the chloride ligands *cis* to ammonia.

It is noted that the values of k_{H_2O} for the first aquation of the complexes in Table V differ by less than a factor of sixteen for the entire series when a chloride is lost from a species of charge –2, –1, 0, or + 1. The effect on the rates of these reactions of the absence of an ionic charge has been considered as the most conclusive evidence against a dissociative type of mechanism for these reactions.

The exchange reactions of bromide ligands in platinum(II) complexes are found to be quite different from those of chloride which have appeared as 'normal' processes. As platinum is a soft acid a Pt–Br bond is likely to be stronger than a corresponding Pt–Cl bond.

Jolley *et al.*[103] have proposed a possible mechanism for the exchange of bromide ligands between *trans*-$[Pt(NH_3)_2Br_2]$ and $[PtBr_4]^{2-}$ by use of ^{82}Br, and is shown in Figure 6.

After formation of a weak interaction, as shown in A, rotation of the two complexes permits the formation of the two weak unsymmetrical bridges, as in B. Movement of the bromide ligands according to the arrows leads to the transition state shown in C where each platinum atom has approximately the trigonal bipyramidal coordination which is considered typical for ligand substitution reactions of platinum(II) complexes.

TABLE V. Kinetics Behaviour Related to Chloride Exchange for the Chloride-Ammonia Complexes of Platinum(II) 25° C and μ = 0.318 *M*.[86]

Complex	$10^5 \times k_{H_2O}$ sec^{-1}	$\Delta H^*_{H_2O}$ kcal	ΔS^* cal/deg	$10^5 \times k_{Cl}$ M^{-1} sec^{-1}	ΔH^*_{CL} kcal	ΔS^* cal/deg
$[PtCl_4]^{2-}$	3.9	21	−8	4	–	–
$[Pt(NH_3)Cl_3]^-$ *cis* Cl	5.6	20	−9	4	–	–
trans Cl	0.62	(15)	(−30)	4	–	–
cis-$[Pt(NH_3)_2Cl_2]$	2.5	20	−14	5	–	–
trans-$[Pt(NH_3)_2Cl_2]$	9.8	19	−11	78	20	−7
$[Pt(NH_3)_3Cl]^+$	2.6	18	−18	7	29	+19
$[PtCl_3(H_2O)]^-$	4	(25)	(+2)	260[a]	15	−18
cis-$[Pt(NH_3)Cl_2(H_2O)\}$	8	–	–	4300[a]	12	−19
trans-$[Pt(NH_3)Cl_2(H_2O)]$	–	–	–	48[a]	15	−24
cis-$[Pt(NH_3)_2Cl(H_2O)]^+$	3.3	20	−11	760[a]	17	−12
trans-$[Pt(NH_3)_2Cl(H_2O)]^+$	(5)	–	–	28000[a]	13	−19
$[Pt(NH_3)_3(H_2O)]^{2+}$	–	–	–	7300[a]	20	+5

[a] These values of k_{Cl} describe replacement of the H_2O ligand for the aquo complexes.
k_{H_2O} = rate constant for the aquation reaction.
k_{Cl} = rate constant for the Cl exchange reaction.

Grinberg and Shagisultanova[104] have studied the exchange of Br^- between $K_2Pt^{82}Br_4$ and both *cis*- and *trans*-$[Pt(NH_3)_2Br_2]$ and found that the exchange reaction of the *trans* complex was faster than the exchange of the *cis* isomer and both isomers exchange faster than KBr does with K_2PtBr_4.

Gano[105] has suggested two possible schemes by which *cis*-$[Pt(NH_3)_2Br_2]$ might exchange with bromide ions. The first scheme consists of three paths for exchange of bromide ligands with Br^-: (i) the reversible aquation reaction of *cis*-$[Pt(NH_3)_2Br_2]$, (ii) direct exchange of Br^- with *cis*-$[Pt(NH_3)_2Br_2]$ and (iii) the reversible aquation of $[Pt(NH_3)_2Br(H_2O)]^+$. The rates for the three paths are: (i) $k_1[Pt(NH_3)_2Br_2]$, (ii) $k_{Br}[Br^-][cis\text{-}[Pt(NH_3)_2Br_2]]$, (iii) $k_2[[Pt(NH_3)_2Br(H_2O)]^+]$. The values obtained for the rate constants k_1, k_{Br}, k_2, were 3.0×10^{-5} sec^{-1}, 3.3×10^{-4} *M* sec^{-1}, and 2×10^{-4} sec^{-1}, respectively, for this first scheme at 25° C. Gano reports the value for k_2 as unusually high and suggests the exchange is characterised equally well by a second scheme in which k_2 is given a lower value and another means of exchange of Br^- with $[Pt(NH_3)_2Br(H_2O)]^+$ *via* a dimer path is provided. The rate for this path would be $k_{d2}[[Pt(NH_3)_2Br(H_2O)]^+][[cis\text{-}Pt(NH_3)_2]]$. For this scheme at 25° C k_1 and k_{Br} retained the same values but k_2 was now 3×10^{-5} sec^{-1} and the addition rate constant k_{d2} was 0.12 M^{-1} sec^{-1}. Presumably the exchange *via* the dimer path could take place by a similar mechanism to that shown in Figure 6.

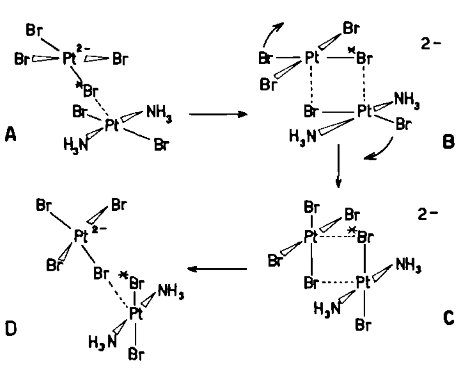
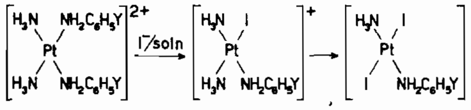


Figure 6.

A later study by Gano, Vendegrift and Martin,[106] of the replacement of the bromide ligands in *cis*-$[Pt(NH_3)_2Br_2]$ by water and by $^{82}Br^-$ in water shows that *cis*-$[Pt(NH_3)_2Br_2]$ undergoes solvation, presumably in stepwise fashion, and that the aquation process provides first order exchange for the complex. Also it appears clear that there is a second order direct nucleophilic replacement of bromide ligands by Br^- ions. The rate law has not been established unambiguously for the process. The principle ambiguity lies in the rate law for the introduction of the $^{82}Br^-$ into $[Pt(NH_3)_2Br(H_2O)]^+$. These workers do not discuss the possibility of exchange *via* a dimer path.

Ablov and Semina[107] report that the substitution by I^- in solution into a platinum(II) tetramine complex containing two molecules of NH_3 in the *cis* position and two molecules of aniline or its derivatives in the inner sphere gives exclusively the *trans*-$[PtI_2(NH_3)(H_2NC_6H_4Y)]$ product. Similar reactions with Br^- and Cl^- yield analogous products, although in the chloride case heating with concentrated hydrochloric acid is required. An order of ease of entering the inner sphere of the complexes is designated as $I^- > Br^- > Cl^-$. It has been suggested that the halogen (X) in the *cis*-$[PtX(NH_3)_2(H_2NC_6H_4Y)]^+$ cation, the first product of the reaction (see below), increases the strength of the bond formed to the neighbouring aromatic amine from the central atom (*cis* effect).

(xxviii)



Makashev *et al.*[98] have studied the aquation reactions of the complexes *trans*-$[Pt(NH_3)_2X_2]$ (X = Br, I) by spectrophotometric, potentiometric and electrical conductivity studies. The rate of aquation was found to decrease with X in the order $I > Br > Cl$ and is explained by the decrease in Pt-X bond stability.

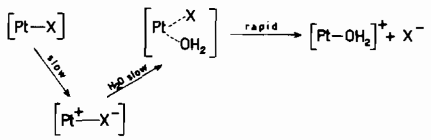
A study of the aquation of *cis*-$[Pt(EtNH_2)_2Cl_2]$ in aqueous-organic solvents[100] reveals that the aquation takes place by the 'normal' route for platinum(II) complexes. The first step involves a significant polarisation of the Pt–Cl bond and the second step is insertion of H_2O from the outer into the inner coordination sphere of the platinum(II).

Perumareddi and Adamson,[108] in a photochemical study of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ and $[Pt(NH_3)_2(H_2O)_2]^{2+}$, have shown that both the geometric isomers of dichlorodiammineplatinum(II) photoaquate releasing chloride ligands, the quantum yield being much larger for the *cis* complex. An aqueous solution of $[Pt(NH_3)_2(H_2O)_2]^{2+}$ decomposes on photolysis but preliminary studies show that an acidified solution of the same isomerises to the corresponding *trans* complex cation. The quantum yields for platinum(II) complexes are generally 0.1–0.5, show little wavelength dependence, and the temperature coefficients correspond to 2–3 kcal of activation energy.

B. Acid-Base Properties and Hydrolysis Reactions

The rate of base hydrolysis of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ has been shown to be first order with respect to complex and zero order with respect to base[109,110] for both stages of the hydrolysis in which the final product is *cis*- and *trans*-$[Pt(NH_3)_2(OH)_2]$.

Panasyuk and Malashok[97,111] have studied the acid hydrolysis of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ in aqueous solution and in mixed aqueous-organic solvents. In aqueous solution the reaction is first order with respect to complex and for the *trans* complex the reverse reaction is second order with respect to complex, but in aqueous solutions of MeOH, EtOH or Me_2CO these authors[111] suggest the aquation reaction proceeds predominantly by a non-limiting S_N1 mechanism. They elaborate to say that a more general mechanism for the aquation of platinum(II) complexes is that involving two slow processes in the stage of activated complex formation; an increase in the polarity of the bond between the central atom and the group being replaced, with the simultaneous introduction of a water molecule from the solvate sheath:



The authors conclude that both S_N1 and S_N2 can be considered as extreme cases of this more general method.

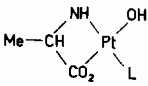
A study by Staples and Thompson[112] of the acid catalysed replacement of a nitro group from a series of complexes *cis*- and *trans*-$[PtA_2(NO_2)_2]$ in aqueous solutions of H_2SO_4 shows that the ease of removal of the nitro group for a given group A is *cis* > *trans* where A = PEt_3 or SEt_2, but *trans* > *cis* when A = pyridine or NH_3. The results are explained in terms of the *trans* effects of the ligands A.

The acid dissociation of a molecule of NH_3 from the complexes $[Pt(NH_3)_3L](NO_3)_2$ where $L = C_2H_4$ and Me_2SO have been studied by Gel'fman *et al.*[113] The reaction under consideration is:

$$\text{(xxix)}\quad [Pt(NH_3)_2L(NH_3)]^{2+} + H^+ \rightleftharpoons NH_4^+ + [Pt(NH_3)_2L(H_2O)]^{2+}$$

The results of their experiments show that the introduction of π-acceptors such as C_2H_4 or Me_2SO into the inner sphere of a platinum(II) complex brings about the acid dissociation of NH_3 molecules in the *trans* position. The values of pK_a $(L = C_2H_4) = 8.6 \pm 0.1$, and $(L = Me_2SO) = 9.1 \pm 0.1$, confirm that the π-acceptor power of Me_2SO is weaker than C_2H_4.

In the complex



where L = NH_3, py, or Et_2SO, the nature of L has a marked influence on the acidic properties of the H_2O molecule.[114] The amine has the weakest acidic properties, since NH_3 exhibits only σ-donor properties, but as the π-acceptor properties begin to dominate over the σ-donor properties the effective charge on the platinum atom should decrease and hence the acidic character of the H_2O molecule should increase. This was borne out in practise since the acid dissociation constant increased with L in the order: $NH_3 <$ py $< Et_2SO$. Grinberg *et al.*[115] have found similar results with other aquo amine complexes of platinum(II).

Aqueous solutions of *cis*- and *trans*-$[Pt(NH_3)_2(NH_2OH)_2]Cl_2$ show completely different behaviour when titrated with alkali.[116] The *cis* isomer reacts in two stages with a clearly defined jump but the solution of the *trans* isomer becomes alkaline smoothly without a jump. Initially $\{[Pt(NH_3)_2(NH_2OH)_2]OH\}^+$ ions and $[Pt(NH_3)_2(NH_2OH)_2](OH)_2$ are formed and as a result of the imido reaction of NH_2OH in the field of Pt^{2+}, these may split off H_2O molecules to form $[Pt(NH_2O)(NH_3)_2(NH_2OH)]^+$ ions and $[Pt(NH_2O)_2(NH_3)_2]$ molecules. An interpretation is offered involving the dissociation of the different species present.

C. Redox Reactions

On contact with activated carbon (prepared from sucrose), *cis*-$[Pt(NH_3)_2Cl_2]$ is isomerised in aqueous solution to the *trans* isomer.[13] The authors explain this as due to the *cis* diammine being adsorbed on the surface of the carbon where it undergoes partial reduction with the formation of an intermediate complex of covalent platinum and finally platinum(O):

$$\text{(xxx)}\quad [Pt(NH_3)_2Cl_2] + 2e^- \rightarrow [Pt^0(NH_3)_2Cl_2]^{2-} \rightarrow Pt^0 + 2NH_3 + 2Cl^-$$

The Pt^0 atoms formed can exchange with Pt^{II} and enter into the composition of the complex. This exchange has been observed in experiments using the radioactive isotope of platinum, ^{197}Pt.

$$\text{(xxxi)}\quad Pt^0 + [Pt(NH_3)_2Cl_2] \rightleftarrows Pt^{2+} + [Pt^0(NH_3)_2Cl_2]^{2-}$$

The Pt^{2+} ions, by reacting with NH_3 molecules and Cl^- ions form the *trans*-$[Pt(NH_3)_2Cl_2]$ which is thermodynamically more stable.

Both Zemskov and Ptitsyn[117] in a study of the oxidation of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ by $NaVO_3$ and $Ce^{IV}SO_4$, and Peloso and Basato[118] in a study of the oxidation of $[Pt(MeNH_2)_2Br_2]$ by Fe^{3+} in the presence of Br^- postulate the formation of a 'Pt(III)' species as a transient intermediate in the reactions.
The mechanisms postulated are, respectively:

$$\text{(xxxii)}\quad Pt^{II} + VO_2{}^+ \xrightarrow{\text{slow}} Pt^{III} + VO_2;$$
$$Pt^{III} + VO_2{}^+ \xrightarrow{\text{fast}} Pt^{IV} + VO_2.$$

$$\text{(xxxiii)}\quad Fe^{III} + Br^- \underset{\text{fast}}{\overset{\text{fast}}{\rightleftharpoons}} Fe^{III}Br;$$
$$Pt^{II} + Fe^{III}Br \overset{\text{slow}}{\rightleftharpoons} Pt^{III}Br + Fe^{II};$$
$$Pt^{III}Br + Fe^{III}Br \overset{\text{fast}}{\rightleftharpoons} Pt^{IV}Br_2 + Fe^{II}.$$

Chernyaev and Leonova[119] have studied the oxidation of platinum(II) complexes by Cl_2, Br_2, I_2, and H_2O_2 either in solution or by reaction of oxidant on the dry material. The complexes studied were *trans*-$[Pt(MeNH_2)_2X_2]$ (X = Cl, Br, I, NO_2, SCN, or CN), and it is interesting to note that although Cl_2 oxidises coordinated bromide and iodide ligands in general, the reaction of Cl_2 with *trans*-$[Pt(MeNH_2)_2Br_2]$ leads to the formation of *trans*-$[Pt(MeNH_2)_2Cl_3Br]$ where the second bromide ligand is not replaced. A similar reaction occurs between I_2 and *trans*-$[Pt(MeNH_2)_2Cl_2]$, when $[Pt(MeNH_2)_2I_3Cl]$ is the product.

In an investigation into the reaction of several isomeric diamines with 10% hydrochloric acid, Chernyaev and co-workers[120] report the formation of products representative of a new class of platinum(IV) complexes containing a monochloroamine in the inner sphere during the reaction. The mechanism of these reactions is discussed. The same authors[121] report the formation of platinum(IV) nitrosyl complexes of unknown structure on reaction of *cis*-$[Pt(NH_3)_2(NO_2)_2]$ with excess concentrated or 10% hydrochloric acid in the dark at 0–5° C. The complex formed is of composition $[Pt(NH_3)_2(NO_2)(NO)Cl_2]$ and the NH_3 groups are in the *cis* position in the newly formed product, but after standing the complex isolated has these groups in the *trans* position. With excess acid and heat the product formed is *cis*-$[Pt(NH_3)_2(NO_2)_2Cl_2]$.

The normal redox potentials for several Pt^{IV}–Pt^{II} systems have been determined.[122] It is also reported that dihalogen complexes of the type $[Pt^{IV}X_2(NO_2)_2(NH_3)_2]$ (X = halogen) are reduced to the platinum(II) diammines in the presence of light.[122]

In three studies[123–5] Muraveiskaya and Antokol'skaya have investigated the reactions of dinitrodiammineplatium(II) with hydrohalic acids. The mechanisms of the oxidation of the different isomers are discussed and involve two main stages. The first is the formation of nitrosyl complexes and the second stage the conversion of these into platinum(IV) species which involves the participation of bridged complexes which are responsible for the electron transfer.

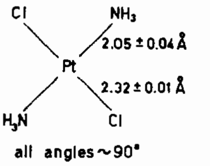
Kukushkin and Dkhara[126] have studied the effect of several acido ligands on the oxidation–reduction potentials of systems of the type $[Pt(NH_3)_2X_2Cl_2]$–$[Pt(NH_3)_2X_2]$. The ligands X can be arranged in the following sequence with respect to the oxidation–reduction potential of the system:

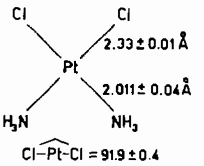
$$I^- < CN^- < SCN^- < Br^- < Cl^- < NO_2{}^-$$

The polarographic reductions of several platinum(II) ammine complexes have been studied by Sundholm including *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$,[127–130] *cis*-$[Pt(NH_3)_2(NO_2)_2]$,[127] $[Pt(NH_3)_4]^{2+}$ [127] and $[Pt(NH_3)Cl_3]^-$.[131,132] Chakravarty and Banerjee[133] have studied the polarographic behaviour of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$, *cis*- and *trans*-$[Pt(NH_3)_2(OH)_2]$ and *cis*- and *trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.

5. Structures

The following scheme shows the bond lengths and angles of *cis*- and *trans*-$[Pt(NH_3)_2Cl_2]$ taken from an X-ray study by Milburn and Truter.[134]

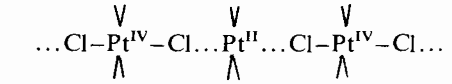




The *cis* isomer has a triclinic structure (a 6.75, b 6.55, c 6.23 Å, α 92.2°, β 84.6°, γ 110.7°) and the separations between the Pt atoms are 3.372 and 3.409 Å perpendicular to the molecular planes. The *trans* isomer retains the same structure at low temperature as at room temperature.

Miller[135] has reported the colours and unit cell dimensions of several complex salts of general formula $[ML_4][M'X_4]$ (where M = Pd, Pt; L = NH_3, $MeNH_2$; M' = Pd, Pt; X = Cl, Br) which are isostructural with Magnus' green salt, $[Pt(NH_3)_4][PtCl_4]$. The ions of this salt are colourless and red, respectively, but the crystals are green, as are all the above complexes when both ions contain platinum(II). The metal-metal distances in corresponding NH_3 and $MeNH_2$ salts are not very different (see Table VI) and this is because the whole of the $MeNH_2$ molecule lies in the plane of the complex ion. Models show that $EtNH_2$ would be too large to do this, and it is found that the complex $[Pt(EtNH_2)_4][PtCl_4]$ is pink in colour and has a totally different structure.

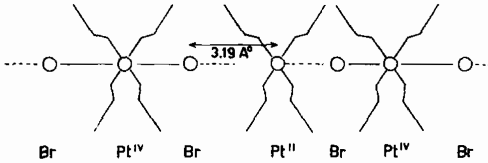
The crystal structure of Wolfram's red salt has been investigated by Craven and Hall.[136] They found the formula to be $[Pt(EtNH_2)_2Cl_2][Pt(EtNH_2)_4]Cl_4.4H_2O$. The structure is tetragonal or pseudo-tetragonal, containing chains parallel to c of the sort:



$$\ldots Cl-\overset{\vee}{\underset{\wedge}{Pt^{IV}}}-Cl\ldots\overset{\vee}{\underset{\wedge}{Pt^{II}}}\ldots Cl-\overset{\vee}{\underset{\wedge}{Pt^{IV}}}-Cl\ldots$$

The Pt–Cl distances are 2.26 and 3.13 Å for Pt^{IV} and Pt^{II} atoms respectively, the second being a result of a weak interaction. There is no long-range order in the solid structure because of occasional slips in the packing of the chains. The chloride ions lie in cylindrical holes between the chains, although the position of the water molecules remains undetermined.

The same authors[137] have reported the crystal structure of the salt $Pt^{II}(EtNH_2)_4.Pt^{IV}(EtNH_2)_4.Br_2.Br_4$ which they obtained by slow evaporation of a solution of Wolfram's red salt in excess hydrobromic acid. The crystals are tetragonal with a subcell of dimensions a = 11.86, c = 12.14 Å. The structure may be represented as:



although there is no distinction between the Pt^{II} and Pt^{IV} atoms, as all $Pt(EtNH_2)_4$ groups appear to have two shared bromide ligands coordinated axially. The Br^- ions exist independently.

In the complex *trans*-$[Pt(C_2H_4)\{NH(CH_3)_2\}Cl_2]$ the ethylene molecule is found to be symmetrically bound to the platinum atom.[138] The C–C bond (1.47 Å) is longer than a normal double bond but the significance of this, according to the authors, depends upon the method used to assess the errors. The other bond lengths appear to be normal. The crystal dimensions are shown in Figure 7.

Investigations of the complex *cis*-$[Pt(NH_3)(C_2H_4)Br_2]$,[139, 140] show that the olefin double bond is perpendicular to the plane of the complex and bonded to the platinum atom by a three point bond. The Pt–C bonds are found to be 2.3 Å and 2.4 Å and the Pt–NH_3 bond 2.13 Å in length. The difference in the Pt–Br bond length along the NH_3–Pt–Br coordinate (2.4 Å)

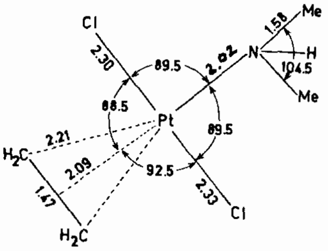


Figure 7. Crystal dimensions of the complex *trans*-$[Pt(C_2H_4)\{NH(CH_3)_2\}Cl_2]$.

TABLE VI.

Complex	Colour	Unit cell dimensions		M–M distance (c/2)
		a (Å)	c (Å)	(Å)
$[Pt(NH_3)_4][PdCl_4]$	pink	8.96	6.45	3.22_5
$[Pt(NH_3)_4][PtCl_4]$	green	8.96	6.46	3.23
$[Pt(MeNH_2)_4][PtCl_4]$	green	10.35	6.49	3.24_5
$[Pt(NH_3)_4][PtBr_4]$	green	9.32	6.62	3.31
$[Pt(MeNH_2)_4][PtBr_4]$	green	10.55	6.61	3.30_5
$[Pt(NH_3)_4][Pt(SCN)_4]$	pink	10.60	6.69	3.34_5

and the C_2H_4–Pt–Br coordinate (2.51 Å) is due to the strong *trans* effect of C_2H_4.[140]

6. Cis and Trans Effects and Influences

Many kinetic studies have been conducted on square-planar complexes and it has been found that ligands can be arranged in a series based upon their ability to labilise the group *trans* to themselves in the complexes of platinum(II). The phenomenon is called the *trans* effect and qualitatively it decreases in the order[141]:

(xxxiv) $$C_2H_4 \sim NO \sim CO \sim CN^- > R_3P \sim H^- \sim SC(NH_2)_2 > CH_3^- > C_6H_5^- > SCN^- > NO_2^- > I^- > Br^- > Cl^- > RNH_2 \sim NH_3 > OH^- > H_2O$$

The above series is based upon the relative rates of substitution of the ligand *trans* to the *trans* director L (in the series above) as L is varied.

The *trans* effect is a kinetic effect, since it is the influence of the *trans* director on the rate of substitution of the *trans* ligand, and so to explain it one should consider the effects of L on the activation energy of the reaction.[142] The *trans* director can lower the activation energy for the substitution reaction by destabilising the ground state of the complex or by stabilising the activated complex or both. Earlier theories emphasised the destabilisation of the ground state by weakening of the bond *trans* to L, but more recent explanations have emphasised the effect of L on the energy of the activated complex for both π- and σ-bonding *trans* directors.[142]

Another phenomenon characteristic of square-planar platinum(II) complexes which deals specifically with the effect of a ligand on the metal-ligand bond *trans* to itself in the ground state of the complex has been called the *trans* influence. This effect is different from the kinetic *trans* effect since it focusses attention on the strength of the *trans* bond rather than on the kinetic labilisation of the *trans* ligand. The two phenomena may or may not be related.[142]

The *trans* influence series for ligands in platinum(II) complexes has been the subject of infrared,[4,72,142] electron absorption spectra[143] and nuclear magnetic resonance studies[144–146] and a qualitative *trans* influence series has been established which is found to be quite similar to the *trans* effect series in (xxxiv).

Preparative studies of amine complexes with dimethyl and diethyl sulphoxide show that both these ligands have a strong *trans* effect in platinum(II) complexes, at least stronger than that of the chloride ligand. Similar studies with phosphites[150] show that the *trans* effect for $P(O^iPr)_3$ is greater than for $P(OEt)_3$. Other studies[112,113,151] confirm the *trans* effect series given in (xxxiv).

Two phenomena similar to *trans* effect and *trans* influence are *cis* effect and *cis* influence. Ligand series of decreasing *cis* effect for weak nucleophiles and *cis* influence are virtually the reverse of that for the *trans* effect and *trans* influence.[147]

Fryer and Smith[147] have used the ^{35}Cl NQR frequencies in the complexes *trans*-$[PtL_2Cl_2]$ (L = amine or other ligand), as a measure of the Pt–Cl bond strength in the complexes. They report that the bonds are progressively weakened as the *cis* ligand, L, is changed from left to right in the order

(xxxv) L $^nBu_3P$, py, $(CH_3)_3NH$, NH_3.

and this is the order of *cis* influence. The weakening of the Pt–Cl bond in the ground state appears to assist nucleophilic substitution reactions of the chloride ligand and the rate of replacement of chloride in the complexes *trans*-$[PtL_2Cl_2]$ by weak nucleophiles has been observed to increase in a similar order,[147] although with strong nucleophiles the order is not preserved.

One possible explanation for the fact that the order of *cis* effect and *cis* influence is almost the reverse of *trans* effect and *trans* influence is that the π-acceptor abilities of the ligands in series (xxxiv) increase from right to left resulting in an increased *trans* effect in the same order[147] whereas the total charge donated by the ligands (σ-donation less π-withdrawal) increases from right to left in the series (xxxv) allowing the *cis* Pt–Cl bond to become increasingly polarised which is an important step in the attack by weak nucleophiles. A second explanation is that ligands which weaken the *trans* bond simultaneously strengthen the *cis* bond.[151] This effect has been observed in a comparison of the force constants of the Pt–Cl bonds in the $[Pt(CO)Cl_3]^-$ and $[Pt(NH_3)Cl_3]^-$ ions.[147]

Ablov and Semina[107] suggest that the halogen (X) in the *cis*-$[PtX(NH_3)_2(H_2NC_6H_4Y)]^+$ cation increases the strength of the bond formed by the neighbouring aromatic amine with the central atom (the *cis* effect) and on substitution by halogens, I^- enters more easily than does Br^- which enters more easily than Cl^-. Thus iodide has the greatest *cis* influence of the three halogens.

7. Platinum(II) Amines as Anticancer Agents

Rosenberg *et al.*[152] discovered that when platinum electrodes were used to apply an alternating current across a chamber in which bacteria (in this case *Escherichia coli*) were growing the division of cells in the bacteria stopped. After further work it was concluded that the effective agent in blocking cell division and leading to the growth of long filamentous E. coli rods was a small concentration (~ 10 p.p.m.) of some platinum complex in solution, electrolytically formed by the applied electric field. The complexes responsible were found to be *cis*-dichlorodiammineplatinum(II) and *cis*-tetrachlorodiammineplatinum(IV).[153,154] The *trans* isomers of these complexes have been found to be ineffective in blocking cell division in bacteria.

The two complexes *cis*-$[Pt(NH_3)_2Cl_2]$ and *cis*-$[Pt(NH_3)_2Cl_4]$ were both tested for antitumour activity because of their activity in inhibiting cell division in bacteria. Rosenberg *et al.*[155] found that one dose of *cis*-$[Pt(NH_3)_2Cl_2]$ inhibited the growth of a single transplantable Sarcoma 180 tumour (a standard test tumour in cancer research) in Swiss white mice. The dose used was approximately 57% of the LD_{50}. It was also found that if treatment of the tumour was delayed for eight days then a single injection of *cis*-$[Pt(NH_3)_2Cl_2]$ caused the complete regression of the by now large tumour in close to 100% of the animals.[156] In addition to producing such extensive 'cures' of advanced sarcomas, they found that even up to eleven months afterwards the animals remained immune to a challenge from the same tumour.

Since these early results *cis*-$[Pt(NH_3)_2Cl_2]$ has been tested extensively on other transplantable tumour systems such as the Walker 256 carcinosarcoma,[157] the Dunning Ascitic Leukaemia,[157] the Lewis lung carcinoma,[158] the B–16 melanocarcinoma,[158] the P388 leukaemia, and the ADJ–PC6A[158] tumours. It has shown a marked effectiveness in all these tumour systems. Haddow and Connors[158] have shown the complex to be inactive against the Rabbit VX2 carcinoma, the Gardner tumour, and a strain of the Walker 256 carcinosarcoma that is resistant to alkylating agents.

Although transplantable tumours form the best screening systems for evaluating the effectiveness of new antitumour agents, there are other types of tumour systems which are more relevant to the cancers which occur in human beings. Two other such types of tumour are those caused by injections of chemical agents (carcinogens) into the animal which induce the formation of tumours, and those which are caused by the injection of certain classes of viruses. Welsch[159] has investigated the activity of *cis*-$[Pt(NH_3)_2Cl_2]$ against the dimethylbenzanthracene-induced mammary tumour in the rat and reported the complete regression of a very large number of extensively developed mammary tumours in rats, with at least three out of fourteen rats completely 'cured' of all tumours. Since this particular tumour is the best model system for human mammary tumours, these results are of significant interest. Hinz[160] has reported the same complex active against a virally induced tumour, the Rous Sarcoma Virus, causing complete regression in 95% of the animals.

Leonard *et al.*[161] have reported *cis*-$[Pt(NH_3)_2Cl_2]$ and *cis*-$[Pt(NH_3)_2Cl_4]$ to be active against myeloid and lymphatic leukaemias induced by feeding mice and rats with ICI 42,464 {(2γ-chloro-β-isopropylamine)-ethylnaphthalene hydrochloride}. The complexes do not have any undesirable effects on the normal cells of the marrow, gonads and intestine.

From the accumulating results of antitumour activity against transplantable, carcinogenically induced and virally induced tumours Rosenberg[162] concludes that these complexes have one of the broadest spectra of action of any class of antitumour agents yet discovered. From the fact that they can cause regression of large tumours and rescue animals when injected a few days prior to their death, Rosenberg[162] deduces that these complexes are very potent antitumour agents.

Any slight adverse side effects of these platinum complexes such as the effects on the cells of the intestinal lining and the bone marrow[163] are reversible, and the animals recover. They exhibit no long-lasting side effects caused by therapeutic treatment.

Cleare and Hoeschele[15] have investigated the antitumour activity of a wide variety of platinum(II) complexes against Sarcoma 180 in Swiss white female mice. A series of complexes of the type *cis*-$[PtA_2X_2]$ (where A_2 is either two monodentate or one bidentate amine ligand and X_2 is either two monodentate or one bidentate anionic ligand) have been studied with A and X systematically varied. This has resulted in the identification of at least ten potentially active antitumour drugs. They found only neutral *cis* complexes active and complexes containing highly reactive ligands such as *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ to be highly toxic. Palladium(II) complexes analogous to the active platinum(II) complexes have been found to be inactive.[15]

Connors *et al.*[164] have found a class of compounds which are some thirty to forty times more active against a mouse plasma cell tumour (ADJ/PC6A) than the complex *cis*-$[Pt(NH_3)_2Cl_2]$. The two most active complexes found were *cis*-$[Pt(\text{cyclopentylamine})_2Cl_2]$ and *cis*-$[Pt(\text{cyclohexylamine})_2Cl_2]$. The cyclopentylamine derivative is at present undergoing clinical trials at the European Organisation for Research on Treatment of Cancer (OERTC).

Harder[165] has measured the ability of treated cells to manufacture nucleic acids (DNA and RNA) and proteins and found that only those platinum complexes which are active antitumour agents are capable of inhibiting the synthesis of DNA. Those which are inactive do not produce such inhibition. Further, at the dose level that appears in the tumour tissues of the animals, the DNA replication is selectively inhibited while RNA and protein synthesis are not. Similar results have been found by Gale and Howle *in vivo*.[166] From the evidence available Rosenberg[162] concludes that the platinum complexes most propably act by causing a primary lesion in the DNA of the cell. The distance between the two active chloride groups in *cis*-$[Pt(NH_3)_2Cl_2]$ is 3.3 Å and the stacking spaces of the purine bases in the Watson-Crick model of DNA is 3.4 Å, which leads to the suggestion that the primary lesion caused by the platinum complexes is an intrastrand purine dimer. *In vitro* studies with purine dimers tend to validate this hypothesis,[162] but much work must be done to prove or disprove it conclusively. This mode of action differs from that of the bifunctional alkylating agents which are thought to act by the formation of an interstrand crosslink between the guanine bases, at the N–7 position, in double standed DNA.

8. Appendix of Additional References

1. Reaction of methionine with Peiron's chloride, L. M. Volshtein, L. F. Krylova and M. F. Mogilevkina, *Zh. Neorg. Khim.*, *11*, 614 (1966). Reaction of methionine with *cis*-$[Pt(NH_3)_2Cl_2]$ produces the complex $[Pt(MtH)_2(NH_3)]Cl_2$ (MtH = methionine), where one methionine molecule is joined to platinum cyclically through the amino group and the sulphur atom and the second is present as the bipolar $MtH^{\pm}$ ion, joined to platinum only through the sulphur atom.
2. Reaction of methionine with diamminedichloroplatinum(II), L. M. Volshtein, L. F. Krylova and M. F. Mogilevkina, *Zh. Neorg. Khim.*, *10*, 1976 (1965). Reaction of methionine with *trans*-$[Pt(NH_3)_2Cl_2]$ in a 2:1 ratio forms the very soluble *trans*-$[Pt(NH_3)_2(MtH)_2]Cl_2$ which, on reaction with K_2HgI_4 produces a yellow precipitate of *trans*-$[Pt(NH_3)_2(MtH)_2].HgI_4$. The methionine molecules are attached to platinum through the sulphur atom only in both complexes.
3. Two isomers of chloroamminemethionineplatochloride, L. M. Volshtein and M. F. Mogilevkine, *Dokl. Akad. Nauk S.S.S.R.*, *163*, 1385 (1965). The preparations of the complexes *cis*- and *trans*-$[Pt(NH_3)(Mt)Cl]$ are described.
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