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The Chemistry of Antitumour Platinum Complexes

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The antitumour activities of platinum complexes have been characterised in connection with their composition, structure, and properties. A relation has been established between the antiblastoma properties of platinum complexes and the charge and nature of neutral and acido-ligands, the geometrical configuration, and the degree of oxidation of the central atom. Hypotheses are put forward concerning the mechanism of the antitumour activity of platinum complexes. The prospects for the application of platinum and other platinum metal complexes in tumour chemotherapy are assessed.
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I. INTRODUCTION

In many biologically active substances such as haemoglobin, chlorophyll, vitamin B_{12}, and certain enzymes the coordinating atom and active centre is a metal (iron, magnesium, cobalt, copper, zinc, etc.). The need for a comprehensive investigation of the biological activities of complexes, particularly their antitumour properties, is therefore fully justified. The possibility of a wide-scale expansion of such research is supported by the present vast accumulation, in coordination chemistry, of experience on the synthesis of complexes of different metals differing in structure and complexity.

After the publication in 1912 of the communication of Neuberg et al.[1], numerous studies have been carried out in many countries on the search for antitumour substances among metal-containing compounds. In the Soviet Union much work has been done in this field by investigation at the Kiev School of experimental Oncologists, in particular by Magat and coworkers[2], who studied the antitumour properties of the iron tartrate complex. Unfortunately active agents could not be discovered and interest in this branch of the chemotherapy of malignant tumours began to flag. However, in their reviews Larionov and Vermel'[3,4] emphasised that this field should not be forgotten and they believed it useful to investigate metal coordination compounds as potential antitumour agents.

In recent years considerable advances in the search for antitumour preparations were made in the study of organic compounds—alkylating agents, antimetabolities, antibiotics, and plants alkaloids[5,6]. The search for new antitumour prepations has therefore been carried on mainly among these compounds: thus among the 150 000 substances tested at the National Cancer Institute of the USA up to 1970, only 20 were inorganic[7].

The discovery in 1969 by Rosenberg et al.[8] of powerful antitumour properties in *cis*-dichlorodiammineplatinum(II) (henceforth it will be abbreviated to DDP), which is an inorganic substance known since the past century, aroused fresh interest among chemotherapists in metal complexes, particularly platinum complexes. The DDP complex exhibited a pronounced effect on a number of animal and human tumours[9,10].

Since then an intensive search for new antitumour substances has begun in many laboratories of various countries among platinum complexes and studies on the mechanism of their action have been expanded. At the National Cancer Institute of the USA alone approximately 500 different platinum complexes have been investigated towards 1977 [11] and oncological clinical tests have been carried out on five compounds. With each year, the intensity and scale of research into this field of cancer chemotherapy has consistently increased, new laboratories continuously joining in the search. Three International Congresses have been held and more than 1000 communications dealing with various aspects of the antitumour activity of platinum complexes (and certain other metal complexes) under experimental and clinical conditions have been published. Rational ways of synthesising active preparations incorporating coordination compounds are being sought.

On the basis of the authors' own research and literature sources, this review deals with certain problems of the chemistry of platinum complexes with antitumour properties. Particular attention has been devoted to the interrelation between the structure and activity of the compounds, which is one of the most important problems in chemotherapy. The review uses surveys, reports, and symposium and conference proceedings published in recent years[7-10,12-17].

II. CHARACTERISTICS OF THE ANTITUMOUR ACTIVITIES OF PLATINUM COMPLEXES IN RELATION TO THEIR CHEMICAL STRUCTURE AND PROPERTIES

1. Discovery of the Antitumour Activity of Platinum Complexes

The first systematic studies on the antitumour activities of platinum and certain other metal complexes were begun in the USA and the USSR. Using as ligands active antitumour antimetabilities which have already been tested—6-mercaptopurine (Hmp) and butylthiopurine (Butp), Kirschner et al.[18] observed in 1966 the effectiveness of the complexes $Na_2[Pt.(Hmp)_2Cl_4].2H_2O$ and $[Pd(Butp)_3Cl]Cl$ against two strains of mouse tumours. At the same time in 1965–1966 the activity of a number of compounds, particularly platinum and palladium complexes of 6-mercaptopurine and 5-fluorouracil as well as the gold complex of 6-mercaptopurine, was studied at the Institute of Experimental and Clinical Oncology on the Academy of Medical Sciences of the USSR (which has since become the All-Union Oncological Scientific Centre of the

Academy of Medical Sciences of the USSR).[19,20] The palladium and gold complexes of 6-mercaptopurine showed the greatest therapeutic effect:

$[Pd(Hmp)_2]SO_4$—80–92% inhibition of adenocarcinoma AK-755, 50–60% inhibition of Sarcoma 180.
$[Au(Hmp)_3]Cl$—90–95% inhibition of AK-755.

Unfortunately in the above studies[18,20] no advantages were discovered in the activities of the complexes compared with the free antimetabolities and these studies are therefore of merely theoretical interest.

The discovery by Rosenberg of the antiblastoma activity of DDP [8] attracted the attention of investigators to this field and stimulated further search for antitumour agents among metal complexes. By studying the effect of the electric field on a culture of *E.coli*, the authors observed in 1965 the cessation of cell division and the occurrence of unbalanced growth, which was reflected in the lengthening of the microorganisms by a factor up to 300 (the formation of the so-called filamental forms of the bacteria)[21]. The electrolysis was carried out with the aid of platinum electrodes and the nutrient medium contained NH_4Cl, Na_2HPO_4, KH_2PO_4, NaCl, $MgCl_2$, Na_2SO_4, and other ingredients. The study showed that during electrolysis platinum dissolves with formation of a non-electrolytic platinum(IV) complex with a *cis*-structure, which is subsequently reduced in the light to *cis*-$[Pt(NH_3)_2.Cl_2]$ and the latter compound showed a biological activity.

The result of the above investigation[21] was confirmed in a study of the direct effect of *cis*-$[Pt(NH_3)_2Cl_2]$ on tumours[8]. The complex *cis*-$[Pt(NH_3)_2Cl_2]$ (in physiological solution) was administered intra-abdominally on a specific day after transplantation of the tumour; after a time, the mice were killed and the tumour was cut out. The efficiency of the preparation was estimated by comparing the average weight T of the tumours cut out from a batch of mice subjected to chemotherapy and the average weight K of the tumours in mice of a control group; the smaller the ratio T/K, the greater the inhibiting effect of the complex. The following data were obtained in experiments with Sarcoma 180:

Complex	$[Pt(NH_3Cl)_2]$	$[PtEnCl_2]$
Maximum tolerance dose (MTD), mg kg^{-1}	8	16
T/K, %	1	27

Here En is ethylenediamine. The best result was produced by the complex $[Pt(NH_3Cl)_2]$, for which T/K = 1%, which corresponds to 99% inhibition of the growth of the tumour. A considerable proportion of the animals were completely cured. As a result of the primary selection, Rosenberg concluded that non-electrolytic platinum(II) complexes with a *cis*-structure, containing two molecules of a neutral inert ligand (NH_3, amine) and two anions of moderate lability (preferentially Cl^- ions), are biologically active. After a comprehensive experimental investigation of the therapeutic activity and side effects, DDP was subjected to clinical tests and has found extensive applications in the treatment of a number of human tumours, particularly in combination with other antitumour agents[10,22–24].

2. Geometrical Configuration of Non-Electrolytic Platinum(II) Complexes and their Antitumour Activity

Table 1 presents data for the antitumour activities and selectivities of the action of isomeric diacidodiamineplatinum-(II) complexes in relation to two strains of transplantable mouse tumours[7]. The antitumour activity of the complexes administered intra-abdominally single in the maximum tolerance dose (MTD), on Sarcoma 180, was determined 10 days after the injection and was expressed as a percentage inhibition of the growth of the neoplasm. The selectivity of the action of the substances was investigated on mice with plasmacytoma ADJ/PC6 using the same schematic arrangement of the experiments and was expressed by the therapeutic index TI = LD_{50}/ED_{90}, where ED_{90} is the effective dose resulting in 90% inhibition of the growth of tumours on the tenth day after injection. The higher the TI, the greater the antitumour activity and the smaller the toxic effect of the substance on the organism.

The data presented in Table 1 in relation to isomeric complexes with different amines and acido-ligands fully confirmed the conclusion that, when the complex exhibits antiblastoma activity, the latter is characteristic only of the *cis*-isomer; the *trans*-isomers have no antitumour properties (TI = 1).

Since this conclusion is general, the search for new antitumour platinum preparations attention was concentrated on the synthesis of non-electrolytic compounds with the *cis*-structure (Table 2). Such complexes are obtained particularly readily when potassium or sodium chloroplatinites are treated with bidentate amines which combine with platinum like ethylenediamine. Among them, complexes with 1,2-diaminocyclohexane proved to be the most promising.

Table 1. The influence of the geometrical isomerism of non-electrolytic platinum(II) complexes on their antitumour activities[7,17].

Complex	Medium	Dose range, mg kg^{-1}	Toxic limit, mg kg^{-1}	T/K, %	Dose, mg kg^{-1}
cis-$[Pt(NH_3Cl)_2]$	*S*	0.5—20	8	1	8
trans-$[Pt(NH_3)_2Cl_2]$	*S*	2.5—40	40	85	2.5—40
cis-$[Pt(CH_3NH_2Cl)_2]$	*S*	10—30	12—20	25	15
trans-$[Pt(CH_3NH_2)_2Cl_2]$	*S*	5—100	25	100	5—20
cis-$[Pt(C_2H_5NH_2Cl)_2]$	*S*	5—50	45	14	40
trans-$[Pt(C_2H_5NH_2)_2Cl_2]$	*S*	5—20	20	105	5—20
cis-$[Pt(NH_3Br)_2]$	*B*	5—20	15	30	14
trans-$[Pt(NH_3)_2Br_2]$	*B*	10—40	40	110	10—40

ADJ/PC_6 plasmacytoma

Complex	Medium	Dose range, mg kg^{-1}	LD_{50}, mg kg^{-1}	ED_{90}, mg kg^{-1}	TI
cis-$[Pt(NH_3Cl)_2]$	*A*	0.1—40	13.0	1.6	8.1
trans-$[Pt(NH_3)_2Cl_2]$	*A*	0.1—40	27.0	>27.0	<1.0
cis-[Pt($NHCl)_2$]	*A*	2.5—160	56.5	2.6	21.7
trans-[Pt($NH)_2Cl_2$]	*A*	2.5—160	18.0	>18.0	<1.0
cis-[Pt($NHCl)_2$]	*A*	3—200	140	10.8	13.1
trans-[Pt($NH)_2Cl_2$]	*A*	3—200	72	>72	<1.0

Notation: *S* = 0.13 M NaCl; *B* = 0.04 M NaBr; *A* = suspension in groundnut oil.

It is seen from the data in Table 2 that, despite their *cis*-configuration†, some of the complexes show little activity in relation to the plasmacytoma (TI ≅ 2).

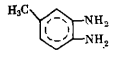
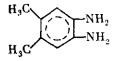
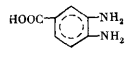
† We shall either indicate the geometrical configuration of the isomers (*cis*- or *trans*-) or shall employ the coordination formulae, for example *cis*-$[Pt(NH_3Cl)_2]$ and *trans*-$[Pt(NH_3)_2.Cl_2]$.

3. The Nature of the Acido-Ligand in the *cis*-Isomers

Among the complex *cis*-non-electrolytes with monodentate acido-ligands, the chloride ligands exhibit a high activity. Thus, in relation to sarcoma 180, the activity varies in the following sequences[7]:

$$[Pt(NH_3X)_2]$$
$$X: \quad Cl^- > Br^- > SCN^- > NO_2^- > I^-$$
$$T/K: \quad 1 \quad 30 \quad 70 \quad 99 \quad 110$$
$$[PtEnX_2]$$
$$X: \quad Cl^- > Br^- > NO_2^- > I^- \cong SCN^-$$
$$T/K: \quad 4 \quad 31 \quad 71 \quad 82 \quad 83$$

Table 2. The activities of certain new complexes of the type $[PtLCl_2]$ with bidentate ligands against plasmacytoma ADJ/PC6.[25–27]

Ligand L	LD_{50}, mg kg^{-1}	ED_{90}, mg kg^{-1}	TI
	14.1	2.1	6.9
	48	2.4	20
	22.5	3.7	5.3
	283	2,5	113
	180	90	2

The Pt–X bond strength increases from Cl^- to I^-, which can be seen from the decrease of the overall instability constant and the decrease of the positive standard free energy:

	$[PtCl_4]^{2-}$	$[PtBr_4]^{2-}$	$[PtI_4]^{2-}$	References
K_{inst}	$2.5 \cdot 10^{-17}$	$4 \cdot 10^{-21}$	$2.5 \cdot 10^{-30}$	[28,29]
ΔG°, kcal mol^{-1}	+34.40	+31.80	+18.40	[30]

Note. The numbers in square brackets denote references (Ed.of Translation).

These data indicate the opposite variation of the Pt–X bond strength and the activity of the complex. Complexes with carboxylate ions bound as bidentate species, of the type $[Pt(NH_3)_2X$ and $[PtEnX]$, exhibit an appreciable activity, malonate and substituted malonate complexes (T/K = 7–12%) being more active than the oxalate complexes (T/K = 25–26%).[7] It was found unexpectedly that, in contrast to $[Pt(NH_3)_2.(C_2O_4)]$, the complex $[PtEn(C_2O_4)]$ exhibits a curare-like activity, like the aquo-cationic complexes. Under the usual conditions, $[PtEn(C_2O_4)]$ is not hydrolysed; the complex apparently undergoes enzymatic hydrolysis in the organism. The compounds $[Pt(NH_3)_2(N_2O_2)]$ and $[PtEn(N_2O_2)]$ were the first complexes with a cyclic acido-ligand, namely the hyponitrite ion $N_2O_2^{2-}$, to be isolated[31].

The antitumour activities of these compounds were studied in relation to three strains of transplantable mouse tumours: adenocarcinoma 755, the Lewis lung cancer (LLC), and leukaemia L-1210. The complexes were dissolved in a physiological solution and were administered to mice intra-abdominally in the maximum tolerance doses. The activity of both hyponitrite complexes was tested on adenocarcinoma 755 (73–80% inhibition of the growth of tumour in relation to the control). In constrast to $[PtEn(C_2O_4)]$, the complex $[PtEn.(N_2O_2)]$ does not exhibit neurotoxicity[32].

The influence of the nature of the acido-ligand on the antitumour activities on a series of non-electrolytic *cis*-complexes of platinum(II) with 1,2-diaminocyclohexane have been studied in detail[33,34] in relation to 15 acido-ligands (Table 3). The activity M was estimated from the formula

$$M = \frac{LD_{50} \times ILT_{opt}}{ID_{99.9} \times 100},$$

where $ID_{99.9}$ is the dose killing 99.9% of the tumour cells and ILT_{opt} is the optimum increase of lifetime (expressed as a percentage). The greater the value of M, the higher the activity of the complex.

Table 3. The activities of non-electrolytic *cis*-complexes of platinum(II) with 1,2-diaminocyclohexane and various acido-ligands against lympholeukaemia L-1210.[33,34]

Ligand	SO_4^{2-}	OH^-	$B_4O_7^{2-}$	$C_2H_5SO_4^-$	$NH_2SO_3^-$	NO_3^-	Cl^-
M, %	100	80	70	50	30	22	18
Ligand	HPO_4^{2-}	SO_3^{2-}	BrO_3^-	SeO_4^{2-}	SiF_6^{2-}	NO_2^-	CNO^-
M, %	14	14	32	7	3	1	0

The sulphide complex is the most active (M = 100%). In this case complexes with less strongly bound acido-ligands also proved to be more active; the activity decreases in the sequence $SO_4^{2-} > B_4O_7^{2-} > C_2H_5SO_4^- > NO_3^- > Cl^-$. The change in the nature of the acido-ligand is reflected not only in the bond strength but also in the solubility of the complex, which influences in its turn its antitumour properties. The complexes of this series are in most cases more soluble and more active.

4. The Nature of the Amine in the *cis*-Isomers

The replacement of NH_3 by amines of different structure greatly alters the activity of the complex; an idea about this can be obtained from Table 1. Thus, in relation to sarcoma 180, the aliphatic amines CH_3NH_2 and $C_2H_5NH_2$ lower the activity of the complex. Aniline and pyridine have little effect on the activity.

The plasmacytoma ADJ/PC6 proved to be extremely sensitive to the nature of the amine in *cis*-$[Pt(ACl)_2]$. Table 4 presents data for the activities of complexes of this type containing NH_3, methyleneamine, heterocyclic bases (aziridine and pyrrolidine), and a number of alicyclic amines (the complexes with amines are sparingly soluble in water and were administered to mice intra-abdominally in the form of a suspension in grount-nut oil). The replacement of NH_3 by heterocyclic bases improved the result by a factor of 2–3. The activity increases particularly markedly following the introduction of alicyclic amines: TI increases up to 200 (cyclopentylamine) or 267 (cyclohexylamine). The increase

of TI is caused by the sharp reduction of the toxicity of the complexes: LD_{50} is 3200 mg kg^{-1} for cyclohexylamine and 13 mg kg^{-1} for NH_3, but the inhibiting activity (ED_{90}) changes only slightly.

Table 4. The influence of the nature of the amine on the antitumour activities of non-electrolytic *cis*-complexes of platinum(II) against plasmacytoma ADJ/PC6.[7,26]

Amine	LD_{50}, mg kg^{-1}	ED_{90}, mg kg^{-1}	TI
The complexes $[Pt(ACl)_2]$			
NH_3	13.0	1.6	8.1
CH_3NH_2	18.5	18.5	1.0
	56.5	2.6	21.7
	140	10.8	13.1
	56.5	2.8	24.6
	67	6	11
	480	2.4	200
	3200	12	267
	625	1.8	35
	660	230	2.9
The complexes $[PtACl_2]$			
	14.1	2.1	6.9
	48.0	2.4	20.4
	283	2.5	113

Such high therapeutic indices are not enountered among other antitumour preparations. The result is hopeful, since, by altering the composition of the complex, it is possible to obtain fairly effective and relatively non-toxic preparations. The disadvantages of the complexes with alicyclic ligands are their low solubility, which hinders their clinical use and a narrower therapeutic spectrum than for DDP; thus their activity in relation to Sarcoma 180 and L-1210 is low. The complex with cyclopentylamine exhibits the most comprehensive activity. The complexes with alicyclic diamines (1,2-diaminocyclohexane) are also active in relation to L-1210. At the same time, one should note that in many instances it is difficult to reach unambiguous conclusions concerning the influence of the nature of the amine or the substituent on the activity of the complex, the effect depends on the tumour strain. For example, $[Pt(PyCl)_2]$ [35] is active towards Ehrlich ascites carcinoma but its activity towards Sarcoma 180 is low. The activity of the complex is also sensitive to the structure of the ligand: the complex $[PtLCl_2]$ containing *trans*-1,2-diaminocyclohexane is more active than the complex with *cis*-1,2-diaminocyclohexane, the activity being a maximum for the complex with the laevorotatory *l-trans*-isomer[36].

In coordination chemistry the reactivity of complexes is usually attributed to the electronic structure of the ligands—their σ-donor and π-acceptor properties. It is difficult to make a comparison of this kind for the antitumour activity, since the latter is determimed not only by chemical and physicochemical characteristics but also by other factors—the lyophilic and lyophobic properties of the complexes, the permeability of cell membranes to them, and pharmacokinetic parameters.

5. The Solubility of the *cis*-Non-Electrolytes

The majority of dichlorodiamineplatinum(II) complexes are sparingly soluble in water and yet a fairly high solubility of complexes is necessary for intravenous injections. The efforts of investigators have therefore been directed to the synthesis of soluble active complexes (Table 5).

Table 5. The influence of the acido-ligand and substituents on the solubilities of the complexes in water at room temperature (L = 1,2-diaminocyclohexane).[7,26,30]

Complex	Solubility, g/100 ml H_2O	Complex	Solubility, g/100 ml H_2O
$[PtEnCl_2]$	0.08	$[Pt(NH_3Cl)_2]$	0.22
[PtEnmal]	1.00	$[Pt(NH_3)_2mal]$	0.04
$[PtEn(C_2H_5\text{-mal})]$	0.10	$[Pt(NH_3)_2(CH_3\text{-mal})]$	0.25
$[PtLCl_2]$	0.10	$[Pt(NH_3)_2(C_2H_5\text{-mal})]$	0.59
[PtLmal]	0.5	$[Pt(iso\text{-}PrNH_2)_2Cl_2]$	0.10
[PtL(OH-mal)]	1.5	$[Pt(iso\text{-}PrNH_2)_2mal]$	3.50

Table 6. Comparison of the solubilities of complexes of the types $[PtL'X_2]$ and $[PtL''X_2]$ (L' = 1,2-diaminocyclohexane and L'' = *o*-phenylenediamine) and their antitumour activities (against L-1210).[37,38]

X in complex $[PtL'X_2]$	Solubility at 25 °C, mg ml^{-1}	M, %	X in complex $[PtL''X_2]$	Solubility at 25 °C, mg ml^{-1}	ILT, %
$BrCH_2COO^-$	1	200	$1/2\ SO_4^{2-}$	5	100
$1/2\ SO_4^{2-}$	3	100	NO_3^-	5	48
$1/2\ mal^{2-}$	0.5	23	$BrCH_2COO^-$	5	43
Cl^-	0.1	18	$1/2\ mal^{2-}$	0,25	23

An increase of the solubility in water can be achieved in the following way: (1) by replacing Cl^- ions by cyclic carboxylate ions, for example malonate and its derivatives; (2) by introducing hydrophilic groups into the ligand; (3) by employing less strongly bound acido-ligands; (4) by using platinum(IV) complexes (but not in all cases). The replacement of $2Cl^-$ by mal^{2-} in the complexes where L = 1,2-diaminocyclohexane or other diamines increases the solubility by a factor of 5–10 (Table 6). This has also been observed to a lesser extent for ammines (with the exception of the replacement of $2Cl^-$ by mal^{2-}). The reason is apparently that in the case of a cyclic acido-ligand the intermolecular bonds are weakened and the lattice energy is lower.

The introduction of an organic substituent (C_2H_5) lowers the solubility of the complex and the introduction of the lyophilic OH group increases it. The increase of the hydrolysability of the complex in the case of less strongly bound ligands (SO_4^{2-} and NO_3^-) also promotes an increase of the solubility of the complexes with 1,2-diaminocyclohexane [33,34,37,38] (Table 6).

The activities of the complexes $[PtL'X_2]$ increases in the following sequence of L': $\frac{1}{2}SO_4^{2-} > OH^- > \frac{1}{2}B_4O_7^{2-}$; their solubilities in water at 40 °C decrease in the same sequence[33]. Hence one can conclude that the more soluble complexes are more active. However, this is not always so; in a series of complexes with branched aliphatic amines and alicyclic amines the less soluble complex is less toxic and therefore has a higher therapeutic index TI.[27]

The antitumour activities have been compared with non-aqueous, lipid solubilities, since the latter are related to the permeability of the membranes to the complexes. For this purpose, the solubilities of the complexes are determined in 1-octanol or chloroform by extremely sensitive methods—the atomic absorption and fluorescence methods[27]. In the series with alicyclic amines complexes with cyclopentyl- and cyclohexyl-amines, whose solubilities in water and chloroform are comparable—the partition coefficients K_{CHCl_3/H_2O} are 0.88 and 0.84—have the best TI. Unfortunately there are many discrepancies, particularly for DDP, where TI = 8 and $K_{CHCl_3/H_2O} = 0.008$. Therefore it is at present difficult to make any predictions about the activity of the complexes on the basis of their partition coefficients between non-aqueous and aqueous phases. One thing is certain, namely that intravenous injections in clinical tests require complexes which are fairly soluble in water.

6. The Nature of the Donor Atom in the Neutral Ligand

The relacement of amines by phosphorus- or sulphur-containing ligands [$P(C_6H_5)_3$, DMSO, $S(C_2H_5)_2$, etc.] in the *cis*-isomers $[Pt(ACl)_2]$ leads to the disappearance of activity: the percentage inhibition of the growth of Sarcoma 180 is in the range 40–20.[7] These ligands exhibit a powerful *trans*-influence. It may be that this entails a marked increase of the mobility of the Cl^- ion in the *trans*-position with respect to the ligand and an increase of the capacity of the complex for non-specific reactions, as in the case of *trans*-$[Pt(NH_3)_2.Cl_2]$. The complex with the cyclically bound glycimate ion, i.e. $[Pt(NH_2CH_2COO)_2]$, is also inactive.

7. The Antitumour Activities of Charged Platinum(II) Complexes

It was mentioned above that antitumour activity is characteristic of non-electrolytic platinum(II) complexes which permeate most effectively through the cell membrane. In 1975 Davidson, Rosenberg, and coworkers[39] observed an antitumour activity in complexes differing in structure from the non-electrolytic complexes—the so-called "platinum pyrimidine blues". These substances are obtained by keeping a solution of $[Pt(NH_3H_2O)_2](NO_3)_2$ at 37 °C in contact with 2,4-dihydroxypyrimidines—uracil, thymine, and their derivatives (Table 7). Amorphous blue or green precipitates are isolated from the resulting blue solution by adding alcohol and cooling. The chemistry of "pyrimidine blues" has not been investigated; only their overall composition is known. The majority of the analyses correspond to the ratios Pt : NH_3 : pyrimidine : OH = 1 : 2 : 1 : 1. It has been observed by electrophoretic and chromatographic methods that platinum pyrimidine blues contain platinum in the form of a cation and have the structure $[Pt(NH_3)_2(pyrimidine)]X_n$, where X = NH_3^-, CH_3COO^-, $\frac{1}{2}SO_4^{2-}$, Cl^-, etc.[40] They form blue precipitates with a number of anions [for example, $B(C_6H_5)_4^-$, PF_6^-, or $P_2O_7^{4-}$]. Thus these compounds belong to the class of the few active cationic complexes.

The "blues" are mixtures of polymeric species whose molecular weight is in the range 1000–3000. Bridging hydroxo- and olate groups and base anions are involved in the polymerisation.

According to X-ray electron spectroscopic data, the "blues" contain platinum(II) (ionisation energy $E_{Pt\ 4f}$ = 74 eV). At the same time the paramagnetic properties of these compounds are attributed to the presence of platinum-(III), the content of which can reach 25%, which corresponds to an average degree of oxidation of platinum of 2.25.[40,41] Approximately 70 complexes of the "blues" type have been studied in relation to several strains of mouse tumours. Among them 14 complexes showed a higher therapeutic effect against Sarcoma 180 than DDP (see Table 7).

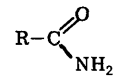
Table 7. The antitumour activities of platinum pyridimine "blues" (against ascites Sarcoma 180).[39,42]

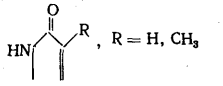
Complex	Toxic dose, mg k^{-1}	ILT, %	Single dose, mg kg^{-1}	Number of cured mice/number of experimental mice
cis-$[Pt(NH_3Cl)_2]$	10	49	7	1/12
	Platinum pyridine "blues"			
Uracil	400	91	200	5/6
5,6-Dihydrouracil	400	92	200	4/6
6-Methyluracil	800	87	600	3/6
5,6-Dimethyluracil	400	100	400	5/6
5-Fluorouracil	100	90	100	4/6
Free 5-flurouracil		8	60	0
5-Chlorouracil	200	67	50	3/6
Thymine	450	72	300	2/6

The advantages of the "blues" include high solubility in water (5% against 0.1% for DDP) and a lower toxicity than that of DDP (LD_{50} = 200–500 mg kg^{-1}, the corresponding value for DDP being 12–14 mg kg^{-1}). The activity of the platinum(II) complex of 5-fluorouracil is much higher than that of the free ligand[39]. Biochemical and electron-microscope studies have shown that the "blues" hardly interact with proteins but are strongly bound by nuclear DNA; with their aid, it is possible to "label" DNA and to follow the changes in it[40,41].

It has been suggested[39] that the mechanism of the action of the "blues", which are charged complexes, differs from that of the non-electrolytes.

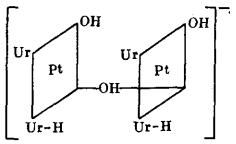
"Blues" of another type, formed when aliphatic nitriles RCN are treated with silver nitrate and kept at 37 °C for 4–6 days, have also been isolated. Blue substances insoluble in acetone exhibited the most effective antitumour properties—they increased the lifetime of mice with ascites Sarcoma 180 by 90%. It has been suggested that the nitrile is slowly hydrolysed, which yields platinum complexes of amides


. Uracil and thymine, which give rise to "pyrimidine blues", also contain a fragment having a similar structure[43]:



Also one monomeric cationic complex, which does not belong to the class of the "blues", has been found to be active[44]. The complex with spermine, a tetradentate polyamine, is active against leukaemia R-388, but is inferior to *cis*-dichlorodiammineplatinum as regards the inhibiting effect.

Certain anionic platinum(II) complexes have also been found to be active[45]. The interaction of the non-electrolytic urea complex *trans*-$[PtUr_2Cl_2]$ in an alkaline medium (pH ~ 9.5) is accompanied by the formation of an intensely blue solution, from which blue precipitates, having the composition $M[Pt_2Ur_2(Ur - H)_2(OH)_3]$, where $M = Na^+$ or K^+ and (Ur − H) is a deprotonated urea molecule, are isolated by the addition of alcohol. These substances are readily soluble in water; the complex anion remains unchanged in double decomposition reactions, which follows from the isolation of blue sparingly soluble precipitates with silver(I) and thallium(I) salts. The ionisation energy of platinum $E_{Pt\ 4f} = 73.3$ eV (according to data obtained by Nefedov[45] at the Institute of General and Inorganic Chemistry of the USSR Academy of Sciences), which corresponds to the +2 oxidation state of platinum. The electron absorption spectrum of an aqueous solution of the complex is characterised by an absorption band with $\lambda_{max} = 620$ nm and $\varepsilon_{max} = 3300$. The complexes are stable in aqueous solutions; the absorption spectrum does not change for 24 h. The position of the absorption band of these "anionic blues" differs from that of the cationic pyrimidine blues ($\lambda_{max} = 752$ nm) [40] and is close to that observed in the spectra of the blue complexes obtained on treatment of potassium chloroplatinite with the monoamide of oxalic acid $NH_2COCOOH$ ($\lambda_{max} = 620$–625 nm).[46] The following structure with two terminal and one bridging OH groups can be proposed for the anionic complexes[45]:



The anionic comples $K[Pt_2Ur_2(Ur - H)_2(OH)_3]$ has been tested for antitumour activity in relation to six strains of transplantable mouse tumours: lympholeukaemia L-1210, haemocytoblastoma La, plasmacytoma MOPC-406, the mammary gland adenocarcinoma (AK-755), the large intestine adenocarcinoma (AKATOL strain), and the flat cell cancer RshM-5 of the neck of the uterus[45]. It has been established that the complex is relatively non-toxic: the single maximum tolerance dose is in excess of 500 mg kg^{-1}. An appreciable antitumour activity of the anionic complex has been noted in relation to three strains of solid mouse tumours: AK-755 (85% inhibition of the growth of tumour), RShM-5 (81%), and AKATOL (55%). The complex proved to be inactive in relation to the two leukaemias and the plasmacytoma MOPC-406.

The above examples show that the "charge prohibition" is not insurmountable: there exist cationic and anionic complexes with a definite activity, although smaller than that of the non-electrolytic complexes. It is of interest that the active cationic and anionic complexes have a polymeric structure.

8. The Antitumour Activity of Platinum(IV) Complexes

Two active non-electrolytic platinum (IV) complexes have been described[8,9]: *cis*-$[Pt(NH_3)_2Cl_4]$ and $[PtEnCl_4]$. It has been suggested that these compounds are reduced in a biological medium to platinum(II) complexes which constitute the active principle. The possibility of such reduction follows from a comparison of the oxidation-reduction potentials of these compounds in a biological medium for which $E^0 = 0$ to 0.5 V:[30,47]

	E°, V
$[PtCl_6]^{2-} + 2e \rightleftarrows [PtCl_4]^{2-} + 2Cl^-$	+0.77
$[PtBr_6]^{2-} + 2e \rightleftarrows [PtBr_4]^{2-} + 2Br^-$	+0.64
cis-$[Pt(NH_3)_2Cl_4] + 2e \rightleftarrows$ *cis*-$[Pt(NH_3)_2Cl_2] + 2Cl^-$	+0.67
$[PtEnCl_4] + 2e \rightleftarrows [PtEnCl_2] + 2Cl^-$	+0.684

Analogous processes take place also with rhodium(III) complexes in a biological medium, where they are reduced to active rhodium(II) complexes[48].

The platinum(IV) complexes are more stable and more inert than the platinum(II) complexes, so that the attention of investigators has been concentrated on the latter. However, it has been suggested that the platinum(IV) complexes permeate more readily through a membrane. The interest in the platinum(IV) complexes increased after it had been discovered that certain non-electrolytic platinum(IV) complexes, namely the tetrachloro-complexes $[PtA_2Cl_4]$ and particularly the dihydroxo-complexes $[PtA_2Cl_2(OH)_2]$ dissolve more readily than the initial dichlorodiammineplatinum(II) complexes. In certain cases oxidation results also in an increase of solubility in $CHCl_3$, which characterises the behaviour in relation to lipids[27].

Unfortunately, comparison of the inhibiting activities and toxic properties of the platinum(II) and platinum(IV) complexes does not allow an unambiguous conclusion concerning the change in these characteristics on oxidation. Thus the platinum(IV) complexes with alicyclic ligands[27] and with 1,2-diaminocyclohexane[38] are less active and more toxic than the platinum(II) complexes. At the same time the toxicity of the platinum(IV) complexes with $L = NH_3$ or iso-$C_3H_7NH_2$ is smaller; for $L = NH_3$, the therapeutic activity of the platinum(IV) complexes is also greater.

Table 8. The antitumour activity of the complex $[Pt(NH_3Cl)_2.(OH)_2]$.

Dose, mg kg^{-1}	Interval, h	Number of injections	Increase of life of mice, %%		Inhibition of the growth of tumours on 10th day after therapy, %%		
			L-1210	haepatoma 22 (ascites)	AK-755	AKATOL	Sarcoma 180
50		1	50	*	96	45	76
25	24	5	90	*	83	87	76
15	24	5	90	160	83	87	*

*Not investigated.

In 1977 two groups of investigators discovered simultaneously and independently (in the USSR [49] and in England[27]) the high activity of the complex $[Pt(NH_3Cl)_2(OH)_2]$, which is not inferior to that of DDP. Konovalova et al.[49] investigated the compound in relation to five strains of transplantable mouse tumours and leukaemias (Table 8), while Tobe and Khokhar[27] tested it only on the plasmacytoma ADJ/PC6.

It is noteworthy that the complex $[Pt(NH_3Cl)_2(OH)_2]$ is ten times less toxic than DDP. This compound is now being investigated in depth at the All-Union Oncological Scientific Centre of the Academy of Medical Sciences of the USSR; it has been shown that the *trans*-isomer of this compound is inactive[49].

It is of interest that the anionic platinum(IV) complexes of the type $(NH_4)_2[PtHal_4(OH)_2]$ exhibit[50] a definite activity; the maximum activity was found in $(NH_4)_2[PtBr_4(OH)_2]$. This compound appreciably inhibited (by 70%) the growth of the mouse mammary gland adenocarcinoma (strain AK-755) and increased by 65% the life of animals with leukaemia L-1210. The authors[50] explained this by the fact that the bromide-containing platinum(II) anions are more readily reduced than the chloride-containing anions and are more labile than the iodide-containing anions.

Thus the majority of investigators are inclined to the view that the mechanism of the action of the non-electrolytic platinum(IV) complexes includes a stage of their preliminary reduction to the platinum(II) complexes. However, one cannot rule out completely also the possibility of the direct action of the platinum(IV) complexes on tumour cells: two platinum(IV) complexes with substituted ethylenediamines, namely $[PtACl_4]$, are active [it has been found that TI = 3.05 for A = $(CH_3)_2N(CH_2)_2NHCH_3$ and TI = 1.7 for A = $(CH_3)_2.N(CH_2)_2N(CH_3)(C_2H_5)$], while the corresponding and non-electrolytic platinum(II) complexes are inactive[30].

9. The Most Promising Complexes

Summarising the available literature data, it is possible to distinguish approximately 30 most active non-electrolytic platinum(II) and platinum(IV) complexes with ammonia, amines, and various acido-ligands.

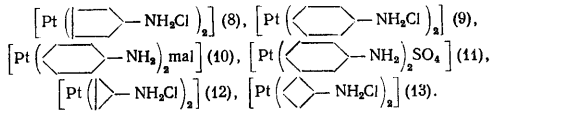
I. Platinum(II) complexes with NH_3:

$[Pt(NH_3Cl)_2]$ (1), $[Pt(NH_3)_2C_2O_4]$ (2), $[Pt(NH_3)_2mal]$ (3), $[Pt(NH_3)_2N_2O_2]$ (4), $[Pt(NH_3)_2L]$ (L = cyclobutane-1,1-dicarboxylate anion) (5).

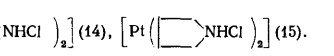
II. Platinum(II) complexes with aliphatic monoamines:

$[Pt(iso\text{-}C_3H_7NH_2Cl)_2]$ (6), $[Pt(iso\text{-}C_5H_{11}NH_2Cl)_2]$ (7).

III. Platinum (II) complexes with alicyclic monoamines:



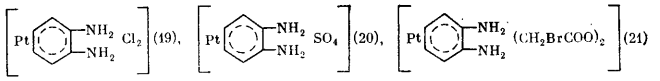
IV. Platinum(II) complexes with heterocyclic monoamines:



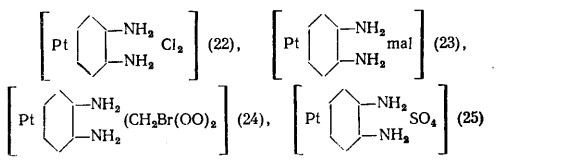
V. Platinum(II) complexes with aliphatic diamines:

$[PtEnCl_2]$ (16), $[PtEn\,mal]$ (17), $[PtEnN_2O_2]$ (18).

VI. Platinum(II) complexes with aromatic diamines:



VII. Platinum(II) complexes with alicyclic diamines:



VIII. Platinum(IV) complexes:

$[Pt(NH_3)_2Cl_4]$ (26), $[PtEnCl_4]$ (27), $[Pt(NH_3Cl)_2(OH)_2]$ (28), $[Pt(iso\text{-}C_3H_7NH_2Cl)_2(OH)_2]$ (29).

IX. Platinum pyrimidine blues and certain other charged complexes (30).

However, as regards clinical tests, only approximately half of these compounds are promising: the complex must exhibit a high activity against a wide spectrum of experimental tumours, should be relatively non-toxic, and should be fairly soluble in water. Complexes (1), (5)–(13), (22)–(26), (28), and (29) possess a set of such properties to a smaller or greater extent; some of these compounds are now passing through various stages of clinical tests. The effect of DDP has been studied in detail and the second phase of tests is being completed; more than 1000 patients have been treated with this compound. Detailed data concerning the results of the clinical tests on the complexes as well as their toxic properties and the measures taken to eliminate them have been published in a review[10].

III. THE MECHANISM OF THE ANTITUMOUR ACTIVITY OF PLATINUM COMPLEXES

One of the main requirements which must be met by the experimental and clinical chemotherapy of malignant tumours is selectivity of action of the therapeutic agents on the cells of the cancer tumour and the smallest possible damaging effect of such agents on the normal cells. Compared with normal cells, tumour cells are characterised by a higher level of synthesis of DNA and the action of a number of antitumour preparations, particularly alkylating agents, is in fact directed to such macromolecules.

Molecular-biological studies *in vitro* using tritium-labelled thymidine, uridine, and leucine[51,52] and experiments *in vivo*[53] have shown that the complex $[Pt(NH_3Cl)_2]$, which exhibits an antitumour activity, selectively suppresses the synthesis of DNA but has little effect on the synthesis of RNA and proteins. Thus the target attacked by the platinum complexes in the organism has been identified at the intermolecular level.

There exist several points of view concerning the causes of the different antitumour activities of platinum complexes of different composition and structure. Biophysical factors play a definite role; the non-electrolytic complexes are more capable of permeating the cell membrane than the charged complexes, which is promoted by their higher solubility in lipids.

1. The Role of Chemical and Physicochemical Factors

The formation of stable bonds with nitrogen-containing ligands is characteristic of platinum, which makes it likely that the acido-ligands in the complex undergo nucleophilic substitution by nitrogen-containing DNA bases. However, in order to "reach" the cell DNA, the complexes must react with other biologically active ligands "on the way", namely with proteins, aminoacids, etc. This is the reason for the relation between the chemical reactivity, thermodynamic stability, and kinetic lability of the platinum complexes, on the one hand, and their antitumour activity, on the other. The available data[54] concerning the influence of the complex $[Pt(NH_3Cl)_2]$ on the physicochemical characteristics of DNA show that this interaction proceeds with participation of the aquo-form of the complex as a result of the continuous shift

of the hydrolytic equilibrium

$$[Pt(NH_3Cl)_2] + 2H_2O \rightleftarrows [Pt(NH_3Cl)(NH_3H_2O)]^+ + Cl^- + H_2O \rightleftarrows [Pt(NH_3H_2O)_2]^{2+} + 2Cl^-.$$

There is almost no hydrolysis in the intercellular liquid, where the concentration of Cl^- ions is high (0.103 M). In the cytoplasm and particularly in the nucleus the concentration of Cl^- is much lower (0.004 M); aquo-complexes are formed in the cytoplasm under these conditions and then interact further with the nitrogen-containing DNA bases. A thermodynamic study of all possible equilibria in solutions of platinum complexes and measurement of their kinetic parameters are necessary[12].

2. Thermodynamic Stability of the Platinum Complexes

In aqueous solutions of dichlorodiamineplatinum(II) complexes stepwise hydrolytic and acid–base equilibria obtain:

$$[Pt(NH_3Cl)_2] + H_2O \rightleftarrows [Pt(NH_3Cl)(NH_3H_2O)]^+ + Cl^- ,$$
$$[Pt(NH_3Cl)(NH_3H_2O)]^+ + H_2O \rightleftarrows [Pt(NH_3H_2O)_2]^{2+} + Cl^- ,$$
$$[Pt(NH_3Cl)(NH_3H_2O)]^+ \rightleftarrows [Pt(NH_3Cl)(NH_3OH)] + H^+ ;$$
$$[Pt(NH_3H_2O)_2]^{2+} \rightleftarrows [Pt(NH_3H_2O)(NH_3OH)] + H^+ ;$$
$$[Pt(NH_3H_2O)(NH_3OH)]^+ \rightleftarrows [Pt(NH_3OH)_2] + H^+ .$$

In order to determine the concentrations of all possible equilibrium forms, it is necessary to investigate quantitatively the hydrolytic and acid–base equilibria in solutions of the platinum(II) complexes and to determine the hydrolysis constants K_1 and K_2 and acid dissociation constants K_3, K_4, and K_5, which makes it possible to calculate the contents of all the equilibrium forms existing at the specified concentrations of Cl^- ions and pH values. Such a calculation has been performed for $[PtEnCl_2]$, for which all five equilibrium constants are known; $K_1 = 2.76 \times 10^{-3}$, $K_2 = 1.38 \times 10^{-4}$, $K_3 = 4.0 \times 10^{-8}$, $K_4 = 1.6 \times 10^{-6}$, and $K_5 = 3.1 \times 10^{-8}$. The concentration ratios of the different equilibrium forms in $[PtEnCl_2]$ solutions at pH 7.4 and a Cl^- concentration of 0.103 M in the plasma or 4.8×10^{-3} M in the cell are[54] given below:

	$[PtEnCl_2]$	$[PtEn\,ClH_2O]^+$	$[PtEn(H_2O)_2]^{2+}$	$[PtEn\,ClOH]$	$[PtEnH_2O\,OH]^+$	$[PtEn(OH)_2]$
Plasma	37.3	1	0.00134	1	0.053	0.0033
Cell	1.45	1	0.0345	1	1.38	0.86

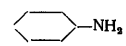
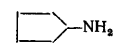
It is seen from the above data that the substance exists in the plasma mainly as the dichlorodiamine complex, while in the cell all the forms (with the exception of the diaquo-complex) are present in comparable amounts. A less detailed approximate calculation has been carried out for $[Pt(NH_3Cl)_2]$ (because K_3 is unknown), from which it follows that the degree of hydrolysis of the complex in the plasma is close to 3%, while the cell contains 42% of the reactive hydrolysis products.

The equilibrium constant corresponding to the elimination of the first chloride ion is usually known for other dichlorodiamineplatinum(II) complexes. The characteristics of the acid properties of the platinum(II) complexes as well as the influence of the σ-donor and π-acceptor properties of the ligands on the acidity of the aquo-complexes have been considered in reviews[55,56].

When concentrated solutions of the platinum(II) complexes are allowed to stand for a long time, polymerisation processes, accompanied by the formation of the complexes $[(NH_3)_2.Pt(OH)_2Pt(NH_3)_2](NO_3)_2$, $\{Pt[(NH_3)_2OH]_3\}(NO_3)_3$, etc. with bridging OH groups, take place[57,58].

For a number of isomeric complexes of the type $[PtA_2Cl_2]$ (A = NH_3 or amines), the hydrolytic stability of the *trans*-isomer is greater than that of the *cis*-isomer. Thus the equilibrium constant for the elimination of the first Cl^- ion in the *trans*-isomer of $[Pt(NH_3)_2Cl_2]$ is 4–5 times smaller and in the *trans*-isomers of $[PtA_2Cl_2]$ (A = methylamine or ethylamine) it is 13–18 times smaller than the corresponding value for the *cis*-isomer[59]. The influence of the strength of binding of the acido-ligand on the antitumour activity of the non-electrolytic platinum(II) *cis*-complexes has already been mentioned. The most stable complexes are the least active: in the $[Pt(AHal)_2]$ (Hal = Cl, Br, or I) series the Pt–Hal bond strength increases and the antitumour activity of the complex falls.

A change in the nature of the amine in the *trans*-position relative to the chloride ions influences the Pt–Cl bond strength in accordance with Chernyaev's principle of *trans*-influence. When NH_3 is replaced by alicyclic ligands, the toxicity is appreciably reduced and the antitumour activity of the complexes increases (see Table 5). Owing to the very poor solubility of the platinum(II) complexes with alicyclic amines, it is not possible to measure their stability constants. A study has therefore been made[60] of the interaction of nickel(II), an electronic analogue of platinum(II), with these amines and the first formation constants β_1 of the nickel complexes were determined (by potentiometric pH titration using a glass electrode) under conditions close to biological conditions (0.150 M NaCl, 37 °C). The basic properties of the ligands increase in the same direction:

L	NH_3		
$lg\beta_1$	2.80	5.340	6.824
pK_a	9.47	9.97	10.33

It may be that the same behaviour would be observed also for the $[PtL_2Cl_2]$ complexes. In this case the Pt–Cl bond weakens as the Pt–L bond strengthens and the complex becomes less reactive in relation to DNA. However, the use of findings obtained *in vitro* for nickel(II) complexes to explain the differences in the antitumour activities of the platinum(II) complexes *in vivo* must be treated with caution. In order to understand the mechanism of the antitumour activity of the platinum(II) complexes, data for equilibria in the systems containing these compounds together with purines or pyrimidines are particularly necessary. There have been virtually no studies of this kind; one of the causes of this may be the difficulty of the measurements associated with the slowness of the attainment of equilibrium as a consequence of the inertness of the nitrogen-containing platinum(II) complexes. An attempt has been made[61] to estimate the stability constants of the 1 : 1 complexes formed after solutions of mixtures of $[Pt(NH_3H_2O)_2]^{2+}$ with nucleosides (adenosine, guanosine, cytidine, uridine, and thymidine) have been allowed to stand for a long time (4–6 h) at 25 °C in the presence of different Pt : ligand ratios. The quantity ΔA, equal to the difference between the absorbances of the complex and its individual components, has been measured by differential spectroscopy. If it is assumed that only one complex, with the 1 : 1 composition, is formed in the system, then its stability constant K can be found from the equation

$$\frac{b(a-c)}{\Delta A} = \frac{(a-c)}{\Delta\varepsilon} + \frac{1}{K\Delta\varepsilon} ,$$

where a and b are the initial concentrations of the complex and the nucleoside, c is the equilibrium concentration of the complex, and $\Delta\varepsilon$ is the difference between the molar extinction coefficients of the complex and its constituents. By applying the iterative method to the determination of $\Delta\varepsilon$ and c, it is possible to find the optimum values of $\Delta\varepsilon$ and K. $\Delta\varepsilon$ can be determined also directly on the basis of Beer's law. The plot of $b(a-c)/\Delta A = f(a-c)$ is linear, its slope determining the quantity $1/\Delta\varepsilon$ and the intercept on the ordinate axis the quantity $1/K\Delta\varepsilon$.

When $[Pt(NH_3H_2O)_2]^{2+}$ solutions are kept in contact with pyrimidines (uridine and thymidine), no changes are observed in the absorption spectra, which led to the conclusion that there is no interaction. The formation constants of the 1 : 1 complexes with adenosine, guanosine, and cytidine are similar: $pK = 3.5–3.7$. Consequently the reaction of $[Pt(NH_3H_2O)_2]^{2+}$ with the guanosine–cytidine pair is much more probable than with the adenosine–thymine pair: $K_GK_C \cong 10^8$ for the guanosine–cytidine pair and $K_AK_T \cong 10^4$ for the adenosine–thymine pair.

This conclusion is consistent with the experimental finding that $[Pt(NH_3Cl)_2]$ is bound preferentially by DNA enriched in guanosine and cytidine. The selectivity of the reactions of DNA with bases depends on the nature of the metal: copper(II) and silver(I) ions interact preferentially with guanosine, while OsO_4, CH_3Hg(II) and Hg(II) interact preferentially with thymidine[62].

3. Kinetic Lability of the Platinum(II) Complexes

The biological reactivity of the non-electrolytic platinum(II) *cis*- and *trans*-complexes is determined by the kinetics of their hydrolysis and nucleophilic substitution reactions. The kinetic equation for nucleophilic substitution in the platinum(II) complexes has the following form[47]:

$$v = k_1c_c + k_2[L]c_c,$$

where c_c is the concentration of the complex and [L] the concentration of the entering ligand. The first term corresponds to the hydrolytic (solvolytic) pathway and the second to a second-order association reaction with the entering ligand. In the presence of an excess of the latter, we have

$$v = k_{obs}c_c,$$

where $k_{obs} = k_1 + k_2[L]$.

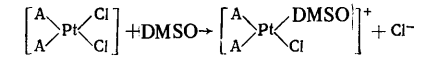
Table 9. Comparison of the kinetic labilities of the *cis*- and *trans*-isomers of $[Pt(NH_3)_2Cl_2]$ at 25 °C.[63–65]

Isomer	Ligand	10^5k_1, s^{-1}	Isomer	Ligand	10^5k_1, s^{-1}
cis-	H_2O	2.5	*cis*-	Cl	0.3
trans-	H_2O	9.8	*trans*-	Cl	7.8
cis-	OH^-	2.5	*cis*-	NH_3	1.0
trans-	OH^-	10.1	*trans*-	NH_3	29.0

In the light of the foregoing, the necessity for a kinetic investigation of the hydrolysis (solvolysis) of the platinum(II) complexes and their reactions with the DNA component is clear. The first process has been studied in fair detail[47]. On the other hand, there are almost no data concerning the rates of reaction of the complex platinum(II) non-electrolytes with the DNA bases and for this reason we shall characterise the kinetics of the second-order reactions using the rates of reaction of the isomeric non-electrolytes with other donor molecules of ions: NH_3, OH^-, Cl^-, etc. Table 9 lists the rate constants for the first-order acid and base hydrolytic reactions and the second-order isotope exchange and nucleophilic substitution reactions with the isomeric platinum(II) non-electrolytes. Evidently the *trans*-isomers are kinetically more labile than the *cis*-isomers. This is usually explained by the greater *trans*-influence of the Cl^- ions compared with the NH_3 molecules.

Numerous studies have been carried out in order to characterise kinetically the *trans*-influence[66,67]. The absence of antitumour activity in the *trans*-isomer can be attributed to its greater lability: on the way to nuclear DNA, the *trans*-isomer enters into rapid and non-specific exchange reactions with a series of nucleophiles. The *cis*-isomer is less labile and is able to reach the tumour cell in an unchanged form and to diffuse through its membrane. In the plasma the concentration of Cl^- ions (0.103 M) is sufficient to suppress the hydrolysis of the complex and only in the cell, where the Cl^- concentration is smaller (0.004 M), is the complex hydrolysed, which is accompanied by the reversible conversion of the aquo-complex into complexes with DNA bases.

The solvolysis of the *cis*-non-electrolytes $[Pt(ACl)_2]$, where A is an alicyclic amine, has been studied in dimethyl sulphoxide[68,69]:



It was established that, on passing from cyclopropyl- to cyclohexyl-amine, the rate of solvolysis falls by a factor of ~2.5; the basic properties of the ligands increase in this direction. The equilibrium constants of the processes

$$cis\text{-}[PtA(DMSO)Cl_2] + A \rightleftharpoons cis\text{-}[PtA_2(DMSO)Cl]^+ + Cl^-,$$
$$[Pt(DMSO)Cl_3]^- + A \rightleftharpoons trans\text{-}[PtA(DMSO)Cl_2] + Cl^-,$$

were determined by a kinetic method (by investigating the rate constants for the forward and reverse reactions).

Kinetic considerations are invoked also to account for the influence of the anion X in $[Pt(AX)_2]$ on the antitumour activity of the *cis*-complex, which decreases in the sequence $Cl^- > Br^- > SCN^- > NO_2^- > I^-$. The rates of certain substitution reactions involving the platinum(II) complexes decrease in approximately the same sequence. For example, the rate constant for the reaction[70]

$$[Pt\,dien\,X]^+ + Py \rightarrow [Pt\,dien\,Py]^{2+} + X^-$$

(dien = diethylenetriamine) diminishes by a factor of 10^6 in the sequence $NO_3^- > H_2O > Cl^- > Br^- > SCN^- > NO_2^-$. Hence one may conclude that the antitumour activity is characteristic of complexes with ligands of moderate lability (Cl^- and Br^-).

One should note that the concepts of the "lability" and "inertness" of the ligand are relative and depend on the charge of the complex and the nature of the remaining ligands and the entering group. Thus the anionic complexes $[PtBr_4]^{2-}$ and $[PtI_4]^{2-}$ are more labile with respect to hydrolysis, isotope exchange, and substitution by NH_3 than $[PtCl_4]^{2-}$:[47]

	10^4K_1, s^{-1}		10^4K_2, litre mol^{-1} s^{-1}
$[PtCl_4]^{2-} + H_2O$	0.39	$[PtCl_4]^{2-} + NH_3$	4.2
$[PtBr_4]^{2-} + H_2O$	1.75	$[PtBr_4]^{2-} + NH_3$	25.0

A more rigorous estimate of the influence of the kinetic lability of the ligand and of the geometrical configuration of the complexes on their biological activity can be obtained after determining the rate constants for the hydrolysis and the interaction with purine and pyrimidine bases of a series of *cis*-isomers $[Pt(NH_3X)_2]$ (X = acido-ligand). One of the few studies of this kind is that of Robins[71], who found that adenine, guanine, and cytosine, their nucleosides, and nucleotides react with $[Pt^{14}C\text{–}EnCl_2]$ (ethylenediamine complex), while thymine and its derivatives do not. Among nucleosides, the reaction is fastest with guanosine and slower with adenosine. This also applies to the reactions with DNA: DNA enriched with deoxyguanosine reacts faster. The presence of the phosphate group in the adenine nucleotides accelerates the interaction.

The absence of antitumour activity in the palladium complex $[Pd(NH_3Cl)_2]$ is due to its kinetic lability; palladium(II) compounds react approximately 10^5 times faster than the analogous platinum(II) complexes[7]. Nickel(II) complexes are still more labile and are therefore relatively unpromising as antitumour preparations. However, one cannot rule out the possibility that the change in the nature of the neutral and acido-ligands in the palladium(II) complexes will reduce their lability and one can then expect that such complexes would be active.

In conformity with the principle of the *trans*-influence, the lability of the ligand is in many respects determined by the nature of the *trans*-ligand. Phosphorus- and sulphur-containing ligands exhibit a strong *trans*-influence and they are responsible for an appreciable increase of the lability of the chlorine bond in *cis*-$[Pt(ACl)_2]$, which is the reason why such complexes are inactive.

Thus comparison of the physicochemical characteristics of the *cis*- and *trans*-isomers of $[Pt(NH_3)_2Cl_2]$ shows that the *cis*-isomer, which exhibits antitumour activity, is kinetically more stable than the *trans*-isomer, but at the same time its thermodynamic stability is lower. It may be that the combination of a moderate lability and a moderate stability of the Pt–Cl bond in the *cis*-isomer ensures the integrity of the complex during its journey to nuclear DNA and its interaction with the latter. While admitting the due importance of these factors, one must nevertheless emphasise that the geometrical correspondence between the *cis*-isomer and the DNA structure exerts a decisive influence on the differences between the antitumour activities of the isomers.

4. Structure Factors and the Interaction with DNA

The structure factors determine the interaction of alkylating antitumour agents (sarcolysine, cyclicphosphoramide, etc.) with DNA. The distance between the chlorine atoms in these molecules is close to 8 Å, which corresponds to the distance between two guanine molecules in two DNA helices[8]. Alkylating agents therefore induce the *interstrand cross-linking* of DNA, which prevents its replication. The structure of $[Pt(NH_3Cl)_2]$ differs from that of alkylating agents, which is reflected in the type of linkage. The distance between the two chlorine in DDP (3.3 Å [72]) approximately corresponds to the distance between the planes of the bases in the DNA helices (3.4 Å), which permits *intrastrand cross-linking* with formation of a chelate complex in which there are two molecules of the nucleoside per platinum(II) atom. The inhibition of the DNA synthesis in the presence of $[Pt(NH_3Cl)_2]$ in a single-strand bacteriophage and the formation of a chelate with the dinucleotide ApA confirm this type of linkage[13,73]. It has also been established that the antitumour activity of DDP is manifested in the proportions of 1 DDP molecule to 1000 DNA base molecules, while interstrand cross-linking requires 20 times as much of the complex[74,75]. For DDP, yet another example of the geometrical correspondence with the DNA structure has been observed. In the crystalline state the distance between the $[Pt(NH_3Cl)_2]$ molecules in the chain structure is 3.47 Å, which permits the combination of the chains of the complex with DNA in which the new double chain contains one nucleoside molecule per platinum(II) atom[76].

The possibility of the interstrand cross-linking of DNA as a result of interaction with DDP also cannot be ruled out[74,75,77], but the majority of investigators give preference to intrastrand cross-linking. They believe that the promising results obtained in the combined chemotherapy with the aid of DDP and alkylating agents are associated with the different mechanisms of their action on DNA.

The problem of which DNA bases interact with DDP and which atoms are involved in such binding has been studied in detail. According to a number of workers, among the purine bases the greatest tendency towards the reaction with DDP is shown by guanine, which is bound to platinum(II) via the $N_{(7)}$ atom[71], while among pyrimidine bases cytosine is most effective, being coordinated via the $N_{(3)}$ atom[78]. In neutral solution thymine does not react with DDP. On this basis, it is suggested that platinum complexes be used to determine the content of the gua-cyt pair in DNA and the sequence of the bases by electron microscopy.

The interaction of DDP and other platinum(II) complexes with DNA containing different amounts of guanine and cytosine has been investigated in detail in a series of studies[79–88] by physicochemical and physical methods (atomic absorption spectroscopy, the fluorescence method, the study of circular dichroism spectra, and the potentiometric determination of the concentration of Cl^- ions). It has been established[87,88] that DDP interacts specifically in the first place with the guanine (gua) of the DNA molecule, forming an intrastrand chelate:

$$[Pt(NH_3Cl)_2] + \text{gua} \rightarrow [Pt(NH_3)_2 N(7)\,\text{gua}\,O(6)]Cl_2 \quad (1).$$

This reaction is accompanied by the liberation of two Cl^- ions per molecule of the contacts, but there is no change of pH. After saturation of the guanine binding sites by the complex, the second mode of binding—the interstrand cross-linking gua $N_{(1)}$–Pt–cyt $N_{(3)}$—is observed in the second stage of the process and is accompanied by the elimination of a proton from the $N_{(1)}H$ group of guanine.

However, this type of binding is non-specific; it obtains also in other platinum(II) complexes without antitumour activity. Apart from the incorporation of the interstrand mechanism, in the second stage of the interaction of DDP with DNA there is a possibility of the formation of an intrastrand chelate with adenine via the $N_{(7)}$ atom and the NH_2 group[85]. This process proceeds via pathways of the type of reaction (1) without the elimination of the proton and with liberation of two Cl^- ions.

It is also believed[87] that DDP initially forms an intrastrand chelate with the DNA guanine, which weakens the cyt–$N_{(1)}$–gua hydrogen bonds, as a result of which a second DDP molecule can be bound to the $N_{(1)}$ atom of guanine. This distorts the initial configuration of the DNA molecule and permits interstrand cross-linking with participation of the $N_{(1)}$ atom of adenine.

The formation of a chelate between DDP and DNA with participation of the $N_{(7)}$ and $O_{(6)}$ atoms of guanine was demonstrated by the investigation of the X-ray electron spectra of the isolated solid platinum complexes of DNA: the ionisation energy of the $N_{(1S)}$ atom of guanine in the series of complexes $[Pt(NH_3Cl)_2]$, *trans*-$[Pt(NH_3)_2Cl_2]$, and $K_2[PtCl_4]$ decreases by 0.5–0.7 eV during their coordination, while the ionisation energy of the $O_{(1S)}$ atom decreases only in the case of the DNA complex with DDP, remaining unaltered in all other cases[80].

In order to examine the interaction of DDP with DNA, a comparative study was made (*in vivo* and *in vitro*) of the reactions of DNA with DDP and other, inactive platinum complexes: *trans*-$[Pt(NH_3)_2Cl_2]$, [Pt dien Cl]Cl, $[Pt(NH_3)_3Cl]Cl$, $K[Pt(C_2H_4)Cl_3]$, $K_2[PtCl_3]$, etc.[89] These complexes also react with DNA but in a different manner. On reaction with DNA, the complexes *trans*-$[Pt(NH_3)_2Cl_2]$ and [Pt dien Cl]Cl split off one Cl^- ion per platinum(II) atom, which indicates their monodentate binding to the central atom. The binding site is again the $N_{(7)}$ atom of guanine[89].

The influence of the platinum(II) complexes on the fluorescence intensity in the DNA–EtdBr system, where EtdBr is ethidium bromide, has been investigated[86]. The triammine complexes [Pt dien Cl]Cl and $[Pt(NH_3)_3Cl]Cl$, which bind to DNA as monodentate species, decrease the fluoresence intensity by only 15–20%; under the same conditions, DDP, $[PtEnCl_2]$, and their aquo-forms, which are capable of chelate formation, exert a much greater influence, reducing the fluorescence intensity by 70%. The inert complexes $[Pt(NH_3)_4]Cl_2$ and $[PtEn_2]Cl_2$ do not react with DNA. The interaction of *trans*-$[Pt(NH_3)_2Cl_2]$ with DNA is interesting: in solutions with an equimolar content of Cl^- ions this substance behaves as a monodentate ligand in relation to DNA, while in the absence of Cl^- ions it greatly reduces the fluorescence intensity and strongly influences the DNA structure. The authors[86] believe that in this case *trans*-$[Pt(NH_3)_2Cl_2]$ forms an unusal chelate with DNA via the $N_{(7)}$ atom of guanine and the oxygen atom of the phosphate group.

The atomic absorption method proved to be promising for the characterisation of the interaction of isomeric non-electrolytes with DNA; it has been observed[90] that the absorption intensity in atomic absorption spectra of the chelate complexes $[Pt(NH_3)_2N_{(7)}guaO_{(6)}]Cl_2$ and $[PtEnN_{(7)}guaO_{(6)}]\cdot Cl_2$ is lower by a factor of 2 than for complexes bound as monodentate species, for example, *trans*-$[Pt(NH_3)_2N_{(7)}guaCl]\cdot Cl$ and [Pt dien $N_{(7)}$gua]Cl_2.[90] Thus the interaction of DDP with DNA is distinguished by the following features:

(1) *In vivo* certain platinum complexes with a labile Cl–Pt–Cl *trans*-coordinate, for example, $K_2[PtCl_4]$, $K[Pt(C_2H_4)Cl_3]$, $K[Pt(NH_3)Cl_3]$, and *trans*-$[Pt(NH_3)_2Cl_2]$, are kinetically unstable in relation to many biologically active ligands (aminoacids and proteins) and do not therefore reach the nuclear DNA, since they react with these substances already in the plasma. In particular, this applies to the complex $K_2[PtCl_4]$, which is more effective in relation to proteins and enzymes than to DNA [87] and differs sharply in its physiological action from DDP; it is bactericidal, highly toxic, and inactive against tumours.

(2) *In vitro* many platinum(II) complexes are capable of reacting with DNA (with the exception of inert tetramine complexes) preferentially as a result of binding to guanine. However, complexes of different structure are formed and differ in the mode of binding. The primary binding of DDP and other *cis*-non-electrolytes leads to the formation of the intrastrand chelate $N_{(7)}guaO_{(6)}$, while *trans*-$[Pt(NH_3)_2Cl_2]$ and triamine complexes are bound as monodentate species via the $N_{(7)}$ atom of guanine. In the concluding report at the IIIrd International Symposium on the Applications of Platinum Complexes in Tumour Chemotherapy Rosenberg[89] emphasised particularly the importance of the formation of this type of chelate for the manifestation of antitumour activity by the complex.

The complex $K_2[PtCl_4]$ binds to DNA via an interstrand mechanism involving the $N_{(1)}$ atom of guanine and the $N_{(3)}$ atom of cytosine, which is accompanied by the elimination of a proton from the $N_{(1)}H$ group. In the solid complex obtained by treating DNA with $K_2[PtCl_4]$ and containing a DNA molecule and two Cl^- ions per platinum atom, interstrand binding via the $N_{(1)}$ atom of adenine and the $N_{(3)}$ atom of thymine as well as monodenate binding via the $N_{(7)}$ or $N_{(3)}$ atoms of guanine and adenine are also postulated.

It follows from the foregoing that the study of the reactions of isomeric non-electrolytes and other platinum complexes with individual DNA bases can throw light on the mechanism of the interaction of these compounds with DNA.

Thus one of the principal causes of the antitumour activity of platinum complexes is inhibition of the replication of DNA. However, this interaction alone cannot ensure the complete destruction of the tumour and its metastases; this requires the operation of additional mechanisms. Such an additional mechanism is the immune system of the organism[13]. The involvement of the immune system is confirmed by the following facts: (1) in mice with grafted Sarcoma 180 and cured with DDP immunity to repeated implantation persists for 11 months; (2) the combination of DDP with an immunostimulant (zymosan) increases the therapeutic effect of the complex or the combination with an immunodepressant (hydrocortisone) lowers the antitumour activity of DDP.[91]

IV. THE ANTITUMOUR ACTIVITIES OF OTHER METAL COMPLEXES

A brief survey of studies on the antitumour activities of metal complexes before Rosenberg's discovery of antiblastoma properties of platinum complexes was given by Cleare[7]. Thus copper, nickel, and cobalt diphthalate complexes proved to be active against leukaemia[92], while iron ascorbate inhibited the growth of Ehrlich carcinosarcoma in mice[93]. The chelate copper complex of dimethylglyoxime $[Cu(DH)_2]$, where DH is the dimethylglyoximate anion, increased the life of animals with Ehrlich ascites tumour and Sarcoma 180 by 200–300%.[94] It has been suggested that coordination masks the hydrophilic oxime group and promotes the permeability of the cell membrane to the complex. An activity has been observed also in the copper(II) chelate complexes of thiosemicarbazones. It has been established[95,96] that the aminoacid complexes of bivalent copper show a definite antitumour activity *in vivo* (against the ascites form of Sarcoma 180) and *in vitro* (against lympholeukaemia L-1210). Mixed complexes with cyclically bound aminoacids (*l*-serine, glycine, *l*-alanine, and *l*-threonine) have been investigated[97] and the syntheses and structure of these compounds have been described[98–100]. They showed a pronounced therapeutic effect on mice with dense tumours of two strains—the mammary gland adenocarcinoma (AK-755) and the cancer of the neck of the uterus (RShM-5); the percentage inhibition of AK-755 was, depending on the compound, the method of injection, and time, 80–90% (on the fifth day after a single injection) and 80–50% (24 h after the end of a five day course). However, the effect is unstable and diminishes 1–2 weeks after the course. The best results were obtained for the complexes with *l*-serine and glycine.



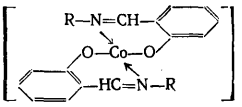
In this case a high percentage inhibition of AK-755 after a single injection persists also on the 19th day. Certain cobalt(III) complexes, namely $[Co(NH_3)_4Cl_2]Cl$ and $[Co(NH_3)_4\cdot(CO_3)]NO_3\cdot\frac{1}{2}H_2O$ retarded the growth of Yoshida sarcoma[101]. There is evidence for the antitumour activity of cyanocobalamin (vitamin B_{12}) [102] and cobalt-protophorphyrin[103].

Complexes of Group VIII elements have been studied in greater detail (after Rosenberg's investigation of the antitumour activities of platinum complexes). Nickel(II) and palladium(II) atoms have the d^7 electronic configuration [d^8, Ed] and are electronic analogues of platinum(II), but the complexes of these elements show a much greater kinetic lability, as can be seen from a comparison of the relative rates of nucleophilic substitution reactions[104]:

Ni (II)	Pd (II)	Pt (II)
$5\cdot10^6$	10^5	1

For these reasons, one can hardly expect antitumour activity of the palladium(II) and nickel(II) complexes; this can also

be said of gold(III) complexes. When the non-electrolytic palladium(II) complexes *cis*-$[Pd(NH_3Cl)_2]$ (the DDP analogue), $[PdEnCl_2]$, $[Pd(NH_3)_2mal]$, [PdEnmal], etc. were tested, no activity against Sarcoma 180 was observed[105]. Nevertheless, one cannot rule out the possibility that palladium(II) can be stabilised by the introduction of cyclic ligands and would then prove active. It may be that this is why the complex $[Pd(dtp)_2]$, where dtp is dimethyl hydrogen thiophosphate, shows some antitumour activity against Walker sarcoma[106]. The cyclic planar cobalt(II) complexes of Schiff bases cause a moderate inhibition of the growth of Walker sarcoma in rats. The best results were observed for the complexes



where R = $(CH_2)_2CH_2OH$ (T/K = 21%) or $C(CH_3)_2CH_2OH$ (T/K = 24%).[107,108] Iridium(III) complexes are inert and inactive, like $(NH_4)_2[IrCl_6]$—an anionic iridium(IV) complex. However, photochemical activation of the latter leads to the formation of the complex *cis*-$[Ir(NH_3)_2Cl_4]$, which has some activity[109].

Rhodium(III) complexes are the most promising. The complexes *trans*-$[RhL_4X_2]Y$, where L = pyridine and its substituted derivatives, and *trans*-$[RhL_2X_2]Y$, where L = 2,2'-bipyridyl, 1,10-phenanthroline, or ethylenediamine (X = Cl, Br, or I; Y = Cl, Br, NO_3, or ClO_4), showed an antibacterial activity and caused the formation of bacterial filaments. In contrast to platinum(II) complexes, this capacity was shown to a greater extent by bromide complexes and not chloride complexes and by complexes with the *trans*-structure and not the *cis*-structure. The introduction of a lipophilic substituent into the pyridine molecule increased and the introduction of a lyophilic substituent decreased the bacteriostatic activity of the complexes. Complexes with pronounced oxidising properties (with less negative half-wave potentials $E_{1/2}$ in polarographic reduction) proved to be more active[110]. The *mer* isomer $[Rh(NH_3)_3Cl_3]$ as well as *trans*-$[RhPy_4Cl_2]Cl$ and *trans*-$[RhEn_2Cl_2]NO_3$ inhibit the growth of Sarcoma 180 and Walker carcinosarcoma (T/C = 17–40%). It has been suggested that under biological conditions the rhodium(III) complexes are reduced to active rhodium(I) complexes.

The antitumour activities of the dimeric rhodium(II) carboxylates of the type $Rh_2(CO_2R)_4$, where CO_2R are acetate, propionate, and butyrate ions, have been studied in detail (in relation to chemical properties)[111,112]. These complexes increased the life of mice with Ehrlich ascites tumour and leukaemia L-1210. The antitumour activity increases in the sequence acetate < propionate < butyrate. In the latter case the life of mice increases by 20%. Rhodium(II) carboxylate complexes inhibit preferentially the DNA synthesis in the tumour both *in vivo* and *in vitro*. However, in contrast to the platinum(II) complexes, they also influence the RNA synthesis (according to data obtained by experiments with tritium-labelled uridine). It has been established that rhodium(II) carboxylates bind preferentially to adenine and its nucleosides and nucleotides. In order to simulate the interaction of the dimeric rhodium(II) carboxylates with DNA, a study was made of their reactions with 5'-AMP, which proceed via an oxidative addition mechanism[113]:

$$[Rh_2(CO_2R)_4] + 2\,(5'\text{-AMP}) \rightarrow [Rh_2(CO_2R)_4(5'\text{-AMP})_2].$$

The changes in the absorption spectra observed in this process are analogous to those which occur on coordination of other N-donor ligands. The formation constants K_1 and K_2 of the rhodium(II) acetate and propionate complexes with 5'-AMP have been determined spectrophotometrically: the propionate complex is approximately twice as stable (K_1 = 4235) than the acetate complex (K_1 = 1893). The stability of the complexes with 5'-ADP and 5'-ATP increases in the same sequence (propionate > acetate > methoxyacetate)[113].

Ruthenium complexes are also capable of interacting with purines and biologically active macromolecules[114,115,116]. The complex $[Ru(NH_3)_5(H_2O)]^{2+}$ is reactive, reacting with purines (guanosine, 5'-GMP, xanthosine, and inosine), which involves coordination via the $N_{(7)}$ atom. In the presence of an excess of ruthenium complex adenine was found to bind via the $N_{(1)}$ atom. The reactions of $[Ru(NH_3)_5(H_2O)]^{2+}$ with DNA occurred similarly. The formation of complexes with DNA and the inhibition of its synthesis by the ruthenium complexes make them potential antitumour agents.

Antitumour activity has been found in compounds of Group III elements: $Ga(NO_3)_3$, which causes 90% inhibition of the development of many tumours, is particularly promising[117]. In contrast to platinum(II) complexes, the gallium(III) compounds accumulate selectively in tumour cells and have a cytotoxic effect on them.

The available data suggest that not only platinum complexes but also other metal complexes, capable of reacting with biologically active molecules, behave as antitumour agents.

Compared with other metal complexes, platinum complexes are stable—they do not undergo extensive hydrolysis and retain their geometric configuration in solution. These complexes served, as it were, as the "starting point" in coordination chemistry: a number of characteristics have been discovered using them—the influence of coordination on the properties of the ligands and the central atom, the mutual influence of ligands, primarily the *trans*-influence, etc. Presumably in the chemotherapy of tumours the platinum complexes will play a similar role and their study will promote the investigation and application of other metal complexes as antitumour agents.

This has been confirmed by the results of the latest studies[118–121], devoted to the search for platinum and other metal complexes and the investigation of the mechanism of their action and their physicochemical properties. Among promising complexes, 4-carboxyphthalato-1,2-diaminocyclohexaneplatinum(II) has been mentioned[122]; promising data have been obtained also for other transition metal complexes[123]. New platinum(II) complexes with pyrimidines[124], adenine, and adenosine[125,126] have been isolated. The presence of oligomers in neutral solutions of diaquodiammineplatinum(II) complexes has been demonstrated by ^{195}Pt NMR.[127] The dependence of the antitumour activity on the structure of the complexes has been analysed[128,129] and the possible mechanisms of their binding to DNA have been examined[130,131].

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