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Platinum(II) Complexes of Purine and Pyrimidine Bases and Their Nucleosides

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The results of studies on the synthesis, structure, and physicochemical properties and reactivities of platinum(II) complexes of purine and pyrimidine bases and their nucleosides, carried out mainly during the last decade, are summarised. Attention is directed to the characteristic features of these compounds as ambident and bridging ligands. The methods of study are characterised and the influence of coordination on the physicochemical characteristics of the purine and pyrimidine ligands and the effect of the mutual influence of the ligands in the platinum(II) complexes are analysed. The data concerning the ways in which the purine and pyrimidine ligands are bound in the platinum(II) complexes are compared with the manifestation of the antitumour activity by these complexes.
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I. INTRODUCTION

The antiblastoma activity of *cis*-dichlorodiammineplatinum-(II), i.e. *cis*-$[Pt(NH_3)_2Cl_2]$ (*cis*-DDP) was discovered in 1969.[1] At the present time this compound is used as an effective antitumour agent with a broad spectrum of activity.[2,3] Under the names "Platind", "*cis*-Platina", Neoplatin", and "Platidiam", *cis*-DDP is manufactured in the USA, England, Czechoslovakia, Finland, and certain other countries.

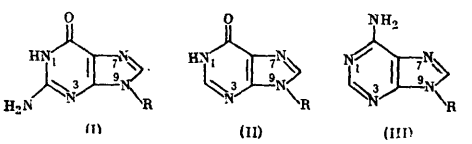
Other platinum complexes are also being vigorously investigated in the search for active water-soluble compounds with a low toxicity. Complexes of chelating dicarboxylate dianions having the *cis*-structure and constituting the so-called second generation of cytostatic platinum(II) complexes are in the stage of clinical tests. They include cyclobutane-1,1-dicarboxylatodiammineplatinum(II), a series of platinum(II) complexes of diaminocyclohexane (malonates and substituted malonates as well as 4-carboxyphthalate), and a platinum(IV) complex—*cis*-dichlorodiisopropyl-*trans*-dihydroxoplatinum-(IV).[4-7] The antitumour activity of the platinum complexes depends on many factors—the charge on the complex, the degree of oxidation of the central atom, the nature of the neutral and acido-ligands, and the kinetic and thermodynamic stability of the complexes.[4] One of the main factors is the geometrical configuration of the complexes: only the *cis*-isomers are active, the *trans*-isomers being inactive.

The mechanism of the antitumour action of the platinum complexes has so far been inadequately investigated. It has been established that the active complexes inhibit the synthesis of DNA *in vitro* and *in vivo* via reactions with heterocyclic DNA bases.[8-13] Among the DNA bases, the purine base guanine and the pyrimidine base cytosine show the greatest tendency to react with *cis*-DDP.[14-19] The specific action of *cis*-DDP on tumour cells is caused both by the faster division of these cells compared with normal cells and by the fact that the damage induced by *cis*-DDP is made good faster in normal cells than in tumour cells.[12]

cis-DDP can interact with DNA bases in different strands of the double helix, effecting the so-called intercross-linking,[20-22] for example, with the complementary bases—guanine and cytosine. However, this type of linkage is not dominant, since only 1% of the total amount of the platinum bound to DNA participates in intercross-linking.[23,24] The binding of *cis*-DDP by the molecules of the bases of a single DNA strand, the so-called intracross-linking, is more probable.[25-27] Nor can one rule out also the reactions of *cis*-DDP with the same DNA base via a chelating mechanism.[28-31] Intracross-linking can in fact explain the dependence of the antitumour activity on the geometrical configuration of the complexes: (1) the distance between the planes of the bases in DNA is 3.4 Å, which corresponds to the distance between the chlorine atoms in DDP (3.3 Å) and differs from the distance in the *trans*-isomer (4.66 Å); (2) only the *cis*-isomers are capable of forming chelate bonds. Apart from the direct interaction with DNA, the active complexes can influence the bond between DNA and proteins.[32-34]

II. METHODS OF STUDY, SYNTHESIS, STRUCTURE, AND PROPERTIES OF PLATINUM(II) COMPLEXES OF PURINE BASES AND THEIR NUCLEOSIDES

The purine bases with R = H include guanine (Gu) (I), hypoxanthine (Hyp) (II), and adenine (Ad) (III). Their nucleosides (with R = β-D-ribofuranosyl) are guanosine (Gua), inosine (Ino), and adenosine (Ado).



(I) (II) (III)

The presence of several endocyclic nitrogen atoms and also of

the potentially electron-donating exocyclic groups and atoms (NH_2, O) is responsible for the ambident nature of the ligands and complicates the determination of the structure of their complexes. Physical, mainly spectroscopic, methods are used for this purpose: UV, IR, and Raman spectroscopy, X-ray electronic spectroscopy, circular dichroism, fluorescence analysis, atomic absorption, and, to the greatest extent, ^1H, ^{13}C, ^{15}N, and ^{195}Pt ($I = 1/2$) microwave spectroscopy. The complexity of the IR spectra of the ligands and the low sensitivity of the UV spectra to changes in the type of bond limit the application of these methods to the determination of the structures of the complexes. The NMR methods are most informative and unambiguous. In many studies spectroscopic methods have been used to investigate the formation of complexes between platinum(II) and purine and pyrimidine bases in solutions. However, under these conditions there is a possibility of the existence of a series of complexes. More definite information about the compositions and structures of the complexes can be obtained by means of spectroscopic study of the complexes isolated. X-Ray diffraction studies lead to final conclusions about the structures of the complexes, but they cannot always be carried out owing to the difficulty of growing single crystals. Potentiometric titration with alkali is used to detect protonated NH groups in the coordinated ligands, to characterise the influence of coordination on the acidity of the ligands, and to investigate the state of the complexes in different media—pH and $[Cl^-]$ determinations. The conductimetric method is used to study the kinetics of the substitution of chloride ions in the reactions of *cis*-DDP with purine and pyrimidine bases and their nucleosides. The NMR methods play the main role in the determination of the structures of the complexes. Here we shall indicate in greater detail the possibility of the use of proton magnetic resonance (^1H NMR). Comparison of the ^1H NMR spectra of free and coordinated ligands in D_2O can yield information about the non-labile protons [for example H(2) and H(8) in the adenosine molecule]. Coordination induces changes in the ^1H NMR spectra of the ligand. As a consequence of the decrease of electron density on formation of the donor–acceptor bond, the deshielding of the proton near the electron-donating atom and the downfield shift of its signal are observed. Furthermore, owing to the spin–spin coupling with the ^{195}Pt magnetic nucleus (nuclear spin $I = 1/2$), the signal of the nearest proton becomes a triplet with the intensity ratios 1 : 4 : 1 in conformity with the content of the ^{195}Pt isotope in natural platinum (34%). The spin–spin coupling constant $J_{^{195}Pt-^1H}$ depends on the distance between the ^1H and ^{195}Pt nuclei: thus, in the platinum(II) complexes with the thymine anion, we have $^3J = 38$ Hz, $^4J = 4$–15 Hz, and $^5J \approx 0$. The study of the ^1H NMR spectra in DMSO-d_6 makes it possible to characterise also the distance between the labile protons of the NH_2, OH, and SH groups in the coordinated ligands.

Examples of the application also of other microwave spectroscopic methods to the study of the structures of the platinum(II) complexes of purine and pyrimidine bases will be given below.

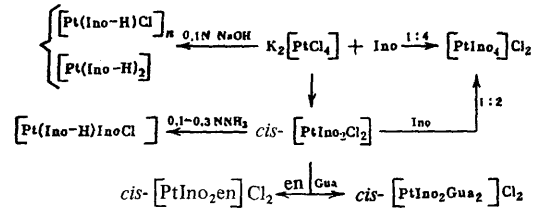
1. Platinum(II) Complexes of 6-Oxopurines and Their Nucleosides

Since *cis*-DDP is bound preferentially by the guanine in DNA, the interaction of guanine and guanosine with platinum(II) complexes has been investigated in most studies. Fewer studies have been devoted to the reactions with their antimetabolites—hypoxanthine and inosine. Guanine, hypoxanthine, and their nucleosides can be coordinated both in the form of neutral molecules and in the form of anions via different electron-donating atoms. There is a possibility of the following main types of coordination under these conditions: (a) monodentate—via the N(7), N(1), and N(9) heteroatoms (for the bases); (b) bidentate—via the N(7) and O(6) atoms; (c) bridged—with participation of the N(7) and N(1) or O(6) atoms.

(a) The Monodentate Type of Bond

The interaction of *cis*-DDP and *trans*-$[Pt(NH_3)_2Cl_2]$ with guanosine and inosine in solutions at different pH has been investigated by a differential spectrophotometric method.[13] It has been shown that the *cis*- and *trans*-isomers react with oxopurines in the same way, the latter being coordinated as monodentate species. At low pH, the bond is formed via the N(7) atom, while at high pH (pH > 9) it is formed via the deprotonated N(1) atom. The conclusion that this type of binding obtains has been confirmed by data for 7- and 1-methyl-substituted inosine and guanosine. The bonding of platinum(II) via N(7) has been established spectrophotometrically also for hypoxanthine.[35,36] However, the spectrophotometric method, especially when applied to solutions containing mixtures of products, cannot provide an exact answer about the ligand binding site. Studies in which the complexes are isolated are more promising. Platinum complexes of different types have been obtained with guanosine and inosine—neutral, cationic, and anionic with different numbers of purine molecules. The reaction of nucleosides with *cis*-$[Pt(NH_3)_2Cl_2]$ and $[PtenCl_2]$ (en = ethylenediamine) lead to the formation of mixed tetrammines having the composition $[PtA_2L_2]Cl_2$, where L = guanosine, inosine, and xanthine.[37] The reactions of $K_2[PtX_4]$ with nucleosides for a nucleoside to platinum ratio of 2, are accompanied by the formation of the *cis*-nonelectrolytes $[PtL_2X_2]$ (X = Cl or Br; L = Ino or Gua).[38] When the ratio is unity, the anionic complexes $K[PtLCl_3]$ are formed.[39] Cationic complexes with four nucleoside molecules have been isolated—$[PtIno_4]Cl_2$, $[PtGua_4]Cl_2$, and *cis*-$[PtIno_2Gua_2]Cl_2$.[40,41] All these compounds contain nucleoside molecules bound as monodentate species.

The reactions of inosine with platinum(II) complexes can be represented by the scheme



The coordination site in inosine has been determined by ^1H NMR. The signal of the H(8) proton in the ^1H NMR spectra of the compounds isolated by Kong and Theophanides[37] shifted downfield by 0.8 p.p.m. and that of the H(2) proton shifted by only 0.4 p.p.m. The H(2) signal in the spectra of the complexes remained as a singlet, while the H(8) signal was a triplet as a result of spin–spin splitting by the ^{195}Pt nucleus. These data enabled the authors to conclude that inosine is linked to platinum(II) via N(7). A similar type of bonding occurs also in other platinum(II) complexes with inosine and guanosine coordinated as monodentate species.[38–41] The ^1H and ^{13}C NMR methods, with the aid of which the occurrence of Pt–N(7) coordination was demonstrated,[2] were used to determine the donor atom of guanosine:

The H(8) signal is a triplet with $^3J[^{195}Pt - ^1H(8)] = 24$ Hz; in the ^{13}C NMR spectrum, $\Delta\delta$[C(5)] and $\Delta\delta$[C(9)] exceed on coordination the changes in the chemical shifts of signals due to other carbon atoms. X-Ray diffraction studies confirmed the monodentate mode of binding of guanosine and inosine via the N(7) atom in the complexes $[Pt(NH_3)_2Gua_2].Cl_{3/2}(ClO_4)_{1/2}$,[42] $[PtenGua_2]Cl_{3/2}I_{1/2}.2H_2O$,[43] and [PtdienGua].$(ClO_4)_2$ (dien = diethylenetriamine).[44] The same type of binding has been observed in the complexes of 9-methylguanine $[Pt(9\text{-}CH_3Gu)_4]Cl_2$ [45] and with the inosine nucleotide $[Pt(NH_3)_2(5'\text{-IMP})_2]$ (5'-IMP = inosine 5'-monophosphate).[29]

Among the platinum(II) complexes with monodentate coordination of 6-oxopurines, almost no isomeric triammines of the type $[PtA_2LCl]Cl$, where A = NH_3 or ½en and L = Gu, Gua, Hyp, or Ino, have been isolated. Complexes of this type can be formed in the first stage of the interaction of DDP with DNA bases. They are of interest as objects to be used in tests for antitumour activity, since they contain one labile Cl^- ion together with the molecule of a lipophilic ligand and are readily soluble in water. The isomeric triammine complexes $[Pt(NH_3)_2LCl]Cl$ and *cis*-[PtenLCl]Cl (L = inosine or hypoxanthine) have been synthesised[46,47] by treating the isomeric non-electrolytes $[Pt(NH_3)_2Cl_2]$ and *cis*-$[PtenCl_2]$ with inosine or hypoxanthine in 1:1 proportions. The type of ionic decomposition and the inner-sphere location of the chloride ions have been established conductimetrically (Λ = 110–120 Ω^{-1} cm^2 mol^{-1}) and by IR spectroscopy ν(Pt–Cl) = 328–337 cm^{-1}. The ν(C=O) frequency changes little on coordination. The acid properties of the complexes and their hydrolytic stability have been investigated. Coordination leads to an appreciable intensification of the acid properties of inosine: the pK_a of free inosine is 8.9 [dissociation of N(1)H], while for certain isomeric triammines $[Pt(NH_3)_2InoCl]Cl$ the pK_a is 7.18 (*trans*-form) and 7.85 (*cis*-form) at an ionic strength of 0.3 (0.3 M KCl). Isomeric complexes of the tetrammine type, namely $[Pt(NH_3)_2.Ino_2]Cl_2$ and *cis*-$[PtenIno_2]Cl$, have been isolated and their acid properties have been investigated. The tetrammine complexes exhibit the properties of weak dibasic acids with similar dissociation constants: the pK_a^1 and pK_a^2 are 7.00 and 9.1 for the *cis*-form and 6.65 and 8.0 for the *trans*-form. The lower acidity of the *cis*-isomer reflects the greater *trans*-influence of NH_3 compared with inosine.

In relation to hydrolysis, the *cis*-triammine $[Pt(NH_3)_2.InoCl]Cl$ is less stable: the stability constant (0.1 M KNO_3, 25 °C) is 7.1 × 10^2 litre mol^{-1}, while the value for the *trans*-form is 1.4 × 10^3 litre mol^{-1}.[46,47] The same behaviour has been observed also for isomeric adenosine-containing triammines. Apparently the disposition of the cumbersome nucleoside molecule next to the chlorine ion decreases the stability of the Pt–Cl bond.

It is noteworthy that the synthesis of the triammines involves certain difficulties as a consequence of the possible admixture of complexes of the tetrammine type. These compounds are obtained more readily when substituted ligands are employed. Thus a chloride complex of N^2N^2-dimethyl-9-methylguanine of the triammine type has been isolated. Investigation of its geometry made it possible to attribute a smaller structural *trans*-effect to the N(7)-coordinated purine base compared with the Cl^- ion; the length of the Pt–N bond along the *trans*-coordinate H_3N–Pt–Cl exceeds by 0.3 Å the length of the bond along the *trans*-coordinate H_3N–Pt–purine.[48]

On the basis of the available data, it can be regarded as established that the preferred site where guanosine, inosine, and hypoxanthine are bound to the central platinum(II) is the N(7) atom despite the fact that its basicity is extremely low {pK_b[N(7)] is 11.9 for Gua, 12.1 for Hyp, and 13.0 for Ino}, while the capacity of N(1)H for acid dissociation is appreciable {pK_a[N(1)H] is 8.7 for Ino, 8.8 for Hyp, and 9.2 for Gua},[49] so that it would seem that anionic complexes involving the substitution of the N(1)H proton should be formed rather than complexes with neutral nucleosides. Apparently the basicity of the N(7) nitrogen atom and the acidity of the N(1)H group are not factors determining the stability of the bond between nucleosides and the acid $[Pt(NH_3)_2]^{2+}$, which is much softer than the proton.

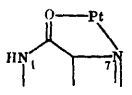
The coordination of guanosine via the N(7) atom in a neutral medium is characteristic also of another "soft" acid, namely CH_3^+Hg.[49]

The monodentate coordination of guanine via the N(7) atom is observed also in reactions of *cis*-DDP with DNA involving the intrastrand binding of *cis*-DDP to the N(7) atoms of neighbouring guanine molecules.[50–52]

In an alkaline medium, one may expect the binding of $Pt(NH_3)_2^{2+}$ and CH_3^+Hg to nucleosides as a result of the dissociation of the proton from N(1)H. The water-insoluble non-electrolytes $[Pt(Ino-H)_2]$ and $[Pt(Gua-H)_2]$,[38] isolated under these conditions, are polymers according to Raman and spectroscopic and ^1H NMR data[53,54] and contain bridging nucleoside anions linked to platinum(II) atoms not only via the deprotonated N(1)H group but also via coordination involving the N(7) atom. The monodentate binding of nucleosides via the protonated N(1)H group is not characteristic of platinum(II) complexes. Only when the N(7) and N(9) atoms in 7,9-dimethylguanine and 7,9-dimethylhypoxanthine are blocked by a methyl group, is it possible to achieve the monodentate coordination of guanine and hypoxanthine via the N(1)H groups. Thus studies have been made of the crystal structures of the following complexes which have been isolated: $[Ptdien7,9\text{-}(CH_3)_2Hyp](PF_6)_2$, $\{Pten[7,9\text{-}(CH_3)_2Hyp]_2\}(PF_6)_2$, and $\{Pt(NH_3)_2[7,9\text{-}(CH_3)_2Hyp]_2\}(NO_3)_2.2H_2O$.[55,57] These complexes are of interest also because their structures are to some extent analogous to those of platinum(II) complexes of cyclic amides—α-pyrrolidinone and α-pyridone,[58,59] containing the NHCO fragment.

(b) Bidentate Binding

The bidentate binding of 6-oxopurines and their nucleosides to platinum(II) of the N(7)–O(6) chelate type has been the subject of numerous discussions and has still not been demonstrated directly by X-ray diffraction. A chelate of this type is possible only for the *cis*-isomer.

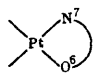


Since only the *cis*-isomer exhibits antitumour activity, many investigators see the cause of the difference between the activities of the $[Pt(NH_3)_2Cl_2]$ isomers in the fact that the *cis*-isomer forms a perfect chelate with the guanine of DNA, while the *trans*-isomer does not.[29,30,31,38,60,61]

In order to model the formation of this type of chelate in the interaction of DDP with DNA, a study has been made of the reaction of DDP with 6-oxopurines. The compounds isolated, whose composition corresponds formally to the bidentate binding of 6-oxopurines and their nucleosides, such as *cis*-$[PtA_2L]^{2+}$ and *cis*-$[PtA_2(L-H)]^+$, where $(L-H)^-$ is the ligand anion, as well as the complexes formed in solutions have been investigated. The following structural formulae can be proposed for the complexes having this composition.

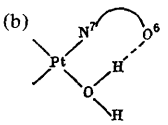
Monomeric complexes:

(a)



direct bidentate chelate bond

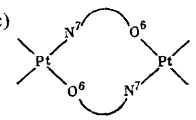
(b)



indirect chelation via the H bond between the O(6) atom and the proton of the coordinated water molecule.

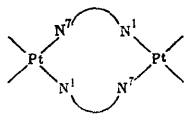
Dinuclear and polynuclear complexes with a bridge bond,

(c)



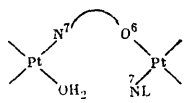
N(7)–O(6) bridge

(d)



N(7)–N(1) bridge

(e)



N(7)–Pt–O(6) bridge with monodentate H_2O and 6-oxopurine molecules.

Analogous bond types have been postulated also for coordinated 6-oxopurine anions. A direct answer to the question concerning their structure can be obtained by the X-ray diffraction method, but this is not always possible owing to the difficulty of isolating crystals suitable for analysis by X-ray diffraction. The possibility of chelation has therefore been investigated mainly by spectroscopic methods—IR, Raman, NMR, fluorescence, and atomic-absorption methods, X-ray electronic spectroscopy, etc. However, under these conditions one obtains at best information about the involvement of the O(6) atom of the oxopurine in the coordinate bond with platinum(II) but not about the mononuclear or polynuclear structure of the complexes. Measurements of the molecular weight are necessary for this purpose, which is hindered by the electrolytic character of the compounds and their poor solubility in non-polar solvents. Owing to the differential binding of *cis*-DDP by the DNA guanine, most of the studies have been devoted to the elucidation of the mode of binding of guanine, guanosine, and their derivatives in platinum(II) complexes.

Complexes whose composition corresponds to bidentate coordination have been isolated and investigated in a number of studies:[62] [PtdatGua]Cl_2, where dat = 3,4-diaminotoluene. The reaction of [PtdatCl$_2$] with guanosine was carried out in dimethylformamide (DMF), the complexes being isolated by adding the 1:1 acetone–ether mixture. Recrystallisation of the complex [PtdatGua]Cl_2 from a methanol–ether mixture leads to the formation of a complex of the triammine type with guanosine bound as a monodentate species, namely [PtdatGuaCl]Cl. The stretching vibration frequency ν(C=O) = 1645 cm^{-1} in the complex $[PtdatGua]^{2+}$ is appreciably smaller than in the complex containing guanosine coordinated as a monodentate species, i.e. $[PtdatGuaCl]^+$ (1685 cm^{-1}) and in free guanosine; on this basis, the authors concluded that an unstable chelate of the N(7)–Pt–O(6) type is formed in the first compound. The change in the N(1)H chemical shift in the spectra of the complexes [in hexadeuteriated dimethyl sulphoxide (DMSO-d_6)] is also consistent with this hypothesis: the shifts are 10.82 p.p.m. for [PtdatGua]Cl_2 and 10.70 p.p.m. for [PtdatGuaCl]Cl; in the first complex, deshielding increases owing to the involvement of O(6) in coordination.

It has been demonstrated by X-ray electronic spectroscopy that in the solid complexes of *cis*-DDP with DNA which have been isolated the 1s[O(6)] ionisation energy of guanine is reduced by 0.5–0.7 eV, whereas no such decrease is observed in the binding of the *trans*-isomer.[63] The DDP and [PtenCl$_2$] complexes, which are capable of chelation, as well as their aquo-forms greatly reduce the intensity of the fluorescence in the DNA–ethidium bromide system.[64] It has been observed by the atomic absorption method that the absorption intensity in the complexes with the postulated chelate linkage, i.e. [Pt$(NH_3)_2$Gua]Cl_2 and [PtenGua]Cl_2, is smaller by a factor of two than in the complexes with the monodentate coordination of guanosine.[65] It has been established by potentiometric measurements that the reaction of DDP with DNA guanine is accompanied by the elimination of two chloride ions per molecule of the complex, while in the reaction with the *trans*-isomer one such ion is removed.[31] The conclusion that a platinum(II) chelate complex with guanine is formed via the N(7) and O(6) atoms was also reached on the basis of circular dichroism spectra.[66]

Complexes in which the bidentate coordination of the neutral guanosine molecule, namely [PtenGua]$(NO_3)_2.2H_2O$ and [PtenGua]$(ClO_4)_2$, synthesised by treating a solution of *cis*-[Pten$(H_2O)_2]^{2+}$ with guanosine in 1:1 proportions at 40 °C for 1 day, have been described.[67] The outer-sphere position of the NO_3^- and ClO_4^- ions follows from IR spectra [$\nu(NO_3^-)$ = 1380 cm^{-1} and $\nu(ClO_4^-)$ = 1100 cm^{-1}] and conductimetric data, which correspond to the decomposition of complexes of the type characteristic of 1:2 electrolytes. Comparative study of the IR spectra in the ν(C=O) region for complexes with monodentate and postulated bidentate coordination of guanosine showed that in the latter the ν(C=O) frequency is reduced by 20 cm^{-1}. When 1 equivalent of NaOH is added to aqueous solutions of the complexes, the pH increases from 4.5 to 7.2, but, as the reaction proceeds, it falls to 6.9. The addition of alcohol entails the formation of the compounds [Pten(Gua – H)]X.$2H_2O$, where X = ClO_4^- or NO_3^-, and [Pten(Gua – H)]I.$3H_2O$. As a result, the authors assume the possibility of the formation of a chelate especially for the anion $(Gua - H)^-$, but in concentrated solutions they do not rule out the possibility of the existence also of polymeric species with bridging anions.

The bidentate coordination of the anions of 6-oxopurines in platinum(II) complexes has been postulated.[38,67,68,69] Dilute solutions (10^{-4} M) of the complexes [Pten(Gua – H)]$(ClO_4)_2$. .$2H_2O$, [Pten(Gua – H)Cl], and [PtenGua]$(NO_3)_2$ contain no polymers judging from circular dichroism spectra: the spectra of these complexes are analogous to those of free guanosine and its anion but differ from the spectra of [PtenGua$_2$]. .Cl_2, where the interaction of two neighbouring guanosine molecules leads to a two-phase signal.[67,70] The ^{195}Pt and ^{15}N NMR methods have been applied to solve the problem of the possible chelation of inosine in reactions with platinum(II) complexes.[71] The ^{195}Pt NMR spectra yield valuable information about the structure of the platinum complexes. The chemical shift of the ^{195}Pt nuclei changes appreciably as a function of the nature of the donor atoms in the coordination

unit and the geometrical configuration of the complex. For example, the chemical shifts in the spectra of the isomeric aquo-complexes $[Pt(NH_3)_2(H_2O)_2]^{2+}$ differ by 209 p.p.m. The ^{195}Pt NMR spectra are usually recorded for specimens enriched in ^{15}N, since the ^{14}N nuclei, which possess a quadrupole moment, broaden the signals. The spin–spin coupling constant $^1J(^{195}Pt-{}^{15}N)$ is sensitive to the nature of the *trans*-ligand and can be used in its turn for the determination of the donor atoms and for the estimation of the *trans*-influence. The formation of polymeric hydroxo-complexes when solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ are allowed to stand, can be followed clearly on the basis of the ^{195}Pt NMR spectra: the chemical shift in the specially prepared solutions is −1593 p.p.m. (using Na_2PtCl_6 as the external standard) and, when the solution is allowed to stand, new signals appear at −1161.8 p.p.m and −1520 p.p.m., referring respectively to $[Pt(NH_3)_2OH]_2^{2+}$ and $[Pt(NH_3)_2.OH]_3^{3+}$.[30,72–74]

Signals of the initial complex [a triplet with $^1J(^{195}Pt-{}^{15}N)$ = 312 Hz] and broad signals due to the formation of complexes of the triammine and tetrammine types with inosine were observed in the $\{^1H\}-{}^{195}Pt$ NMR spectra, with suppressed resonance of the protons, of the 1 : 1 mixture of *cis*-$[Pt(^{15}NH_3)_2Cl_2]$ and inosine, but signals corresponding to the $^{195}Pt-O(6)$ bond, which should have been present in the chelate, were not found.[71] However, the authors assume the formation of the N(7)–Pt–O(6) chelate in the 1 : 1 mixture of *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2]^{2+}$ with inosine, because the $\{^1H\}-{}^{15}N$ NMR spectrum of this system contains an additional signal displaced by 2 p.p.m. towards higher frequencies compared with the spectrum of the monoaquotriammine complex. The signal was absent from the spectrum of a solution of *cis*-$[Pt.(^{15}NH_3)_2(H_2O)_2]^{2+}$ containing adenosine 5'-monophosphate.

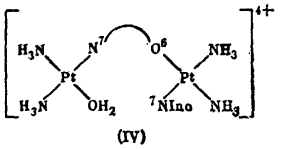
Chelation has been observed indirectly in the cobalt(II),[75] copper(II),[76] and nickel(II) [77] complexes of guanosine. Direct chelation has been demonstrated by X-ray diffraction in the copper(II) complexes of theophylline, which is a structural analogue of guanine.[78] It has been established by the same method that the DDP–*cis*-$Pt(NH_3)_2^{2+}$ fragment bound to DNA is located in the vicinity of the N(7) and O(6) atoms of guanine.[79] Quantum-chemical calculations agree with the occurrence of chelation.[80] Complexes of palladium with the chelated anions, namely $[Pd(Ino-H)_2]$ and $[Pd(Gua-H)_2]$, have been isolated.[81] The coordination of the guanosine anion via the deprotonated N(1) atom has been observed in the reaction of *cis*-$[Pt(DMSO)_2Cl_2]$ with inosine in an alkaline medium.[82]

Stereochemical relations more favourable for chelation obtain for 6-mercaptopurines, since the increase of the C–S bond length promotes the decrease of the strain on formation of the S(6)–N(7) chelate. Palladium(II) complexes with this type of bond have been observed.[83–85] Cationic, anionic, and non-electrolytic platinum(II) and palladium(II) complexes of 6-mercaptopurine bound as a bidentate species have been described.[86] The isomeric diamines $[Pt(NH_3)_2Cl_2]$ react differently with 6-mercaptopurine (6-mp): all the ligands are substituted in the *cis*-isomer and the complex $[Pt(6\text{-}mp-H)_2]$ is formed, while in the *trans*-isomer only two Cl^- ions are substituted, which is caused by the strong *trans*-influence of 6-mercaptopurine. The formation of the Pt–S and Pt–N bonds in the chelate has been confirmed by the EXAFS method.[87]

Experimental and theoretical studies, whose results conflict with the hypothesis of the formation of a direct chelate of the N(7)–O(6) type, have been carried out. Stereochemical objections have been raised by Sletten.[76] The interaction of the complexes $[Pten(H_2O)_2]^{2+}$ and $[PtenCl_2]$ with inosine and its derivatives at different pH has been investigated by the Raman spectroscopic and ^1H NMR methods.[53,54] For the ratio Ino/Pt ≤ 2, complexes with one or two inosine anions are formed in an alkaline medium. The H(8) and H(2) signals undergo an upfield displacement under these conditions. With increase of the Pt/Ino ratio from 1 to 4, the ^1H NMR spectra change qualitatively—the signals become broad, which has been attributed to the formation of polymeric species containing bridging inosine anions with participation of the N(1) and N(7) atoms.

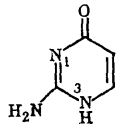
In order to investigate the possible chelation reaction between *cis*-DDP and inosine and hypoxanthine, we investigated the complexes *cis*-$[PtA_2L](NO_3)_2$ (A = NH_3 or ½en and L = inosine or hypoxanthine), whose composition corresponds to bidentate binding, and the spectroscopic characteristics and acid properties of these compounds and the complexes of the triammine type $[PtA_2LCl]Cl$ with monodentate coordination of the ligands were compared. The complexes *cis*-$[PtA_2L](NO_3)_2$ were obtained by treating a solution of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with an equimolar amount of the ligand and were precipitated with acetone.[47] The acid titration curves for the complexes obtained differ sharply from the titration curves for the complexes with ligands bound as monodentate species: the acidity of the complexes *cis*-$[Pt.(NH_3)_2L](NO_3)_2$ is appreciably greater and the curves consist of a short initial section corresponding to the titration of a strong acid (0.20–0.25 equiv. of OH^- per mole) and a second section in the pH range 6–8. From the pH values in this section, one may conclude that it corresponds to the titration of a coordinated water molecule in the complex *cis*-$[PtA_2LH_2O]^{2+}$. Comparison of the titration curves for the complex *cis*-$[Pt(NH_3)_2Ino](NO_3)_2$ and the isomeric monoaquo-ions $[Pt(NH_3)_2InoH_2O]^{2+}$, prepared from the corresponding triammines by removing the Cl^- ion by treatment with $AgNO_3$, leads to the following conclusions: (1) the titration curves for *cis*- and *trans*-$[Pt(NH_3)_2InoH_2O]^{2+}$ differ little from one another; this conflicts with the hypothesis of the existence of the N(7)–Pt–O(6) chelate in solutions, since the capacity for chelation is characteristic only of the *cis*-isomer, which would have led to a difference between the titration curves; (2) the titration curves for the isomeric monoaquo-cations and *cis*-$[Pt(NH_3)_2Ino](NO_3)_2$ are also similar. Hence one may conclude that solutions of these compounds contain species with analogous compositions and structures. These can be (1) the monomeric aquo-cations *cis*-$[Pt(NH_3)_2InoH_2O]^{2+}$ and (2) the dimeric and polymeric cations linked by bridging inosine molecules via the N(7) and O(6) atoms in which the acid dissociation of N(1)H is enhanced. The contents of these species can be estimated from the relative sizes of the corresponding sections of the titration curves: 75% of platinum exists as the monoaquo-cation and 25% as the dimer. The participation of the O(6) atom in the coordinate bond follows from the ^{13}C NMR spectra of the complex $[Pt(NH_3)_2.Ino](NO_3)_2$ in D_2O: (1) the C(5) and C(8) signals of inosine in the complex undergo the greatest downfield shift, which indicates the presence of the Pt–N(7) bond; (2) the C(2) signal changes little under these conditions, i.e. there is no Pt–N(1) bond; (3) the form of the C(6) signal differs sharply from that of the signal in the spectra of complexes with monodentate coordination of inosine—it has a multiplet structure, is appreciably broadened, and has been displaced downfield. Comparison of the X-ray emission spectra of the complexes *cis*-$[Pt(NH_3)_2Hyp]\{B(C_6H_5)_4\}_2$ and *cis*-$[Pt(NH_3)_2.(Hyp)_2]\{B(C_6H_5)_4\}_2$ indicates a decrease of electron density at the O(6) atom in the first compound, which agrees with the involvement of the atom in the coordinate bond. The circular dichroism spectra of these compounds are of the single-phase character (like the spectra of free inosine and the complexes having the *trans*-configuration), in contrast

to *cis*-$[Pt(NH_3)_2Ino_2]Cl_2$, where there is a possibility of band splitting owing to the π-interaction of inosine molecules in close proximity. This set of data has led us to the conclusion that formula (IV) may be attributed to the cationic complex.



(IV)

A paper published a year and a half after our communication[88] also described the application of the method involving the acid titration of the isomers $[Pt(NH_3)_2(9\text{-}C_2H_5Gu)H_2O]^{2+}$ in order to detect chelation. On the basis of the similarity of the titration curves for the isomers, it was concluded that there are no chelates with a N(7)–Pt–O(6) bond. The consumption of alkali in the titration after the jump at pH 8 was in our case 1 equiv.per mole of platinum; a strongly acidic section, corresponding to the consumption of 0.25 equiv.of OH^- per mole, was also observed. The character of the titration curve was likewise explained by the acid dissociation of H_2O in *cis*-$[Pt(NH_3)_2(9\text{-}C_2H_5Gu)H_2O]^{2+}$ and a dimer containing bridging and terminal 9-ethylguanine molecules. It has been suggested that the bridge bonds are formed via the N(7) and N(1) atoms of 9-ethylguanine and that the strong acid properties are due to the dissociation of N(3)H in an unusual tautomeric form of 9-ethylguanine. We believe that the involvement of the N(1) atom in the bridge bond is less probable than the involvement of the O(6) atom. In the analogous complexes of inosine, the presence of the Pt–O(6) bond has been confirmed by a number of methods; furthermore, the unusual tautomeric form of 9-ethylguanine with a proton at N(3) corresponds to one of the tautomeric forms of isocytosine:



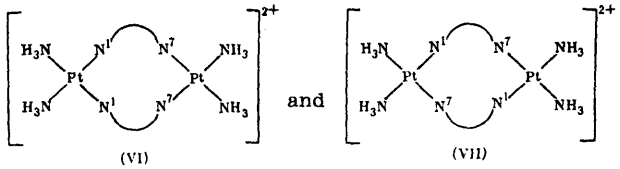
(V)

However, isocytosine has weak acid properties ($K_a = 3.2 \times 10^{-10}$) and K_a for the complex *cis*-$[Pt(NH_3)_2(iso\text{-}Cyt)Cl]Cl$ which we synthesised is 1.3×10^{-7}. The strong acidity along the first section of the titration curve is therefore hardly likely to be associated with the formation of such a tautomer.

A combination of the most modern research techniques has been used by Raudashl-Siever et al.[89], namely high-performance liquid chromatography (HPLQ) and ^{195}Pt NMR, for the investigation of the nature of the products formed in the reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with guanine and its methyl-substituted derivative for different ratios and concentrations of the components, different pH (2 and 7), and different contact times (temperature 60 °C). The HPLQ method makes it possible to detect the formation of a number of compounds in solution. The predominant complexes were isolated on the preparative scale and analysed. They include dinuclear complexes with one or two bridging guanine anions—$[Pt_2(NH_3)_4(Gu-H)](NO_3)_3.2H_2O$ and $[Pt_2(NH_3)_4.(Gu-H)_2](NO_3)_2.2H_2O$—and the monomeric complex $[Pt(NH_3)_2(Gu-H)Gu]NO_3$. The formation of complexes with chelated molecules or anions of guanine has not been observed.

(c) Bridge Type Coordination of Purines and their Nucleosides

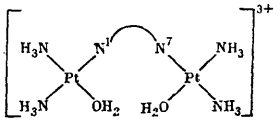
Complexes of this type include the dinuclear complexes with bridging guanine anions. The complex $[Pt_2(NH_3)_4(Gu-H)_2].(NO_3)_2.2H_2O$ contains the coordination unit PtN_4 according to ^{195}Pt NMR spectra; two ^{195}Pt signals (−2416 and −2468 p.p.m.) indicate the presence of two isomers:



(VI) and (VII)

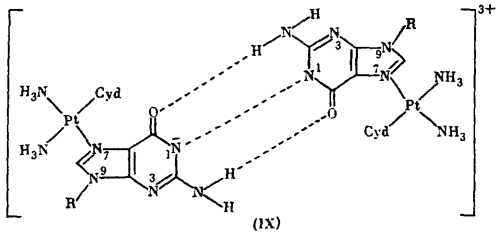
"head to head" "head to tail"

The ^{195}Pt NMR spectra of the dimer $[Pt_2(NH_3)_4(Gu-H)].(NO_3)_3.2H_2O$ contains one signal at −1015 p.p.m., which corresponds to the PtN_3O unit and the coordination formula



(VIII)

In both compounds the bridge is formed via the N(1) and N(7) atoms of the guanine anion. We explain the acid properties of the complexes $[PtA_2L](NO_3)_2$ (A = NH_3 or ½Eu; L = Ino or Gua) by the formation of dimers with an inosine and guanosine bridge bond via the N(7) and O(6) atoms.[47,90] This type of bonding had been postulated earlier in the polymeric platinum(II) and palladium(II) complexes with these ligands.[91,92] The bridge bond via the N(3) and N(9) atoms becomes possible for guanine derivatives dimethylated at N(1) and N(7).[89] The binding of two platinum(II) atoms by the neutral hypoxanthine molecule via N(3) and N(9) has been established in the complex $[Pt_2Gly_2Cl_4Hyp]$, where Gly = glycine, formed in the reaction of $K_2[PtGly_2Cl_2]$ with hypoxanthine, in view of the identical shifts of the H(2) and H(8) signals on coordination.[93] Yet another type of binding, via three hydrogen bonds between guanine and its anion, has been indicated in the dimeric complex $[Pt_2(NH_3)_4.Cyd_2Gu(Gu-H)]^{3+}$, where Cyd = cytidine:[94]



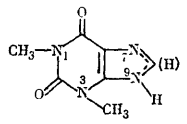
(IX)

In conclusion of this Section, one may say that the presence of the N(7)–Pt–O(6) chelate in the complexes with the ratio L/Pt = 1, where L = 6-oxopurines or their nucleosides, does not follow self-evidently from spectroscopic and physicochemical studies of these compounds and has not been confirmed by X-ray diffraction. The existence of these compounds, especially in solutions, as mixtures of mononuclear monoaquo-complexes and dimeric or polymeric species containing bridging nucleoside ligands with participation of the O(6) atom in the bridge bonds appears more likely. The ratios of these forms depend on the concentration and pH of the solution: in an alkaline medium, the probability of the formation of polymeric structures with bridging anions increases and one cannot rule out the existence of chelates

with the anion. Investigation of the structures of these compounds by X-ray diffraction and the determination of their molecular weight in solution are undoubtedly required.

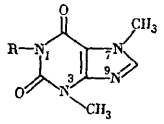
2. Platinum(II) Complexes of 2,6-Dioxopurines

The platinum(II) and platinum(IV) complexes of methylated 2,6-dioxopurines have been investigated:



(X)

N-1,3-dimethylxanthine, theophylline (Thp)



(XI)

R = H: *N*-3,7-dimethylxanthine, theobromine (TeO); R = CH_3: *N*-1,3,7-trimethylxanthine, caffeine (Caf)

Tautomerism is possible for theophylline [the proton is located at the N(7) or N(9) atom]. These ligands are biologically active. Caffeine enhances the antitumour activity of DDP.[95] The ligands contain various nitrogen atoms in the heterocycle blocked by methyl groups, which makes it possible to investigate the bond between the metal and a definite nitrogen atom. By treating a solution of $K_2[PtCl_4]$ in 0.5 *N* HCl with theophylline, it was possible to isolate complexes having the composition $(ThpH)_2[PtCl_4]$ and (ThpH)[PtThp.Cl_3], the former with an outer theophyllinium cation and the latter with an outer cation and coordinated theophylline molecule linked by a bond via the N(9) atom.[96,97] The theophylline anion is coordinated to platinum(IV):[98] the reaction of $[Pt(CH_3)_3(H_2O)_3]^+$ with sodium theophyllinate leads to the formation of the complex $[Pt(CH_3)_3(Thp-H)]$, containing the anion (Thp − H) and the Pt(IV)−N(7) bond. The compound is monomeric in solutions in DMSO and C_2H_5OH. The molecular weight of the complex in $CHCl_3$ and CH_2Cl_2 corresponds to the trimer. On the basis of the $^1H-^{195}Pt$ and $^{13}C-^{195}Pt$ spin–spin coupling constants, it has been established that the theophylline anion plays the role of a tridentate ligand, forming a chelate bond via the N(7) and O(6) atoms with platinum(II) and a bridge bond via N(9) with another platinum(II) atom.

The caffeine complex $(PPh_3CH_3)[PtCafCl_3]$, where $(PPh_3.CH_3)^+$ is the triphenylmethylphosphonium cation, has been isolated and its structure investigated; the bond between caffeine and platinum(II) is formed via the N(9) atom.[99] The anionic complex $K[PtCafCl_3]$ was found to possess antitumour activity: towards lymphocytoleukaemia P-388, the inhibition coefficient was 150%. Mixed non-electrolytes having the composition $(MCafLCl_2)$ [M = Pt(II) or Pd(II); L = Ado, Ino, or Gua] were isolated following the interaction of equimolar amounts of nucleosides and $K[PtCafCl_3]$ in an aqueous DMSO solution.[100] The coordination of caffeine via the N(9) atom and of nucleosides via the N(7) atom has been established by the ^1H and ^{13}C NMR methods. The *cis*-structure of the non-electrolyte follows from the presence of two absorption bands in the Pt–Cl region. Treatment of the complexes with alkaline solutions leads to the isolation of complexes with nucleoside anions: [MCaf.(Ino − H)Cl] and [MCaf(Gua − H)Cl]. The decrease of $\nu(C{=}O)$ in the spectra of the inosine and guanosine anions compared with the free ligand has been interpreted by the authors as a result of the formation of a Pt–O(6) bond, either of the N(7)–Pt–O(6) chelate type or the bridge type.

The product $[Pt(Caf-H)Cl]_2$, isolated in small amounts in the reaction of $K_2[PtCl_4]$ with caffeine (1:1) in 0.5 *N* HCl at 50 °C, is extremely unusual.[100] Its dimeric structure has been confirmed by measurement of its molecular weight. The far IR spectrum shows a $\nu(Pt-Cl)$ band at 305 cm^{-1}, corresponding to the Pt–Cl–Pt bridge bond. The signal of the H(8) proton is absent from the ^1H NMR spectrum of the complex, which has been explained by the formation of the Pt–C(8) σ-bond. However, the proposed structure requires further confirmation, since the presence of the Pt–C(8) σ-bond has not been demonstrated directly by the ^{13}C NMR method and the heterolytic cleavage of the C(8)–H bond in an acid medium is unlikely. It is also noteworthy that not one complex with the caffeine anion has been described hitherto.

A σ-bond of the ylide, carbene type is formed between Ru(III) and the caffeine C(8) atom in the reaction with $[Ru(NH_3)_3(H_2O)_3]^{3+}$.[101] The complex $[Ru(NH_3)_3Cl_2Caf]Cl.H_2O$ with a neutral caffeine molecule, in which the presence of the Ru(III)–C(8) bond has been established by X-ray diffraction, has been isolated. The Ru–C(8) distance (2.03 Å) corresponds to a strong, short bond. Complexes with this type of bond, namely $[Ru(NH_3)_4CafCl]Cl_2.2H_2O$ and $[Ru(NH_3)_4TeoCl]Cl_2.2H_2O$, have been described.[102] In both complexes the Ru(III)–N(9) bond is sterically hindered by the N(7)CH_3 group. Theophylline, in which the group is absent, is capable of binding both via the N(7) atom and the O(6) atom.

As a consequence of acid dissociation at N(7) and N(1)H, theophylline and theobromine are able to form complexes with coordinated anions, both Ru(III)–N(9) and Ru(III)–C(8) bonds being formed in the case of theophylline. A bond of the M–C(8) type is also present in the complexes of $HgCH_3^+$ with xanthine.[103]

Non-electrolytes having the composition $[PtThp_2Cl_2].2H_2O$ and $[PtCaf_2Cl]$ have been obtained in the reactions of $K_2[PtCl_4]$.[104] The isomeric triammines $[Pt(NH_3)_2LCl]Cl$ and the *cis*-tetrammines $[Pt(NH_3)_2(Thp)_2](NO_3)_2$ have been isolated after reactions involving *cis*- and *trans*-$[Pt(NH_3)_2.Cl_2]$. According to ^{13}C NMR data, the greatest downfield shift relative to the proton-donating ligands is observed on coordination for the signals due to the C(4) and C(8) atoms (4–7 p.p.m.), which indicates the presence of the Pt–N(9) bond. In the spectra of isomeric complexes having two theophylline molecules, two sets of ^{13}C signals are observed: one corresponding to coordination via the N(9) atom and the other, with an appreciable shift of the C(5) signal, which justifies the conclusion that the bond linking the second theophylline molecule is formed via the N(7) atom. The signals of the H(8) proton and of the methyl groups are also doubled in these compounds, which agrees with the hypothesis that the theophylline molecules are bound via both the N(9) and N(7) atoms.

3. Platinum(II) Complexes of Adenine and Adenosine

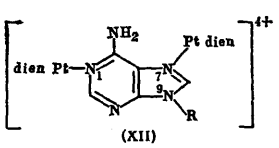
Adenine and its nucleoside adenosine (III) are 6-aminopurines. Adenine and adenosine possess weak basic properties, owing to the possibility of protonation at the N(1) atom: $pK_a[N(1)H^+] = 4.1$ (Ad) and 3.6 (Ado). The N(9)H group in adenine is capable of weak acid dissociation: $pK_a = 9.8$.[49] The following main types of coordinate bonds can be postulated for these ligands: (1) a monodentate bond via the N(1) or N(7) atoms; (2) a bridge bond in which the adenosine molecule binds two platinum atoms via the N(1) and N(7) atoms; (3) a bidentate bond via the N(1) [or N(7)] atom and the NH_2 group.

The monodentate coordination of adenine and adenosine via the NH_2 group is probable owing to the p,π-conjugation of the unshared electron pair of the NH_2 group with the ring.

The involvement in the bonds of the atom N(3), which is blocked by the D-ribose residue in close proximity, is just as unlikely. In addition to these types of bonding, adenine is capable of being coordinated in the form of an anion as a result of the acid dissociation of the HN(9) groups.

The principal conclusions about the interaction of adenine and adenosine with platinum(II) complexes have been reached by Theophanides and co-workers.[37,105] The non-electrolytic complexes $[PtL_2X_2]$ (X = Cl^- or Br^-) were isolated after treating a solution of $K_2[PtCl_4]$ with adenine, adenosine, and tri- and tetra-acetyladenosine. The signal of the H(8) proton undergoes the greatest downfield shift in the ^1H NMR spectra of the complexes: $\Delta\delta_{H(8)} = 0.92$ p.p.m. and $\Delta\delta_{H(2)} = 0.21$ p.p.m.; this indicates the coordination of the ligand via the N(7) atom. The monodentate coordination of adenosine was observed also by Ettore.[106] Adenosine and 9-methyladenine protonated at N(1) are also capable of such coordination: the complexes [Pt(AdoH)Cl_3] and [Pt(9-CH_3.AdH)Cl_3] are formed in 3 *N* HCl.[107] Other adenosine complexes containing the Pt–N(7) bond have also been isolated: the isomeric $[Pt(NH_3)_2Ado_2]Cl_2$ [108] and $[PtAdo_4]Cl_2$.[109] At the same time, for adenine there is much more evidence than for oxopurines and their nucleosides indicating the involvement of the N(1) atom in the monodentate bond with platinum(II). The coordination of adenosine via the N(7) atoms is promoted by an acid medium. It has been shown in relation to the reaction of $[PtdienH_2O]^{2+}$ with adenosine that in a neutral medium there is also a possibility of the formation of complexes with a Pt–N(1) bond.[37,110] The complexity of the ^1H NMR spectrum of the complex $[Pt(TAA)_2Cl_2]$ (TAA = triacetyladenosine), which has four signals instead of two for H(2) and H(8), was explained by the formation of complexes with three bond types:[105] N(7)–Pt–N(7), N(1)–Pt–N(1), and N(7)–Pt–N(1). The same three types of monodentate binding of adenosine were observed in the reactions of $[Pt(NH_3)_3Cl]Cl$ with adenosine with the ratio Ado/Pt = 2.[111] The products were separated by high performance liquid chromatography and their structure was demonstrated by spectrophotometric measurements at different pH. The double binding via the N(1) and N(7) atoms was observed also in the platinum(II) complexes of 9-methyladenine.[112]

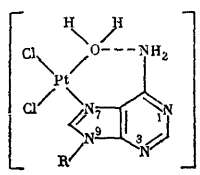
The formation of dinuclear complexes with a bridge type coordination of adenosine was first observed in solutions by the isomolar series (continuous variations) spectrophotometric method.[113] An analogous result was obtained in the study of the ^1H NMR spectra of solutions of [PtdienCl]Cl containing adenosine and an excess of the platinum(II) complexes, i.e. for a ratio Pt/L > 2.[37] Under these conditions, approximately equal downfield shifts of the signals of the H(2) and H(8) protons, amounting to 0.9–1 p.p.m., are observed. Both signals acquire the triplet form as a result of the spin–spin interaction with the ^{195}Pt nucleus [with the constant $^3J_{^{195}Pt-^1H(2,8)} = 26$ Hz]. The authors believe that the dinuclear complexes (XII) with a bridge type coordination of adenosine are formed in solution:



(XII)

The presence in solutions of complexes containing the Pt–N(1)–N(7)–Pt linkage as a result of the reactions of $[PtacacCl_2]^-$ (acac = acetylacetone) and *cis*-$[PtDMSOCl_3]^-$ with adenosine has been demonstrated by ^1H NMR.[114] Isomeric *cis*- and *trans*-complexes with a similar bond have been isolated in a pure state: $[Pt(NH_3)_2ClAdoPt(NH_3)_2Cl]Cl_2$ and $[Pt(NH_3)_2ClAdPt(NH_3)_2Cl]Cl_2$.[115,116] Anionic dinuclear complexes $K_2[PtCl_3AdoPtCl_3]$ with bridging adenosine molecules have also been described.[39] The tendency of adenine and adenosine molecules towards the bridge type of binding is manifested by the formation of polymeric complexes. Polynuclear complexes with 9-methyladenine having the composition $[Pt(9\text{-}CH_3Ad)Cl_2]$ have been described.[105] The formation of a series of polymeric complexes in the reaction of $K_2[PtCl_4]$ with adenine has been indicated.[117] A trinuclear complex with adenine anions $(Ad-H)^-$ having the composition $[Pt_2Ad(Ad-H)_2C_2H_5OH][PtI_4]$ has been isolated.[118]

The bidentate binding of adenine and adenosine to platinum(II) presupposes the involvement in the coordination of the NH_2 group and one of the nitrogen heteroatoms—N(1) or N(7) (most probably). The hypothesis of the bidentate binding of these ligands has been put forward on the basis of spectrophotometric measurements.[13,113] Complexes whose composition corresponds to this coordination have been isolated: $[PtAdX_2].2H_2O$ (X = Cl^- or Br^-) and $[PtAdoI_2].2H_2O$.[119] A strong downfield shift of the signal of the NH_2 group is observed in the ^1H NMR spectra of these compounds in DMSO-d_6, which is regarded as evidence for its involvement in binding. The complexes $[PtAdoCl_2]$, $[PtAdCl_2H_2O]$, and $[PtAdCl_2]$ have been isolated.[120] The complex [PtAdo.Cl_2] is anhydrous and monomeric and frequencies characteristic of Pt–Cl–Pt bridge bonds are absent from its IR spectrum; according to far IR spectroscopic data, it has the *cis*-configuration. A chelate structure involving the NH_2 group and the N(7) atom has been proposed for this complex. The formation of a chelate in which the NH_2 group of the adenine molecule is bound by a hydrogen bond to the oxygen atom of a water molecule is more probable for the hydrated complex:



(XIII)

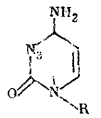
The insoluble complex $[PtAdCl_2]$ is apparently polymeric. Solutions of the non-electrolytic complexes $[PtAdCl_2H_2O]$ and $[PtAdoCl_2]$ in DMSO exhibit an inhibiting effect amounting to 50–60% on four strains of tumours[121] and at the same time they are less toxic than *cis*-DDP. The cationic complexes *cis*-$[Pt(NH_3)_2Ado](NO_3)_2$, in which the formation of a chelate involving N(7) and the NH_2 group can also be postulated, have been described.[115,116] The complexes differ from compounds with monodentate coordination of adenosine in their ^1H NMR spectra and acid properties. However, a final conclusion about the structure can be reached on the basis of X-ray diffraction analysis, which so far has not been possible owing to the lack of crystals suitable for this purpose.

III. THE SYNTHESIS, STRUCTURE, AND PROPERTIES OF PLATINUM(II) COMPLEXES OF PYRIMIDINE BASES AND THEIR NUCLEOSIDES

1. Complexes of Cytosine and Its Derivatives

Cytosine [Cyt, (XIV), R = H] together with guanine belong to the class of DNA bases which react preferentially with platinum complexes. In terms of their ability to interact with DDP, cytosine is in the second place after guanine and

among pyrimidine bases it is in the first place. The keto-amino-form is most characteristic of cytosine and its nucleoside cytidine [Cyd, (XIV), R = β-D-ribosofuranosyl]:[122]



(XIV)

Cytosine and cytidine are ambident ligands, since they contain several potential donor atoms. They can be the heterocyclic N(3) and N(1) atoms, the exocyclic NH_2 group, and the exocyclic oxygen atom.

The binding of cytosine and its derivatives via the exocyclic amino-group is unlikely for the same reason as in the case of adenosine. The binding of metal ions via the amino-group becomes possible after its deprotonation. In the free ligands, the acid properties of the NH_2 group are extremely weak ($pK_a = 16$),[125] but coordination enhances them. The ribose residue of cytidine is not involved in the coordinate bond.

The principal site of the coordination of cytosine and cytidine to metal ions is one of the heterocyclic nitrogen atoms. In order to determine which particular atom, it is useful to compare the capacities of these atoms for protonation. It follows from spectroscopic (IR and ^1H NMR) and X-ray diffraction studies and also calculations of electron density that cytosine and cytidine are protonated in the N(3) position.[124-126] The pK_a are 4.6 for Cyt N(3)H^+ and 4.2 for Cyd N(3)H^+.[127] On this basis, one can postulate that cytosine and cytidine are also coordinated in the platinum(II) sphere via the N(3) atom. The formation of complexes of cytosine and its derivatives with platinum(II) has been investigated in most cases in solutions with the aid of ^1H NMR. Studies in which individual complexes with these ligands were isolated and their structure demonstrated are less common in the literature.

In one of the first investigations[13] by differential spectrophotometry at different pH, a study was made of the interaction of cytidine with the geometrical isomers of $[Pt(NH_3)_2Cl_2]$ at 37 °C. Analysis of the absorption spectra of the equilibrium mixture led the authors to the conclusion that a chelate is formed with participation of N(3) and the 4-NH_2 group in the reaction with the *cis*-isomer and that there is monodentate binding via the N(3) atom in the reaction with the *trans*-isomer. However, further studies failed to confirm the formation of the chelate.

Studies have been made[37,128] of the ^1H NMR spectra of solutions of the platinum(II) complexes of cytosine and cytidine. Two doublet signals of the H(6) (7.35 p.p.m.) and H(5) (5.60 p.p.m.) protons and also a broad signal of the NH_2 group at 7.1 p.p.m. were observed in the ^1H NMR spectrum of free cytosine in DMSO-d_6.[129] The spin-spin coupling constant $^3J_{H(5)-H(6)} = 7$ Hz. On formation of the cytidine complex in the reaction with [PtdienCl]Cl, the signal of the H(5) proton undergoes a downfield shift of 0.13 p.p.m., which is somewhat greater than the shift of the H(6) proton (0.11 p.p.m.). Spin-spin interaction with the ^{195}Pt nucleus has been observed for the H(5) atom: instead of a doublet, two triplets with the intensity ratios 1:4:1 were produced. The spin-spin coupling constant is $^4J_{^{195}Pt-^1H(5)} = 8$ Hz, which is close to the value observed for the *meta*-proton in the platinum(II) complexes of pyridine.[130] The splitting of the signal of the H(6) proton by the ^{195}Pt nucleus was not observed. These data led the authors to the conclusion that cytidine is coordinated via the N(3) atom. A similar bond is formed also in the coordination of the 5-mononucleotide of cytidine (cytidine 5'-monophosphate or 5'-CMP).[128]

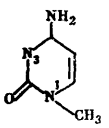
The ^1H and ^{13}C NMR spectra of the complexes of $PtCl_2$.2DMSO and $PdCl_2$.2DMSO with cytosine and cytidine in solutions in DMSO-d_6 have been thoroughly investigated.[129] In these systems too, $\Delta\delta[H(5)] = 0.18$ p.p.m. > $\Delta\delta[H(6)] = 0.11$ p.p.m. In the solutions of cytosine in DMSO-d_6, the signal of the proton in the NH_2 group is at 6.91 p.p.m. and is remote from the signal of N(1)H (10.27 p.p.m.). Coordination leads to a downfield shift of the signal of the NH_2 proton and to its splitting into two components: 8.59 and 8.25 p.p.m., because the rotation about the C–N bond in the complex is hindered. In the ^{13}C NMR spectra, the greatest shift has been observed for the C(2) and C(4) signals, both undergoing an upfield shift: $\Delta\delta[C(4)] = 1.3$ Hz and $\Delta\delta[C(2)] = 3.1$ Hz (WH90 Bruker spectrometer with a field strength of 21.14 kG under pulsed Fourier conditions). Coordination influences also the spin–spin coupling constant $^1J_{^{13}C-^1H}$, which changes to a greater extent for the carbon atoms located nearer the coordination centre: $\Delta^1J_{^{13}C(5)-^1H(5)} = 10$ Hz > $\Delta^1J_{^{13}C(6)-^1H(6)} = 3$ Hz. Thus the results of our study demonstrate convincingly the involvement of the N(3) atom in coordination. The complexity of the spectra due to the fact that the reaction does not go to completion (~80%) and because the solution contains the free ligand is one of the methodological disadvantages of the above study. The authors were also unable to observe the $^{195}Pt-^1H$ spin–spin interaction. It has been stated[131] that one of the causes hindering the manifestation of the spin–spin splitting may be the anisotropy of the relaxation of the chemical shifts arising in recording at high frequencies (~100 MHz).

The formation of chelates of the type N(3)–Pt–NH_2 in reactions with platinum(II) complexes is not characteristic of cytosine and cytidine. A similar relationship has been proposed for [Pt Cyt I_2] complexes,[119] but without a convincing proof.

Cytosine- and cytidine-containing platinum(II) complexes of the triammine type, namely *cis*-$[PtA_2LX]X$ (A = NH_3 or ½en), are of great interest. These compounds can be formed in the first stage of the reaction of DDP and $[PtenCl_2]$ with the pyrimidine bases in DNA. The triammines *cis*-$[PtA_2LX]X$ (L = Cyt or Cyd; A = NH_3 or ½en; X = Cl^-, Br^-, or NO_2^-) have been synthesised.[132,133] The complexes have been obtained on heating *cis*-$[PtA_2X_2]$ with an equimolar amount of the ligand, evaporation, and precipitation with acetone. Their structure was demonstrated by measuring the electrical conductivity (100–120 Ω^{-1} cm^2 mol^{-1}) and by the presence of the ν(Pt – X) absorption band in the long-wavelength absorption spectra. The ^1H NMR spectra of the triammines in D_2O and DMSO-d_6 indicate the coordination of cytosine and cytidine via the N(3) atom: for all the compounds, $\Delta\delta[H(5)] > \Delta\delta[H(6)]$. This conclusion also follows from the ^{13}C NMR spectra: the greatest shift in coordination has been observed for the C(2) and C(4) carbon atoms, which are in neighbouring positions relative to N(3): $\Delta\delta[C(2)] = 8.9$ p.p.m. and $\Delta\delta[C(4)] = 5.6$ p.p.m. in the spectrum of *cis*-$[Pt(NH_3)_2$.CytCl]Cl, while the chemical shifts for the C(5) and C(6) atoms differ by 0.7 and 1.5 p.p.m. respectively. Coordination in the platinum(II) sphere greatly enhances the acid properties of cytosine as a result of the dissociation of N(1)H: $K_a = 6.1 \times 10^{-13}$ for cytosine[127] and $K_a = 5.0 \times 10^{-10}$ for *cis*-$[Pt(NH_3)_2CytCl]Cl$. The replacement of Cl^- by Br^- and NO_2^- leads to some decrease of acidity, apparently a result of the enhancement of the σ-donor properties of the acido-ligands. The hydrolytic stability of the bond in the complex *cis*-$[Pt(NH_3)_2CytCl]Cl$ has also been characterised: $K_{inst} = (4.0 \pm 0.5) \times 10^{-4}$.[134]

The communications examined contain the results of the investigation of the reactions of cytosine and cytidine with platinum(II) complexes having two or one chloride ions. The interaction of these ligands with $K_2[PtCl_4]$ is much more complex. In this case the nucleophilic substitution of the chloride ions is accompanied by the formation of polymeric products—the so-called "platinum pyrimidine blues".[135] The "blues" are obtained in an alkaline medium; their formation is apparently associated with the deprotonation of the ligands. A solid diamagnetic amorphous blue product having the composition $K_{0.2}PtCydCl_{1.5}(OH)_x(OH_2)_y$ has been isolated. On the basis of the ^1H NMR spectra and reactions with reductants ($NaBH_4$), the authors assume that the "blue" contains partially oxidised platinum and the cytosine anion, formed as a result of the deprotonation of the amino-group, is bound to platinum(II) by means of a chelate or bridge type bond via this group and the N(3) atom.

Among cytosine derivatives, the formation of platinum(II) complexes with methylcytosine (XV) (1-CH_3Cyt) has been studied to the greatest extent.

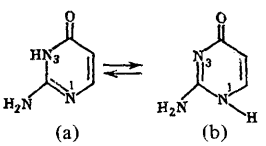


(XV)

Cationic complexes with the *cis*-structure have been isolated—the tetrammines $[Pt(NH_3)_2]$ $(1\text{-}CH_3Cyt)_2(NO_3)_2$. .1-$CH_3$Cyt [136,137] and the triammines *cis*-$[Pt(NH_3)_2(1\text{-}CH_3$. .CytCl]X (X = Cl^- or NO_3^-).[138] It was established by ^1H NMR, on the basis of the greater shift of the signal of the H(5) proton than the shift of the H(6) proton signal on coordination and the triplet splitting of the H(5) proton signal, that the coordination is via the N(3) atom; it was confirmed for the tetrammine by X-ray diffraction. The triammines are unstable both in aqueous solution and on heating. In the latter case NH_2 is split off and *trans*-$[PtNH_3Cl_2(1\text{-}CH_3Cyt)]$ is formed.[139] A tetrammine with three molecules of 1-methylcytosine, namely $[Pt(NH_3)$. .$(1\text{-}CH_3Cyt)_3](ClO_4)_2$, was isolated after starting with the *trans*-non-electrolyte $[PtNH_3Cl_2(1\text{-}CH_3Cyt)]$.[140] The authors regard the formation of this compound as evidence for yet another pathway leading to the interaction between the DDP and DNA bases, namely one involving the displacement of NH_3 and the binding of three DNA bases. However, the elimination of NH_3 from *cis*-DDP under conditions simulating cytoplasm has not been demonstrated experimentally and there are no data indicating the presence of antitumour activity in the mixed *trans*-non-electrolyte $[PtNH_3ACl_2]$.

Among the platinum(II) complexes containing the neutral 1-methylcytosine molecule, there are also rarely encountered monomeric complexes with the terminal ligands OH^- and H_2O, namely $[Pt(NH_3)_2(1\text{-}CH_3Cyt)OH]NO_3.2H_2O$ and $[Pt(NH_3)_2$. .$(1\text{-}CH_3Cyt)H_2O](NO_3)_2.H_2O$.[141] In contrast to cytosine, 1-methylcytosine is capable of being coordinated in the form of an anion via a bridge-type bond involving the N(3) atom and the deprotonated NH_2 group. It has been demonstrated by X-ray diffraction that such a bond occurs in the complex $[Pt(NH_3)_2(1\text{-}CH_3Cyt)_2Pt(NH_3)_2](NO_3)_2$.[142] The complex was isolated after treating the dimer $[Pt(NH_3)_2OH]_2(NO_3)_2$ with 1-methylcytosine in proportions of 2:1. In the same communication it is stated that there is a possibility of obtaining complexes in which platinum has the formal oxidation state of 2.5+: the complex $(H_2O_2)[Pt(NH_3)_2NO_2(1\text{-}CH_3$. .Cyt-H)$_2Pt(NH_3)_2NO_2](NO_3)_2$, with an octahedral environment around the platinum atoms, has been obtained in small amounts—yield 2%. Structural data confirm the presence of the Pt–Pt bond for atoms in an oxidation state higher than 2+; thus the Pt–Pt distance in this complex is 2.584 Å, while in the platinum(II) and platinum(III) dimers these distances are respectively 2.970 Å and 2.466 Å.[143,144] In our view, the properties of this compound and the conditions governing its formation require further study, since there has been no full analysis of the complex, its yield is very low, and finally the formation of the $H_5O_2^+$ cation at pH 6 is unlikely.

The complexes (III) of platinum(II) with isocytosine (iso-Cyt), a cytosine isomer, have been described:[133,145]



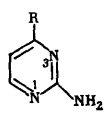
(a) (b)

(XVI)

Isocytosine exists mainly in the form of two tautomeric forms (a) and (b).[146] Complexes of this ligand of the triammine and tetrammine types having the *cis*-structure have been isolated: $[PtA_2(iso\text{-}Cyt)Cl]Cl$ and $[PtA_2(iso\text{-}Cyt)_2]Cl_2$ (A = NH_2 or ½en).[145] Coordination is accompanied by a hypsochromic shift of the ring vibrations and a large downfield shift of the signal of the H(5) proton in the ^1H NMR spectra of the complexes in DMSO-d_6, which suggests the formation of a coordinate bond via the N(3) atom of the tautomeric form (XVIb). Isocytosine is characterised by much more pronounced acid properties than cytosine: $K_a = 3.2 \times 10^{-10}$.[127] The same also applies to platinum(II) complexes of isocytosine: $K_a = 5.0 \times 10^{-10}$ for *cis*-$[Pt(NH_3)_2$. .LCl]Cl (L = Cyt) and 1.3×10^{-7} for the same complex with L = iso-Cyt; $K_a^1 = 4.3 \times 10^{-10}$ for *cis*-$[Pt(NH_3)_2L_2]Cl_2$ when L = Cyt and 3.2×10^{-7} when L = iso-Cyt.[133,145]

2. Platinum(II) Complexes of Aminopyrimidines

Apart from the formation of platinum(II) complexes of natural aminopyrimidines (cytosine and cytidine), studies have also been made of the formation of complexes with other aminopyridimidines. The platinum(II) complexes of 2-aminopyrimidine (2-Apm) and its substituted derivatives (XVII) have been most thoroughly investigated:[116,147–150]



(XVII)

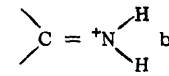
where R = H, CH_3, OCH_3, or C_6H_5.

The presence of several potential donor atoms and groups in aminopyrimidine molecules suggests different types of binding of these ligands to platinum(II). Two main types of coordination—monodentate and bridge type—have been established.

In the reactions of 2-aminopyrimidine with $K_2[PtX_4]$ (X = Cl^-, Br^-, or I^-), non-electrolytic complexes with ligands involved in monodentate coordination, i.e. $[PtL_2X_2]$ with L = 2-Apm, 4-phenyl-2-aminopyrimidine (4-Ph-2-Apm), 4-methyl-2-aminopyrimidine (4-CH_3-2-Apm), and 4-methoxy-2-aminopyrimidine (4-CH_3O-2-Apm), have been isolated.[116,147,150,151] The non-electrolytic character of the complexes has been demonstrated by measuring the molar conductances of their dimethylformamide (DMF) solutions (13 to

15 Ω^{-1} cm^2 mol^{-1}).[147] The far IR spectra show two absorption bands in the region of Pt–X stretching vibrations: 330–340 cm^{-1} (Cl), 231–249 cm^{-1} (Br), and 202–218 cm^{-1} (I), as well as two bands in the Pt–N region (257–290 cm^{-1}), which led to the conclusion that the complexes have the *cis*-configuration. On heating, the complexes isomerise to the *trans*-forms, whose spectra have a single narrow absorption band in the ν_{as}(Pt–X) and ν_{as}(Pt–N) regions. The *cis*-isomers exhibit a definite antitumour effect: in relation to adenocarcinoma AK-755, the inhibition of tumour growth was ~60%.[152] There exist divergent views about the geometrical structure of the non-electrolytic platinum(II) complexes of aminopyrimidines of analogous composition apparently due to the lability of these compounds.[153–155]

Charged complexes with monodentate coordination of 2-aminopyrimidine have been described: the isomeric $[Pt(NH_3)_2L_2]X_2$ and *cis*-$[PtenL_2]X_2$, where L = 2-Apm or 4-Ph-2-Apm and X = Cl^-, NO_3^-, or $\frac{1}{2}[PtCl_4]^{2-}$.[147,148] In order to synthesise chloride complexes with 2-Apm, the isomeric $[Pt(NH_3)_2Cl_2]$ and $[PtenCl_2]$ complexes were dissolved in an aqueous solution of the ligand, while the nitrate complexes were synthesised by treating the aquo-complexes $[Pt(NH_3)_2(H_2O)_2]^{2+}$ and $[Pten(H_2O)_2]^{2+}$ with the ligands; the platinites were precipitated with a $K_2[PtCl_4]$ solution. In order to determine the structure of the complexes, their IR and ^{1}H and ^{13}C NMR spectra were investigated. Coordination leads to an increase of the stretching vibration frequencies of the pyrimidine ring, which indicates the involvement of one of the heterocyclic nitrogen atoms in binding. Comparison of the ^{1}H NMR spectra of the ligands and complexes (Table 1) finally demonstrates this. The ^{1}H NMR spectrum of 2-aminopyrimidine shows a triplet signal due to the H(5) proton and a doublet signal due to the equivalent H(4) and H(6) protons. On coordination, the signals of all the protons undergo a downfield shift owing to deshielding.[148,149] The H(5) triplet signal shifts only slightly under these conditions, while the equivalence of the H(4) and H(6) protons breaks down and their signals become of the doublet of doublets type, which is due to the spin–spin interaction of the H(4) and H(6) nuclei both with H(5) and with one another. Such changes in the ^{1}H NMR spectra of the complexes agree with the formation of monodentate bonds by one of the heterocyclic nitrogen atoms, because, on coordination via the NH_2 group, the equivalence of the H(4) and H(6) protons would have been retained. The involvement of a heterocyclic nitrogen atom in binding is confirmed by the occurrence of the spin–spin interaction of the nearest proton with the ^{195}Pt nucleus. The ^{1}H NMR spectrum of 4-Ph-2-Apm in DMSO contains two doublets of equal intensity due to the non-equivalent H(5) and H(6) protons with a spin–spin coupling constant of 5 Hz (see Table 1), a singlet signal due to the NH_2 group (6.50 p.p.m.), and complex signals due to the protons of the phenyl group (7.40 and 7.94 p.p.m.). The coordination of 4-Ph-2-Apm in the platinum(II) sphere entails a downfield shift of the signals of the H(5) and H(6) protons, the H(6) doublet being displaced to a greater extent than the H(5) doublet. This permits the conclusion that the coordinate bond of 4-Ph-2-Apm is formed via the ring N(1) atom. An analogous conclusion has been reached on the basis of the ^{13}C NMR spectra of the platinum(II) complexes of 2,6-dimethyl-4-aminopyrimidine.[156–158] The signals of the C(6) carbon atoms ($\Delta\delta$ = 8–12 p.p.m.) and of the methyl groups in the vicinity of the N(1) atom, namely $C(2)H_3$ and $C(6)H_3$ ($\Delta\delta$ = 4–6 p.p.m.) undergo the greatest shift on coordination. The signal due to the protons of the NH_2 group undergoes a downfield shift (1.5–2.3 p.p.m.) and is broadened to a doublet. As in the complexes with cytosine,[129] this is explained by the partial double bond character of the



bond in the complex and the hindered nature of the rotation of the protons about this bond.

Table 1. The chemical shifts and the spin–spin coupling (SSC) constants of the protons of 2-aminopyrimidines in the free and coordinated states (X = Cl^- and NO_3^-)*.

Compound	Solvent	δ, p.p.m.				SSC constants, Hz		
		H(5)	H(4)	H(6)	$^3J_{5-6}$	$^3J_{5-6}$	$^4J_{4-6}$	$^4J_{^{195}Pt-^1H}$
2-Aminopyrimidine	D_2O	6.77	8.30	8.30	5.0	5.0	—	—
cis-$[Pt(NH_3)_2(2\text{-Apm})_2]X_2$	D_2O	6.87	8.38	8.69	4.5	6.0	2.0	40
trans-$[Pt(NH_3)_2(2\text{-Apm})_2]X_2$	D_2O	6.95	8.46	8.80	4.5	6.0	2.0	—
$[Pten(2\text{-Apm})_2]X_2$	D_2O	6.87	8.38	8.69	4.5	6.0	2.0	40
2-Aminopyrimidine	DMF	6.50	8.13	8.13	5.0	5.0	—	—
cis-$[Pt(2\text{-Apm})_2Cl]$	DMF	6.58	8.19	8.80	4.5	6.0	2.0	40
2-Amino-4-phenylpyrimidine	DMSO	7.04	—	8.26	—	5.0	—	—
cis-$[Pt(NH_3)_2(4\text{-Ph-2-Apm})_2]Cl_2$	DMSO	7.32	—	8.72	—	7.0	—	—
trans-$[Pt(NH_3)_2(4\text{-Ph-2-Apm})_2]Cl_2$	DMSO	7.41	—	8.85	—	7.0	—	—
$[Pten(4\text{-Ph-2-Apm})_2]X_2$	DMSO	7.32	—	8.72	—	7.0	—	—
trans-$[Pt(4\text{-Ph-2-Apm})_2Cl_2]$	DMSO	7.20	—	8.76	—	7.0	—	—

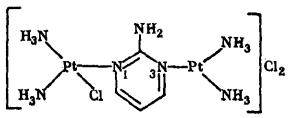
*The chemical shifts listed in the Table refer to the average positions of the proton signals.

Monodentate coordination via one of the heterocyclic nitrogen atoms is possible also for the aminopyrimidinium cation LH^+ protonated at the amino-group: the compounds $[MLHX_3]$ (X = Cl^- or Br^-; L = 2,6-dimethyl-4-aminopyrimidine or thiamine; M = Pt(II) or Pd(II)] have been isolated.[156–158]

Comparison of the spectroscopic (^{1}H NMR and electronic spectra) characteristics of the isomeric tetrammines $[PtA_2L_2].Cl_2$ (A = NH_3; L = 2-Apm, 4-Ph-2-Apm, 4-CH_3-2-Apm, or 4-OCH_3-2-Apm) is of interest. It has been shown[159] that the downfield shift of the signal due to the non-labile H(4), H(5), and H(6) protons on coordination is greater for the *trans*-isomer than for the *cis*-isomer. The hyperchromic effect involving the absorption band of the ligands, observed on coordination, is also more pronounced for the *trans*-form. On this basis, it has been concluded that the *trans*-influence of 2-Apm and of its 4-substituted derivatives is smaller than that of NH_3. The explanation of this phenomenon may be sought in the lower stability of the bonds between aminopyrimidines and platinum(II).

The reactions between the platinum(II) complexes and 2-aminopyrimidines for the ratio Pt/L = 2 are accompanied by the formation of dinuclear complexes with a bridging aminopyrimidine molecule.[149,160] Thus complexes with the *cis*-structure and the composition $[PtA_2ClLPtA_2Cl]Cl_2$ (A = NH_3 or $\frac{1}{2}$en; L = 2-aminopyrimidine) have been isolated. Comparison of the ^{1}H NMR spectra of the ligands and the complexes showed that the signals of all the non-labile protons undergo a downfield shift on coordination and to a greater extent for the H(4) and H(6) protons [$\Delta\delta$(4,6) = 0.6 p.p.m.]. The equivalence of the protons in the complex is maintained, since they give rise to one doublet signal with doubled intensity. This finding indicates the symmetrical binding of the 2-aminopyrimidine molecules to platinum atoms

via the N(1) and N(2) atoms:



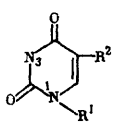
(XVIII)

The amino-group of the ligand in the complexes with bridge type coordination manifests weak acid properties [K_a = (1.8 ± 0.3) × 10^{-10}] as a consequence of the polarising influence of two neighbouring platinum(II) ions.[147]

The bidentate coordination of 2-aminopyrimidines with oxidation of the NH_2 group and the heterocyclic nitrogen atom is not characteristic of the platinum(II) complexes. The reactions of the platinum(II) complexes with 2-Apm in proportions of 1:1 lead to the formation of mixtures of compounds containing a dinuclear and a triammine complex.[159,161] On reaction with palladium (II), the compounds PdX_2.2-Apm (X = Cl^- or SCN^-), in which a chelate bond is postulated, were isolated.[162] In our view the formation of this bond is unlikely owing to the instability and strain of the four-membered ring. The molecular weights of the complexes should be measured, since they could have a dimeric structure with two bridging 2-aminopyrimidine molecules, i.e. $[PdX_2$2-Apm$]_2$. The chelate coordination of 2-hydrazino-4,6-dimethylpyrimidine (2-hd-4,6-dmpm), observed by Saha et al.[163], is more probable, since this entails the formation of stable five-membered rings.

3. Platinum(II) Complexes of 2,4-Dioxopyrimidines

Among compounds of this class, the platinum(II) complexes of uracil (Ur), its nucleoside uridine (Urd), 5-methyluracil (thymine) (Th), its nucleoside thymidine (Thd), and also certain other 5- and 6-substituted uracils have been most thoroughly investigated.

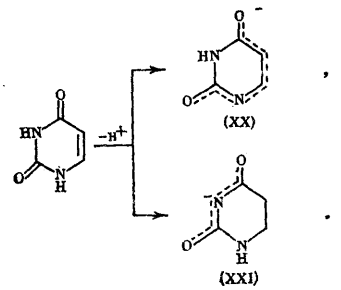


(XIX)

R^2 = H and R^1 = H(Ur) or β-D-ribofuranosyl (Urd); R^2 = = CH_3 and R^1 = H(Th) or β-D-ribofuranosyl (Thd)

Uracil and thymine enter into the composition of natural biopolymers—RNA (Ur) and DNA (Th)—and can react with the antitumour complex *cis*-DDP. Active antitumour platinum complexes containing these ligands and other 2,4-dioxopyrimidines—the so called "platinum pyrimidine blues"—have been isolated.[164,165,166] The "blues" are more soluble in water and are less toxic than *cis*-DDP: LD_{50} is 200 to 500 mg kg^{-1} for the "blues" and 12 mg kg^{-1} for *cis*-DDP. The structure of the "blues" has not been fully established but it has been shown by the electrophoretic, chromatographic, and spectroscopic ("EXAFS") methods that they are cationic oligomeric platinum complexes with a molecular weight of 1000–3000 and a mixed oxidation state of platinum (2+ and 3+).[164,167] The ligands play the role of a bridge and join together the platinum atoms via heterocyclic atoms and O(4).

Uracil and its analogues exist in various tautomeric forms and exhibit ambident properties; for example, the two tautomeric forms (XX) and (XXI) are possible for the uracil anion:



(XX) (XXI)

The determination of the structure of the complexes with these ligands is therefore complicated and requires the application of a series of physical methods. In the absence of direct X-ray diffraction data, the most reliable information about the mode of coordination of these ligands can be obtained by NMR methods.

(a) Platinum(II) Complexes of Uracil, Thymine, and Their Nucleosides

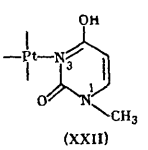
In contrast to the nucleic acid bases determined previously, uracil, thymine, and their nucleosides do not react with *cis*-DDP in a neutral medium.[13,26,37,168] The ability to be coordinated in the platinum(II) sphere is characteristic solely of the uracil and thymine anions and is associated with the manifestation by the latter of acid properties, which cytosine does not possess. The pK_a are 9.4 for uracil, 9.2 for uridine, 9.8 for thymine, and 9.7 for thymidine. The uracil and thymine monoanions consist of approximately equal amounts of forms dissociated at N(3)H and N(1)H.[169,170] As a result of tautomerism, the coordinate bonds linking uracil and thymine are formed both via the N(3) atom and the N(1) atom. Thus the reaction of the cation $[Pt(NH_3)_2 . .(H_2O)_2]^{2+}$ with uracil in a neutral medium leads to the formation of complexes with both types of bonds, via the N(3) and N(1) atoms, and having the composition $[Pt(NH_3)_2(Ur-H) . .NO_3]$.[171] The uridine and 6-uracil anions, in which the N(1) atoms is either linked to D-ribose or is blocked by the neighbouring methyl group, are coordinated solely via the N(3) atom.[110,163]

Complexes with the thymidine anions having the composition $[Pt(NH_3)_3(Thd-H)]NO_3$ and [Pten(Thd − H)$_2$] have been isolated in reactions of thymidine with the corresponding aquo-complexes.[172] Thymidine is coordinated via the N(3) atom, which is accompanied, analogously to the behaviour observed in the complexes with the uracil and uridine anions,[171] by an upfield shift of the H(6) proton signal. The authors determined the formation constant of $[Pt(NH_3)_3(Thd-H)]^+$ ($\lg K_{form}$ = 10.4 ± 0.1) and the successive formation constants of [Pten(Thd − H)$_2$] ($\lg K^1$ = 10.3 ± 0.1 and $\lg K^2$ = 7.4 ± 0.1) from the dependence of the intensity of the H(6) signal on the pH. The ^{13}C NMR method was used to determine the donor atom in solutions of $[PtenCl_2]$ with an excess of uridine or thymidine.[173] Two sets of signals due to carbon atoms can be observed in these systems, one referring to non-coordinated uridine or thymidine and the other to the complexes [Pt(L − H)$_2$], where (L − H) are the uridine and thymidine anions. The greatest shift on coordination of uridine (compared with the non-bonded neutral molecule) is observed for the C(2) and C(4) atoms: their signals have undergone downfield shifts of 5.3 and 8.0 p.p.m. respectively. The C(5) and C(6) signals are displaced to a lesser extent and in the opposite direction—upfield.

A large series of studies on the platinum complexes of uracil and its derivatives have been carried out by Lippert and co-workers. The difficulty of determining the structure of the platinum complexes of unsubstituted uracil and thymidine, for which there is a possibility of the coordination of both tautomeric forms, was noted. In order to determine the type of coordination, IR and NMR spectroscopy are used.[174-177] Thus the stretching vibration frequency $\nu(C-O)$ for the complexes with the Pt–N(1) bond is characterised by an intense band at 1640 cm^{-1} with shoulders in close proximity to regions at lower and higher frequencies, while the Pt–N(3) bond is characterised by a band at 1550 cm^{-1} and another at 1650 cm^{-1}. The ^1H NMR spectra of the tautomeric complexes differ by the triplet splitting of the H(6) proton signal on formation of the Pt–N(1) bond ($^3J_{^1H-^{195}Pt}$ = 38–40 Hz), while in the spectra of the complexes with the Pt–N(3) bond the H(6) signal is not split while the H(5) signal is split but has a smaller spin–spin coupling constant ($^4J_{^1H-^{195}Pt}$ = 4–15 Hz). It has also been stated that the tautomers have different reactivities—the complexes with the Pt–N(1) bond are stable in an acid medium but at the same time they exchange the H(5) proton for deuterium, while the complexes with the Pt–N(3) bond split off the free ligand on heating in an acid medium. The exchange of H(5) with deuterium is observed in an alkaline medium in this case.[110] Factors influencing the formation of a particular tautomeric complex are said to include the nature of the solvent, the pH of the aqueous solution, the solubility of the reaction products, the capacity of the ligands for participation in a hydrogen bond, and even the reaction conditions.

(b) Platinum(II) Complexes of N(1)-Substituted Uracil and Thymine

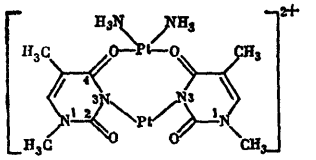
This class of compounds includes the uracil and thymine nucleosides and N(1)-methyl-substituted compounds. In many cases studies have been made of the reactions of 1-methyluracil and 1-methylthymine with platinum(II) complexes. The structure of these compounds can be established more readily than that of the complexes with unsubstituted ligands—the Pt–N(3) bond is formed in all cases. The reactions of the anions of 1-methyluracil and 1-methylthymine led to the isolation of the non-electrolytic complexes *cis*-$[Pt(NH_3)_2(1\text{-}CH_3Ur\text{-}H)_2].4H_2O$ and *cis*-$[Pt(NH_3)_2.(1\text{-}CH_3Th-H)_2]$,[176-178] the mixed type cationic complexes *cis*-$[Pt(NH_3)_2(1\text{-}CH_3Th-H)L]ClO_4$ (L = cytosine, guanine, or adenine),[179,180] and even complexes containing not only ligand anions but also ligand molecules—*cis*-$[Pt(NH_3)_2.(1\text{-}CH_3Ur)(1\text{-}CH_3Ur-H)]X.H_2O$.[181] It is suggested that the neutral ligand is coordinated in an unusual tautomeric form (XXII):



(XXII)

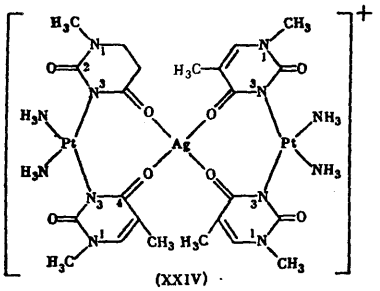
The Pt–N(3) bond with a neutral ligand is unstable, the ligand is readily split off, and X^- enters into the composition of the complex.

Polynuclear complexes with 1-methyluracil and 1-methylthymine can be formed via bridging hydroxo-groups or ligand anions. Dimers of the first type, namely *cis*-$[Pt.(NH_3)_2(L-H)]_2OH$, are formed in an alkaline solution. It has been suggested that the *cis*-Pt–OH–Pt group is capable of interacting with DNA bases, cross linking them via intrastrand or interstrand mechanisms.[180] Polymerisation via bridging 1-methyluracil and 1-methylthymine anions leads to the formation of homopolynuclear and heteropolynuclear complexes.[181-188] Exocyclic oxygen atoms participate in the bridge bond together with the heterocyclic nitrogen atoms. An example of a homonuclear polymer is the dimer *cis*-$[Pt(NH_3)_2(1\text{-}CH_3Th-H)]_2(NO_3)_2$ [182-184] with electron-donating N(3) and O(4) atoms [compound (XXIII)]:



(XXIII)

The bidentate bridge bond via the 1-methylthymine and 1-methyluracil anions exists also in heteronuclear complexes of the type Pt_2M, where M = Ag^+,[186] Mn^{2+},[187] or Cu^{2+},[188] for example in *cis*-$[Pt(NH_3)_2(1\text{-}CH_3Th-H)_2Ag(1\text{-}CH_3Th-H)_2.Pt(NH_3)_2]NO_3$ (XXIV):



(XXIV)

More complex polymeric structures occur when the 1-methyluracil anions exhibit the properties of tridentate ligands being coordinated via the N(3) atom and both exocyclic O(4) and O(2) atoms. An example is provided by the pentanuclear heteronuclear complex of the type Pt_4A_9 – $[Pt_4(NH_3)_8(1\text{-}CH_3Ur-H)_4Ag](NO_3)_5$.[189] After slight heating, the complex gives rise to the blue product $[Pt_4.(NH_3)_8(1\text{-}CH_3Ur-H)_4](NO_3)_5.5H_2O$, in which platinum is in the 2.25+ oxidation state. This product may be formed as a result of the intermolecular oxidation-reduction reaction

$$Ag^{+1} + e \rightarrow Ag^0,\ Pt_4^{5+} - e \rightarrow Pt_4^{9+}$$

The platinum "blues" incorporating the 1-methyluracil anions are obtained also after cautious oxidation of the "head to head" dimer $[Pt(NH_3)_2(1\text{-}CH_3Ur-H)]_2(NO_3)_2$ with nitric acid.[183,185] After more far reaching oxidation, yellow-orange diamagnetic complexes, resembling the platinum(III) dimers with α-pyridone, are formed.[190-192] Platinum "blues" with the thymine anion have also been described.[193]

The ^{195}Pt NMR method combined with high performance liquid chromatography has been used to determine the structure of the platinum(II) complexes of 1-methyluracil [89,194] (Table 2). The spectra of the mononuclear complexes show a single signal whose position is determined by the nature of the electron-donating atoms. Thus the replacement of two H_2O molecules by two Cl^- ions leads to an upfield shift c 500 p.p.m. An even greater upfield shift (820 p.p.m.) is observed after the replacement of two H_2O molecules by two 1-methyluracil anions. Complexes with the PtN_4 coordinatio unit, namely *cis*-$[Pt(NH_3)_2(1\text{-}CH_3Ur-H)_2]$ (−2407 p.p.m.) and $[Pt(NH_3)_4]^{2+}$ (−2579 p.p.m.) are characterised by the greatest upfield chemical shifts. The dimer *cis*-$[Pt(NH_3)_2.(1\text{-}CH_3Ur-H)]_2^{2+}$ with an asymmetric "head to head" structure, in which one of the platinum atoms is involved in the

PtN_4 coordination unit while the other is in the PtN_2O_2 group, gives rise to two signals in the ^{195}Pt spectrum, i.e. at −2210 and −1267 p.p.m., which correspond to two types of coordination.

Table 2. The ^{195}Pt NMR spectra of platinum(II) 1-methyluracilate complexes in D_2O (external standard—Na_2PtCl_6).[89]

Complexes with *cis*-structure	^{195}Pt chemical shift, p.p.m.
cis-DDP	−2097
$[Pt(NH_3)_2(H_2O)_2]^{2+}$	−1588
$[Pt(NH_3)_2(1\text{-}CH_3Ur\text{—}H)_2]$	−2407
$[Pt(NH_3)_2(1\text{-}CH_3Ur\text{—}H)(H_2O)]^+$	−1999
$[Pt(NH_3)_2(1\text{-}CH_3Ur\text{—}H)Cl]$	−2261
$[Pt(NH_3)_2(1\text{-}CH_3Ur\text{—}H)]_2^{2+}$	−2210, −1267

(c) Platinum(II) Complexes of 5-substituted Uracils

In the reactions of *cis*-DDP and its aquo-form with the sodium and lithium salts of 5-substituted uracil, complexes having the *cis*-structure with one and two ligand anions were isolated: $[Pt(NH_3)_2(5\text{-}RUr-H)Cl]$ (R = H, Br, or NO_2) and $[Pt(NH_3)_2(5\text{-}RUr-H)_2]$ (R = H, F, Cl, Br, I, or NO_2).[195] The anionic form of the ligand in the complexes follows from their composition and has been confirmed by the similarity of the UV and IR spectra of the complexes in the initial salt. The type of coordination was determined by the ^1H and ^{13}C NMR methods in relation to complexes with two anions. In the spectrum of the complex with uridine—*cis*-$[Pt(NH_3)_2.(Urd-H)_2]$—in which coordination is possible only via the N(3) atom, the H(6) proton signal is a doublet, as in the free ligand, and has undergone an upfield displacement of 0.2 p.p.m. compared with uridine. Analogous ^1H NMR spectra have been observed also for *cis*-$[Pt(NH_3)_2(Ur-H)_2]$, *cis*-$[Pt(NH_3)_2(5\text{-}FUr-H)_2]$, and *cis*-$[Pt(NH_3)_2(5\text{-}BrUr-H)_2]$, for which coordination of the anions by the N(3) atom is also suggested. The ^1H NMR spectrum of the complex *cis*-$[Pt.(NH_3)_2(5\text{-}NO_2Ur-H)_2]$ has a different form: the H(6) signal is a triplet as a result of the spin–spin interaction with the ^{195}Pt nucleus and its upfield shift is 0.1 p.p.m. In the spectrum of the complex of 5-chlorouracil, two H(6) signals are observed—a singlet with $\Delta\delta = 0.32$ p.p.m. and a triplet for which $\Delta\delta = 0.10$ p.p.m. Both forms of coordination of the ligand, via the N(3) and N(1) atoms, have been proposed for this complex. The conclusions reached have also been confirmed by ^{13}C NMR:[196] in the complexes with the Pt–N(3) bond, the greatest downfield shifts on coordination are observed for the C(2) and C(4) atoms, while in those with the Pt–N(1) bond, the greatest shifts are for C(2) and C(6).

IV. KINETICS OF THE REACTIONS OF PURINE AND PYRIMIDINE BASES AND THEIR NUCLEOSIDES WITH PLATINUM(II) COMPLEXES

In order to characterise the reactivity of the platinum(II) complexes, it is of interest to investigate the kinetics of the reactions of these compounds with the purine and pyrimidine DNA bases and as well as their antimetabolites and nucleosides. Such a study has been carried out for the reactions of the diammines $[Pt(NH_3)_2Cl_2]$ and the isomeric triammines $[(PtNH_3)_2InoCl]Cl$ with inosine and cytidine.[197,198] The interaction of *cis*-DDP with inosine incudes two stages:

$$cis\text{-}[Pt(NH_3)_2Cl_2] + L \xrightarrow{k^1} cis\text{-}[Pt(NH_3)_2LCl]^+ + Cl^- , \quad (1)$$

$$cis\text{-}[Pt(NH_3)_2LCl]^+ + L \xrightarrow{k^2} cis\text{-}[Pt(NH_3)_2L_2]^{2+} + Cl^- . \quad (2)$$

The kinetics of the second stage were investigated initially, because it proceeds with substitution of only one chloride ion by inosine. The conductimetric method was used and the reaction was carried out under pseudo-first-order conditions in an excess of the entering ligand at 50 °C. The constant k^2_{obs} was calculated from the first-order kinetic equation and its dependence on the concentrations of the ligand and the Cl^- ions was determined. Analysis of the data permits a series of conclusions: (1) the reactions of the cytidine complexes are faster than those of the inosine complexes; (2) the incorporation of inosine in the platinum(II) complexes obeys a kinetic equation which differs from the equation for the insertion of NH_3 or amine: for inosine there is no linear relation between k_{obs} and the inosine concentration and k_{obs} diminishes with increase of the concentration of Cl^- ions. This type of dependence has been explained by the fact that inosine is inserted mainly in the hydrolysis product *cis*-$[Pt(NH_3)_2InoH_2O]^{2+}$ and that the reverse insertion of Cl^- ions in the monoaquo-complex competes with this process. The characteristic feature of inosine is manifested by the fact that the rate constant for the insertion of the bulky ligand is lower than the rate constant for the incorporation of Cl^- ions in the monoaquo-complex; (3) the quantity k^2_{obs} depends on the geometrical structure of the triammine: the substitution of the Cl^- ion in the *cis*-triammine is faster than in the *trans*-isomer, which indicates a weaker *trans*-influence of inosine than that of NH_3. The reactions of guanosine with the triammines $[Pt(NH_3)_3Cl]Cl$ and *cis*-$[Pt(NH_3)_2CytCl]Cl$ proceed analogously.[145,199]

The rate constant for the first stage k^1_{obs} was estimated on the basis of the experimental study of the rate of reaction of the isomeric platinum(II) diammines with inosine and the known constants k^2_{obs} for the second stage. The quantity k^1_{obs} was found by solving the kinetic equation for two consecutive irreversible first-order reactions by means of a program specially devised for the CM-4 computer. The quantity k^1_{obs} varies linearly in this instance with the concentration of inosine, which is associated with the greater contribution of the mechanism involving the direct nucleophilic substitution in stage 1. The ratio of the constants k^1_{obs} for the isomeric diammines is the reverse of the ratio of the constants k^2_{obs} for the triammines: $k^1_{obs}(trans) > k^1_{obs}(cis)$ as a consequence of the greater *trans*-influence of Cl^- compared with NH_3.

It has been shown by the spectrophotometric method that the interaction of labile and less stable palladium(II) triammines $[PddienBr]Br$ with inosine proceeds via a more complex mechanism,[200] including not only the stage involving the reversible hydrolysis of Br^- ions but also the reversible substitution of Br^- ions and water molecules by inosine. The conclusions reached in a conductimetric study of the kinetics of the reaction of $[PtdienBr]Br$ with inosine[201] are close to ours. The kinetics of the reaction of $[PdenCl_2]$ with inosine have been studied by the stopped flow method with spectrophotometric measurements.[202] Hydrolytic and direct substitution processes were taken into account in the reaction mechanism, but the formation of complexes with two inosine molecules, which is extremely probable in the presence of a (10–20)-fold excess of the ligand, was not considered.

A conductimetric kinetic study at 50 °C of the interaction of cytidine with the platinum(II) triammine *cis*-$[Pt(NH_3)_2.CydCl]Cl$, the isomeric $[Pt(NH_3)_2InoCl]Cl$ complexes, and

the *cis*-non-electrolyte $[Pt(NH_3)_2Cl_2]$ has been carried out.[197,198] The insertion of cytidine in the complexes obeys, in contrast to inosine and guanosine, the rules observed for other ligands L in the reactions with platinum(II) complexes; $k_{obs} = k_1 + k_2[L]$, where k_{obs} is the pseudo-first order rate constant, k^1 the hydrolysis rate constant, and k^2 the rate constant for direct substitution. It follows from a comparison of the quantities k_{obs} for the same complexes at the same concentrations of the entering ligand that the reactions with cytidine are faster than those with inosine and are somewhat slower than the reactions with guanosine.[197,199] The constant k_{obs} for the reaction of cytidine with *cis*-$[Pt(NH_3)_2$.InoCl]Cl is greater than for the reaction with the *trans*-isomer, which has been explained by the weaker *trans*-influence of inosine compared with NH_3. The interaction of cytidine with *cis*-$[Pt(NH_3)_2Cl_2]$ follows an analogous law, but is somewhat faster. The kinetic parameters of the first stage exceed by factors of 3 for k_1^1 and 200 for k_2^1 the corresponding values for the second stage. The interaction of bifunctional mono- and di-nuclear platinum(II) complexes with oligo- and poly-nucleotides has been investigated.[203,204] The complex *cis*-$[Pt(NH_3)_2(H_2O)(OH)]^+$ binds oligocytidine via the N(3) atom; the reaction product then forms interstrand bonds with the inosine polynucleotide (polyI) via the substitution of the OH^- group by the inosine molecule deprotonated at N(1).[204] The kinetics of the reactions of $[XPt\ dien-(CH_2)_6-dienPtY](NO_3)_n$ ($n = 2-4$, $X = H_2O$, $Y = H_2O$ or Br^-, or $X = Y = Br^-$) with inosine monophosphate (IMP) and polyI have been investigated spectrophotometrically.[205] The decrease of the reaction rate in the presence of Br^- ions indicates the dominant role of the hydrolytic mechanism. The increase of the rate constant on passing from IMP to polyI has been explained by the increased contribution of the S_N2 mechanism in the latter case.

New data on the problems dealt with in this review have been communicated in the reports at the XIVth International Conference on Coordination Chemistry in 1986. The necessity for a comparative study of the interaction of the isomeric dichlorodiammineplatinum(II) complexes with DNA and oligo- and polynucleotides was pointed out.[206-208] A number of studies were devoted to the synthesis and investigation of the structure and kinetics of the formation of "platinum blues" with 1-methyluracil and its derivatives.[209-211] Dinuclear platinum(III) complexes with bridging anions of uracil and its derivatives have been isolated.[177] Treatment of these compounds with an excess of 1-methyluracil and also oxidation of the dimeric platinum(II) complexes of this ligand with nitric acid led to the isolation of the unusual platinum(III) complexes $[Pt_2(NH_3)_4(C_5H_5N_2O_2)_3]Si_6NO_3.7H_2O$, in which the third 1-methyluracil anion is linked to platinum(III) via the C_5 atom.[212] A chelate platinum(IV) complex of cytosine has been isolated.[213] The platinum(II) complex of guanosine $[PtGuaCl_2H_2O]$ was found to exhibit anticancer activity.[214] The stabilities of the bonds of purine and pyrimidine nucleosides and their mononucleotides with palladium(II) via various electron-donating heterocyclic nitrogen atoms [N(7), N(1), and N(3)] have been compared using the ^1H NMR method.[215] The kinetics of the reactions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with nucleic acid bases have been studied and it has been shown that the rate of insertion of the bases varies in the sequence guanine > adenine ≅ cytosine > thymine.[216]

In conclusion, we may note that the results of the study of the structure and properties of the platinum(II) complexes of the purine and pyrimidine bases and their nucleosides and antimetabolites can be used to establish a correlation between the structure of the platinum(II) complexes, their reactivity in relation to DNA, and their antitumour activity. The characteristics of the purine and pyrimidine bases and their derivatives as ligands are manifested in their ambident character and in their tendency to form homo- and heteropolynuclear complexes with bridge bonds and metal–metal bonds. The data on the acid–base properties and the kinetic and thermodynamic stabilities of the platinum(II) complexes of the above ligands make it possible to characterise their behaviour in biological media with different acidities and chloride ion concentrations and to estimate the influence of coordination on the properties of these ligands and the effects of their mutual influence in the platinum(II) coordination sphere.

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