Anti-tumour Platinum Compounds

RELATIONSHIP BETWEEN STRUCTURE AND ACTIVITY

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A wide variety of platinum(II) complexes have been synthesised and tested for anti-tumour activity resulting in the identification of additional potentially active anti-tumour drugs. Several structural features have been shown to be necessary for a complex to show activity. This article follows up the article by Professor Barnett Rosenberg in the April 1971 issue.

In recent years B. Rosenberg and L. Van Camp at Michigan State University have demonstrated potent anti-tumour activity in certain platinum coordination complexes (1, 2). A previous review in this journal has described the early stages of this research (3), which has led to one compound, *cis*-dichlorodiammineplatinum(II), undergoing extensive human clinical trials in the United States under the auspices of the National Cancer Institute. Although these trials are far from being completed, the preliminary Phase I results are quite encouraging and indicate good tumour growth inhibition. While the necessarily lengthy clinical procedures have been getting under way, inorganic chemists have been synthesising related platinum compounds in order to determine what relationships exist between chemical structure and anti-tumour activity. A knowledge of such structure-activity relationships is useful both in designing more effective anti-tumour metal compounds and also in understanding the origin of such activity.

Testing Procedures

Two major research groups have been working in this area during the last two years (4, 5). The authors, in conjunction with Rosenberg and Van Camp, have synthesised a variety of platinum and other precious metal compounds, which have been tested against Sarcoma 180 in Swiss white female mice. P. D. Braddock, A. R. Khokhar and M. L. Tobe of University College, London, have synthesised platinum complexes which have been tested at the Chester Beatty Cancer Institute by T. A. Connors, M. Jones and W. C. J. Ross using the ADJ/PC6 plasma cell tumour in female BALB/c mice. The latter tumour has been used extensively for testing the alkylating agent drugs, some of which have been clinically successful. It is important to realise that the results obtained apply only to the particular tumour system employed and do not necessarily indicate activity against other tumour systems. In fact, several compounds are noted below which are active against ADJ/PC6 and inactive towards S 180 under the test conditions. *Cis*-dichlorodiammineplatinum(II) has, however, shown activity against a broad range of animal tumours—around thirty in all. Both of the tumours mentioned above were transplanted subcutaneously by means of tumour fragments on day 0 of the testing scheme. In both cases the test compounds were given interperitoneally as a solution or suspension in various solvents (usually physiological saline or arachis oil). For S 180 this occurred on day 1 and for the plasma cell tumour on day 24. Ten days after injection the animals were sacrificed and the weights of the excised tumours were compared with those from untreated control animals.

The ratio of tumour weights of treated and control animals (T/C), expressed as a percentage, is a measure of the potency of the

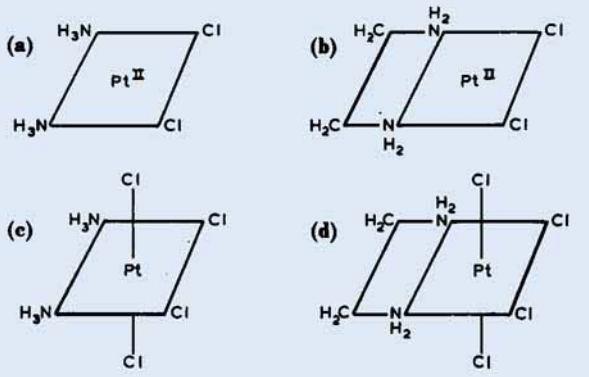


Fig. 1 The original active platinum complexes described by Rosenberg (1). 1a. cis-$[Pt(NH_3)_2Cl_2]$, *cis-dichlorodiammineplatinum(II). 1b.* $[PtenCl_2]$, *dichloroethylenediamineplatinum(II) 1c.* cis-$[Pt(NH_3)_2Cl_4]$, *cis-tetrachlorodiammineplatinum(IV). 1d.* $[PtenCl_4]$, *tetrachloroethylenediamineplatinum(IV)*

anti-tumour effect. T/C values which are less than 50 are generally considered significant. The therapeutic index (T.I.) is the ratio of the dose which kills 50 per cent of the animals (LD_{50}) to that which causes 90 per cent tumour regression (ID_{90}). Normal screening protocols were observed (6).

In the tables the dose range indicates the maximum and minimum doses which have been administered, and the dose response is termed positive (+) for cases where a consistent decrease in tumour size is observed as doses are increased up to toxic levels. In the S 180 data the toxic level is the highest dose at which survivors are greater than or equal to 83 per cent, while the T/C value quoted is the lowest obtained for a compound with a positive dose response. For compounds with marginal or negative responses the T/C values quoted are averages over the dose range given in the final column.

Chemical Procedures

Compounds of the general formula *cis*-$[PtA_2X_2]$ were prepared by two methods:

(1) Exchange of the X ligands was achieved via the diaquo species *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$, which is formed when *cis*-$[Pt(NH_3)_2Cl_2]$ is reacted with silver nitrate (7). The new complex was produced by addition of a solution containing the appropriate anion (X=Br, I, SCN, NO_2, NCO; X_2=ox, mal (substituted malonates)).

(2) The A ligands can be varied using an extension of Dhara's method for preparing *cis*-$[Pt(NH_3)_2Cl_2]$ (8). This consists of reacting $K_2[PtCl_4]$ with the stoichiometric amount of potassium iodide to produce $K_2[PtI_4]$ in solution. The latter solution reacts with most amines to precipitate *cis*-$[PtA_2I_2]$ or $[PtAI_2]$. Reaction with silver nitrate as in the first method affords ready conversion to other *cis*-$[PtA_2X_2]$ species. Many of the amine complexes can be prepared by direct reaction with $K_2[PtCl_4]$, although this is generally a less efficient route.

Cis and *Trans* Complexes

In chemical terms the obvious similarity between the original active compounds shown in Fig. 1 is in the geometric arrangement of the chloride ligands. Each complex contains at least two adjacent (*cis*) reactive ligands. This feature has remained true throughout all the complexes examined to date, and where *trans* isomers exist and have been tested they are inactive in comparison to an active *cis* isomer, as shown in Table I.

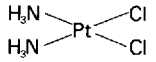
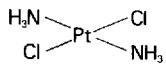
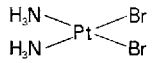
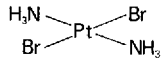
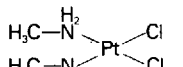
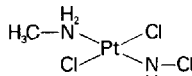
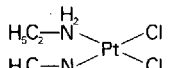
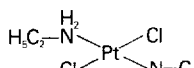
Thus the major effort has been directed towards *cis* complexes of the type $[PtA_2X_2]$, where A_2 is two monodentate or one bidentate amine ligand, and where X_2 is two monodentate or one bidentate anionic ligand.

Trans isomers are considerably more reactive than their *cis* analogues; thus *trans*-

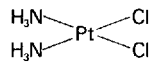
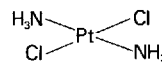
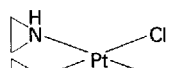
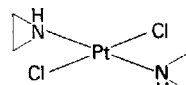
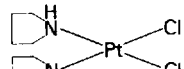
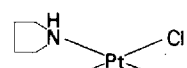
Table I

Comparison of Activities for *cis* and *trans* Isomers

Sarcoma 180

Complex		Solvent	Dose Range mg/kg	Dose Response	Toxic Level mg/kg	T/C	Dose mg/kg
	cis	S	0.5–20	+	9	1	8
	trans	S	2.5–40[b]	—	>40	85	2.5–40
	cis	B	5–20	+	15	30	14
	trans	B	10–40	—	>40	110	10–40
	cis	S	10–30	+	12–20[c]	25	15[a]
	trans	S	5–100	—	25	100	5–20
	cis	S	5–50[b]	+	45	14	40
	trans	SS	5–20	—	>20	105	5–20

ADJ/PC6 Plasma Cell Tumour

Complex		Solvent	Dose Range mg/kg	Dose Response	LD_{50}	ID_{90}	T.I.
	cis	A	0.1–40	+	13.0	1.6	8.1
	trans	A		—	27.0	>27.0	<1.0
	cis	A	2.5–160	+	56.5	2.6	21.7
	trans	A		—	18.0	>18.0	<1.0
	cis	A	6–800	+	240	17.5	13.7
	trans	A		—	72	>72	<1.0

a Only 66 per cent survivors. b Slurry at higher concentrations c Sporadic toxicity over this range

Table II

Variation of X in *cis*-$[Pt(NH_3)_2X_2]$ with Sarcoma 180 Tumour

X	Solvent	Dose Range mg/kg	Dose Response	Toxic Level mg/kg	T/C	Dose mg/kg
NO_3^-	W	6–12	–	7[e]	54	6
NO_3^-	S	2.5–12	+	11	8	10
H_2O[f]	W	2–20	–	5[e]	—	—
Cl^-	S	0.5–20	+	9	1	8
Br^-	B	5–20	+	15	30	14
Br^-	S	2–6[d]	+	5–6[d]	13	5
I^-	WS	10–25	–	>25	110	10–25
$\underline{S}CN^-$	S	5–100[b]	–	~50	70	20–35
$\underline{N}O_2$	SS	5–100	–	>100	99	5–100

b Slurry at higher concentrations d Daily injections for 9 days e Highly toxic – convulsions f Cationic complex ion (2+)

$[Pt(NH_3)_2Cl_2]$ aquates approximately four times faster and undergoes ammonation some thirty times faster than its *cis* isomer (9, 10). This suggests that *trans* compounds will react faster and with a wider variety of body constituents than their respective *cis* isomers, making them less specific in their action. Preliminary distribution and excretion studies involving ^{195m}Pt-enriched $[Pt(NH_3)_2Cl_2]$ isomers indicate that the *cis* isomer is excreted initially faster than the *trans* isomer, although the amounts retained after five days are comparable. However, the relative levels of isomers in the blood indicate a *trans* concentration which is initially some three times higher than for the *cis* compound, and with a higher retention after five days (11). Since only *cis* compounds have the potential to form chelates (assuming that only the chloride ligands are reactive) this might imply that the anti-tumour activity is largely associated with a chelating interaction. DNA appears to be a principal receptor site (12, 13) and both inter- and intrastrand chelated crosslinking is possible; indeed, the former has been demonstrated for HeLa cells in culture (14).

Variation of Anionic Ligand

Table II shows the effect of varying X in *cis*-$[Pt(NH_3)_2X_2]$. Chemical studies on *cis*-$[Pt(NH_3)_2Cl_2]$ have clearly established that the chlorides are the reactive ligands (15, 16), whereas the platinum ammine bonds are very stable and rather inert to nucleophilic attack. Thus it is likely that biological interactions occur with X (in *cis*-$[Pt(NH_3)_2X_2]$) as the leaving group. Although no definite information has been obtained about the effective anti-tumour site(s) of action, the effect of varying the presumed leaving group X can be observed. The order of leaving ability has been established for the reaction

$$[Pt^{II}(dien)X]^+ + py \rightarrow [Pt^{II}(dien)py]^{2+} + X^-$$

where the order of decreasing rate constants is $X = NO_3^- > H_2O > Cl^- > Br^- > I^- > \underline{S}CN^- > \underline{N}O_2^-$ (17).

This seems to be generally true for Pt(II) substitution reactions (18). The spread in reaction rates for the above sequence is nearly 10^6, showing the influence of the Pt-X bond strength on the intrinsic reactivity.

The screening results reflect this order of leaving ability. Where the X ligands are

readily replaced (H_2O, NO_3) the complexes only show activity when administered in saline, wherein the chloro species is reformed prior to and during inoculation. In aqueous solution *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ shows a remarkably high and immediate toxicity, which appears to be due to action at the neuromuscular junction. Recent studies indicate that the solution containing this species has potential as an anti-viral agent (19).

When X is of intermediate leaving ability (Cl, Br) the compounds show considerable anti-tumour activity, which follows the leaving order with chloride somewhat more effective than bromide. The latter appears to require a higher dose (in terms of platinum) to register its maximum effect and has a correspondingly high toxic level. However, its lower solubility must be taken into account. The iodide is extremely insoluble but is inactive up to the doses shown when given as a slurry. This order of halogen complex activity holds for other *cis* amine complexes.

The strongly bound thiocyanate (-SCN) and nitrite ($-NO_2$) ligands give inactive complexes, which the animals can tolerate at relatively high doses. In these cases the ligands are so tightly bound that little or no reaction occurs within the body.

Thus the activity of these complexes is largely dependent on the nature of the Pt-X bond. Labile complexes will react rapidly and indiscriminately, thus preventing a sufficient amount from reaching the site(s) responsible for the anti-tumour activity. Inert compounds, which reach these site(s) in higher concentration, will not react sufficiently to elicit the anti-tumour response. Complexes with mixed monodentate anionic ligands, i.e., *cis*-$[Pt(NH_3)_2XY]$ where $X \neq Y = Cl$, Br, I, NO_2, SCN, have been prepared but the activity was not enhanced (4).

When X_2 is replaced by a chelated dicarboxylate anion, as in Fig. 2, (e.g. oxalate $C_2O_4^{2-}$ and malonates $O_2C.CH(R).CO_2^{2-}$, where R=H, CH_3, C_2H_5) considerable activity is observed (Table III). Indeed, $[Pt(NH_3)_2mal]$ is more effective against the ADJ/PC6 tumour than the parent compound *cis*-$[Pt(NH_3)_2Cl_2]$ and is equally as effective against S 180. It is also active against S 180 tumour after eight days of growth. These chelated complexes are expected to be relatively inert to substitution, and indeed spectral and conductivity changes occur extremely slowly at 37°C (4). Accurate kinetic studies for reactions with chelating N-donor ligands (such as are found in DNA) are desirable. However, at present it is difficult to rationalise the anti-tumour activity in terms of leaving ability of the chelated ligands. A different mechanism could operate, such as biological activation (e.g. enzymatic removal) of the chelated groups. Coordination to a metal should make the methylene ($-CH_2-$) group in malonate more susceptible to nucleophilic attack.

Variation of the Amine Group

Table IV shows the effect of varying the A group. By far the majority of A ligands have been N-donors such as mono- and bidentate neutral aliphatic, aromatic and heterocyclic amines. Whereas the X group largely determines the reactivity of the amine complexes, the nature of the A ligands will modify this in a secondary manner due to differing steric, electronic and basic properties. However, as Tables IV and V illustrate, the nature of the A group has a primary effect on the anti-tumour property, which is very difficult to correlate with any chemical reactivity effects.

In the S 180 test system, complexes with primary amines ($R.NH_2$; R=alkyl) retain

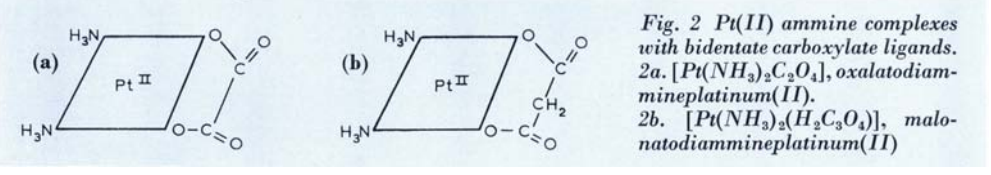
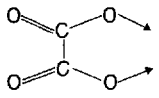
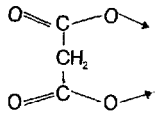
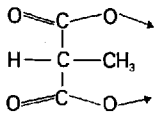
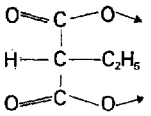
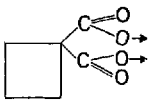
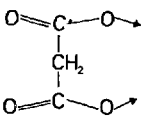


Fig. 2 Pt(II) ammine complexes with bidentate carboxylate ligands. 2a. $[Pt(NH_3)_2C_2O_4]$, oxalatodiammineplatinum(II). 2b. $[Pt(NH_3)_2(H_2C_3O_4)]$, malonatodiammineplatinum(II)

Table III

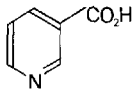
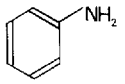
Activity of Ammine Complexes with Chelated Dicarboxylate Ligands X in $[Pt(NH_3)_2X]$

Sarcoma 180 X	Solvent	Dose Range mg/kg	Dose Response	Toxic Level mg/kg	T/C	Dose mg/kg
 oxalate	DMSO (slurry)	5–20	+	16–20	9	15
	WS	12–18	+	17	24	14–16
	W	10–20[g]	+	10	0	10[a]
	W	0.5–6[d]	+	3–4	25	2.5
 malonate	WS	10–60	+	35	7	30
	W	5–24[g]	+	24	28	20–24
	W	1–7[d]	+	8	12	7
 methyl malonate	W	10–80	+	65	7	60
 ethylmalonate	W	30–80	+	>80	17	70–80
 1,1 cyclobutane dicarboxylate	W	20–160	+	150	18	120

ADJ/PC6 Plasma Cell Tumour X	Solvent	Dose Range mg/kg	Dose Response	LD_{50}	ID_{90}	T.I.
 malonate	A	1–320	+	225	18.5	12.2

a 66 per cent survivors only d Daily injections for 9 days g Multiple injections due to low solubility

Table IV **Changes in Activity on Varying A in *cis*-$[PtA_2Cl_2]$**

Sarcoma 180 A	Solvent	Dose Range mg/kg	Dose Response	Toxic Level mg/kg	T/C	Dose mg/kg
H_3N	S	4–15	+	9	3	8
CH_3NH_2	S	10–30	+	12–20[c]	14	14[a]
$(CH_3)_2NH$	S	30–150	+	~100	25	80
$C_2H_5NH_2$	S	5–50	+	~40	14	40
$(C_2H_5)_2NH$	SS	15–60	–	>60	75	60
$HOC_2H_4NH_2$	S	20–225	+	~125	22	125
i-$C_3H_7NH_2$	SS	20–50	±	>50	33	30
	WS	5–40	–	>40	94	5
	Wh	4–80	+	>80	51	40–60
	SS	10–50	+	>50	~33	10–20

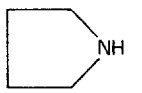
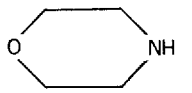
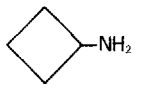
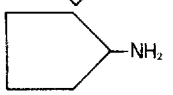
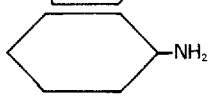
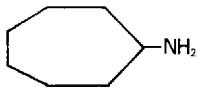
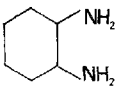
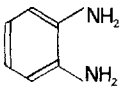
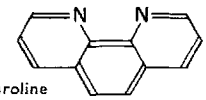
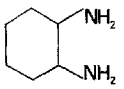
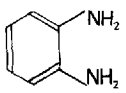
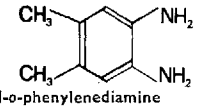
ADJ/PC6 Plasma Cell Tumour A	Solvent	Dose Range mg/kg	Dose Response	LD_{50}	ID_{90}	T.I.
NH_3	A	0.1–40	+	13.0	1.6	8.1
CH_3NH_2	A		–	18.5	18.5	1.0
$ClC_2H_4NH_2$	A		+	45.0	17.5	2.6
	A	2.5–160	+	56.5	2.6	21.7
	A	3–200	+	141	10.8	13.1
	A		–	90	>90	< 1.0
	A		–	18	>18	<1.0
	A	1–80	+	56.5	2.3	24.6
	A	6–750	+	67	<6	>11.1
	A	1–3200	+	480	2.4	200
	A	1–3200	+	>3200	12	>267
	A	5–625	+	>625	18	>35

Table V — **Changes in Activity on Varying A in $[PtACl_2]$**

Sarcoma 180 (For key to columns see Table IV opposite)

$H_2N.CH_2.CH_2.NH_2$ ethylenediamine	S	2–32	+	16	27	12
$HN(CH_3).CH_2.CH_2.NH_2$ N-methylethylenediamine	S	7.5–20	±	10–15	51	15[a]
$HN(CH_3).CH_2.CH_2.NH(CH_3)$ N,N'-dimethylethylenediamine	S	20–80	±	25–35[d]	26	30
$H_3C.N(CH_3).CH_2.CH_2.NH_2$ N,N-dimethylethylenediamine	SS	25–100	–	75–100	60	25–75
$H_3C.N(CH_3).CH_2.CH_2.NH(C_2H_5)$ N,N-dimethyl-N'-ethylethylenediamine	SS	50–125	±	~120	62	100
$HN(C_2H_5).CH_2.CH_2.NH(C_2H_5)$ N,N'-diethylethylenediamine	SS	75–225	–	>225	96	75–225
$H_5C_2.N(C_2H_5).CH_2.CH_2.NH_2$ N,N-diethylethylenediamine	S	10–100	±	>100	54	75–100
$H_2N.CH_2.CH(NH_2).CH_3$ 1,2-propylenediamine	SS	5–20	±	8–12[c]	62	12[a]
$H_2N.CH_2.CH_2.CH_2.NH_2$ 1,3-propylenediamine	SS	8–30	±	10–15[c]	58	15–30
 1,2-diaminocyclohexane	SS	10–30	±	20–35[c]	62	15–30
 o-phenylenediamine	SS	20–80	–	>80	120	20–80
 o-phenanthroline	SS	10–30	–	15	69	10

ADJ/PC6 Plasma Cell Tumour (For key to columns see Table IV opposite)

 1,2-diaminocyclohexane	A	0.3–40	+	141	2.1	6.9
 o-phenylenediamine	A	0.6–80	+	48	2.4	20.4
 4,5-dimethyl-o-phenylenediamine	A	12–1500	+	680	<12	>56.7

activity, although at an apparently reduced level compared to the parent ammine. With secondary amines (R_2NH; R=CH_3, C_2H_5) the response is only marginally apparent. Where the alkyl moiety exceeds two carbon atoms the compounds are highly insoluble and show marginal activity at best, although this may be enhanced when the chlorides are converted to more soluble analogues, such as malonates. Aromatic, heterocyclic and alicyclic amine complexes have shown little or no activity at the levels which have been tested so far. The pyridine complex shows some activity against the Ehrlich ascites tumour (20). In the case of bidentate amines the ethylenediamine complex shows a good response (as reported originally by Rosenberg (1)) but alkyl-substituted ethylenediamine complexes are only marginally active (Table V). Again, the more extensive the alkyl substitution the higher is the dosage required to obtain the optimum effect, although the differences in response are not very distinct. No distinction could be found between the aryl and alkyl compounds 1,2-diaminocyclohexane and *o*-phenylenediamine.

In the ADJ/PC6 test system, the primary amine methylamine, CH_3NH_2, gave rise to greatly reduced activity but with no change in toxicity. Effects like this have been noted in other cases and indicate that toxicity may not be so closely related to anti-tumour activity as to prevent the existence of other compounds with a low toxicity and a high activity. In fact, the series of compounds with cyclic nitrogen ligands gives good results for this tumour with the ethyleneimine, $\underline{CH_2.CH_2.NH}$, and pyrrolidine, $\underline{CH_2.(CH_2)_3.NH}$, complexes some two to three times more selective than the parent compound. Again, relatively small changes, such as in morpholine and a substituted ethyleneimine, lead to loss of activity. Although ethyleneimines are anti-tumour agents in their own right, the molecule is greatly stabilised on coordination and it seems unlikely that ethyleneimine itself plays a role in the anti-tumour response. Unfortunately the ethyleneimine complex has shown little sign of activity against S 180.

Complexes with aromatic or alicyclic diamines or with two alicyclic amines give outstanding results against the ADJ/PC6 tumour and some have T.I.s which are very much better than that of the parent compound. The cyclopentylamine and cyclohexylamine compounds are the best ever tried against this tumour. Preliminary results for activity of the hexylamine derivative against other tumours (S 180 (21), Leukemia L-1210 and Walker 256 Carcinosarcoma (22)) are rather disappointing and suggest that the anti-tumour activity is very specific. However, recent data on the cyclopentylamine derivative are much more promising (22).

Activity and Amine Structure

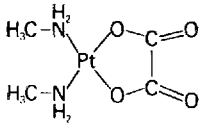
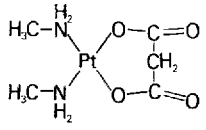
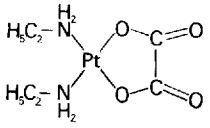
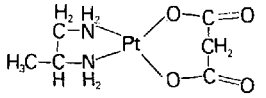
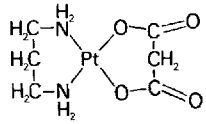
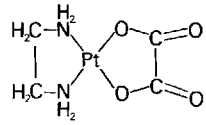
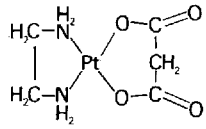
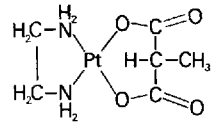
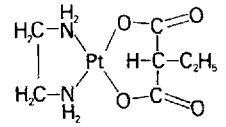
At present there is no obvious explanation for the variation of activity with amine structure. It does not seem very likely that kinetic effects alone are responsible, and hydrogen bonding interactions between the amine ligands and biological molecules (receptors) may be important in stabilising the receptor-drug complex. Increasing substitution of the hydrogens in NH_3 by alkyl groups will tend to decrease the hydrogen bonding potential and this could be related to the decrease in activity on alkyl substitution. Membrane interactions may also be important.

A variety of X ligands were used in conjunction with these amines, and in general where a chloro complex was active the corresponding oxalates and malonates also showed a good response (Table VI). Halide complex activity was in the order Cl > Br > I.

Relatively few complexes have been tested in which the A ligands are non-N-donors. As yet none have shown activity against any test tumour. Although there is no justification at present to suggest that these complexes cannot give rise to anti-tumour activity, there does appear to be a clear preference for amine-based systems. Apart from oxygen, the variation of different donors will naturally involve ligands which are for the most part either more strongly labilising neutral groups, such as S- and P-donor atom ligands and various π-acceptor systems, or charged ligands which give rise to charged complexes.

Table VI

Various Amine Complexes Containing Oxalate and Malonate Ligands [PtA_2X] or [PtAX]

Sarcoma 180 Complex	Solvent	Dose Range mg/kg	Dose Response	Toxic Level mg/kg	T/C	Dose mg/kg
 oxalatobis(methylamine)platinum(II)	W	5–80	+	20–30[i]	21	30
 malonatobis(methylamine)platinum(II)	W	80–180	+	>180	20	120–180
 oxalatobis(ethylamine)platinum(II)	W	10–80	±	20–40	21	10
 malonato-1,2-propylenediamineplatinum(II)	W	45–90	+	65	9	60
 malonato-1,3-propylenediamineplatinum(II)	W	20–80	+	90	28	60–80
 oxalatoethylenediamineplatinum(II)	W	0.25–16	–	3[e]	75	0.25–2
 malonatoethylenediamineplatinum(II)	W	5–80	+	45–60	18	40
 methylmalonatoethylene-diamineplatinum(II)	W	30–90	+	>90	4	90
 ethylmalonatoethylene-diamineplatinum(II)	WS	40–120	±	>120	51	90–120

e Highly toxic – convulsions

i Only 50 per cent survivors

Charge Effects

Although platinum(II) substitution reaction rates are largely independent of charge (23), the charge type of the complex appears to play an important role in the anti-tumour property. As yet only neutral species have shown any appreciable activity. Even when the criterion of *cis* leaving groups of intermediate lability (e.g. Cl) has been satisfied, the charged complexes which have been tested are inactive and relatively non-toxic. This effect would seem to be biophysical in nature and may be related to transport across cell membranes or to the greater efficiency with which charged compounds (which are generally quite water-soluble) are eliminated from the body. Some active neutral complexes (e.g. *cis*-$[Pt(MeNH_2)_2Cl_2]$, [Pten(mal)], $[Pt(NH_3)_2$Memal], $[Pt(NH_3)_2$Etmal]) are considerably more water-soluble than *cis*-$[Pt(NH_3)_2Cl_2]$. This might be advantageous in clinical studies, although there is some evidence that a higher aqueous solubility results in a higher therapeutic dose due to the increased rate of excretion.

Highly Toxic Compounds

Apart from [Pt(en)ox] (Table VI) these are all aquo species. They appear to act on the neuromuscular system, and cause the animals to undergo periodic but violent convulsions, with death occurring within a few hours. [Pt(en)ox] was the most severe example and this may support the suggestion that enzymatic removal of chelated groups is occurring, since the reactivities of oxalate and water, when coordinated to platinum(II), are not in any way comparable. The high toxicity of these aquo species emphasises how important it is that hydrolysis should *not* be allowed to occur prior to inoculation.

Other Metal Compounds

Palladium(II) analogues of active platinum(II) complexes have been tested against Sarcoma 180 but only marginal activity was observed. It is likely that the greater reactivity of palladium(II) (its complexes generally react some 10^5 times faster than comparable platinum(II) species (24)) is responsible for this effect. A few ammine complexes of rhodium(III) and iridium(III) have been tested against S 180, and only *mer*-$[Rh(NH_3)_3Cl_3]$ has shown any signs of promise. G. R. Gale and co-workers have found that a photochemical reaction product of ammonium hexachloroiridate(IV) shows some activity towards Leukemia L 1210, although their suggestion that *cis*-$[Ir(NH_3)_2Cl_4]$ is the effective species seems rather unlikely.

Conclusion

The following physical, chemical and structural parameters appear to be essential for the observance of anti-cancer activity:

(1) The complex should be neutral.

(2) It should contain a pair of *cis* leaving groups, the reactivity of which should generally fall within a range of lability approximately centred on that of the chlorides in *cis*-$[Pt(NH_3)_2Cl_2]$. However, *cis* leaving groups which are relatively non-labile *in vitro* (i.e. malonate) can give rise to active compounds.

(3) The requirement of *cis* leaving groups is a necessary but insufficient criterion for observing activity.

(4) The other ligands play an important role. They should be relatively inert and neutral. There appears to be a clear preference for amine type systems, although variation of this structure has given complex results and no clear pattern has emerged. However, the activity of compounds such as those containing alicyclic amines (e.g. cyclohexylamine) indicates that some platinum compounds may be highly selective. Continuing synthetic work may uncover many more interesting compounds and should further clarify these outlines of the structure-activity relationships.

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Abbreviations

Solvents: W=water; WS=water slurry
S =saline (0.15 *M*); SS=saline slurry
B =sodium bromide (0.04 *M*)
A =arachis oil
DMSO=dimethylsulphoxide

ox=oxalate mal=malonate
en=ethylenediamine dien=diethylenetriamine
Memal=methylmalonate
Etmal=ethylmalonate

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Rustenburg to Expand Platinum Production Again

PROBLEMS OF THE EXHAUST CATALYST DEMAND

The big question facing the platinum producers, particularly Rustenburg, the largest of them, is the extent to which platinum metals will be used in catalytic convertors to deal with automobile exhaust emissions. Because the automobile producers hope that the legislation facing them may be eased in its severity or delayed in its application, and because the catalyst technology they may have to rely upon is still being developed, they are naturally reluctant to commit themselves to platinum producers other than in somewhat elastic terms.

The lead time for getting substantial additional production of platinum metals into effect has been seriously eroded by the period of indecision of the automotive industry at large. Rustenburg's problem is compounded by the fact that it serves a large proportion of the world's needs of platinum for established uses, and its customers must not be made to feel that their future security of supplies is threatened by the prospective new use.

Therefore Rustenburg has taken the bold decision, with the attendant risk, of initiating the expansion of production at both the Rustenburg and Union mines to the optimum level as well as opening a new mine in an area where extensive exploration has already been done in anticipation of such a move.

The refineries operated jointly with Johnson Matthey must correspondingly be enlarged to give a total production capability, when fully established, of the order of twice the present output.

H. R. B.