Complex compounds of platinum(II) and (IV) with amino acids, peptides and their derivatives

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CONTENTS

ABSTRACT

This article reviews all the known Pt(II) and Pt(IV) complexes with amino acids, peptides and their analogues referred in the literature. It gives details on the work done after 1975 since excellent reviews on the subject before that date have been published previously. The compounds described have been classified, in the first place, according to the metal ion oxidation state and in the second according to the binding site(s) of the ligand(s).

Section 1 refers briefly to the reasons for studying platinum complexes with amino acids and similar molecules and gives the orientation of the research on the topic in recent years.

In Sect. 2, the known Pt(II) complexes are reviewed in four sub-sections. The first describes the complexes with the metal ion binding to the terminal amino group or/and to a ring nitrogen of a side chain of the amino acid. This coordination mode is easily achieved and results in various products when the ligand contains more than one nitrogen donor atom.

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The second sub-section describes the complexes with the metal simultaneously binding to a nitrogen and one or more oxygen donor atoms of the ligand. A large number of stable chelates are thus formed. In contrast, binding of an amino acid or analogue through only an oxygen donor atom is not easily achieved.

The third sub-section describes the complexes formed with sulphur-containing ligands. In such complexes, coordination of sulphur, which is the primary binding site, may result in bridged or oligomeric complexes.

The fourth sub-section refers to the organometallic Pt(II) complexes which contain an amino acid or analogue coordinated through an amino terminal group or chelated through nitrogen and oxygen donor atoms.

In Sect. 3, the known Pt(IV) complexes are reviewed in four sub-sections corresponding to those in Sect. 2. The same amino acid coordination modes are also found here.

Finally, Sect. 4 summarizes the conclusions drawn from the previous three sections and emphasizes their most important features.

1. INTRODUCTION

Compounds of platinum with amino acids, peptides and their derivatives attracted the attention of inorganic chemists a long time ago, but their study generated additional interest after the discovery of the antitumour properties of platinum compounds by Rosenberg. The way that the antitumour drug *cis*-DDP reacts with various biologically important molecules has, since then, been a very interesting research subject. These reactions are mostly correlated with the toxicological properties of the drug since its antitumour action is due to a special reaction with DNA during the replication of the latter [1,2].

As a consequence, today's research on such compounds has the following orientations: (1) The construction of model compounds, the study of which would give information on the interaction of the metal ion with proteins in living organisms [3–5]. (2) The selective tracing of parts of a protein to obtain information on the conformation of the latter near the bonding site [3,4,6]. (3) The study of the influence of the metal on the conformation and the physicochemical properties of a coordinated amino acid or peptide. (4) In ternary complexes of Pt with amino acids–peptides and nucleobases–nucleosides, etc., study of the interactions of the various ligands coordinated with the same metal ion.

Some amino acid complexes of Pt(II) presented certain antitumour properties [7–11]. The idea for the synthesis of new compounds of this type is based on the possibility for selective and easier transportation of the anticancer $(NH_3)_2Pt^{2+}$ moiety through membranes into the interior of the cancerous cells, since amino acids are used for growth of the cells [7,8].

Many amino acid platinum complexes and their derivatives prepared before 1975 were reviewed by Volstein [12]. Beck [13] also reviewed the use of Pt(II) and Pt(IV) as protecting groups of coordinated amino acids in the synthesis of peptides or other reactions.

The present paper reviews the results of more recent studies (published after 1975) on complexes of Pt(II) and Pt(IV) with amino acids, peptides and their derivatives. The complexes described were mostly prepared by reaction of the amino acids with K_2PtCl_4 or K_2PtCl_6 in aqueous solutions in various metal:ligand (1:n) ratios, with $n = 1, 2, 3, 4$ and were examined according to the mode of amino acid coordination.

2. PLATINUM(II) COMPLEXES WITH AMINO ACIDS, PEPTIDES AND THEIR DERIVATIVES

2.1 Amino acid coordination through nitrogen

Amino acids can coordinate as monodentate ligands with platinum only through their amino groups. This type of coordination requires the reaction to be carried out in alkaline media so that the amino acid is in its anionic form $H_2N–CHR–COO^-$ [14–16]. Otherwise, amino group coordination can be achieved in acid or neutral solution in two steps: (a) coordination of the ionized carboxylate group and (b) deprotonation of the amino group with a simultaneous recoordination of the amino acid. However, this type of reordering is only known for glycine, while it may not be possible for other amino acids for steric reasons [16].

Amino acids which contain nitrogen atoms in their side groups R (e.g. histidine, lysine, arginine, asparagine, glutamine, etc.) can coordinate in a monodentate fashion either through the amino group or the nitrogen atom of the side chain, as, for example, in the case of arginine [13,17]. Chelate formation with platinum is also possible by using both nitrogen atoms for coordination by the amino acids. However, structures with the amino acid bridging two atoms of Pt(II) through the amino group and the nitrogen atom of the side group are limited [17]. Only in a single case [17] were two nitrogen atoms of the side chain of arginine found to bridge two Pt(II) atoms of the complex $[(terpy)Pt]^{2+}$. The structure of the analogous complex of canavanine was determined by X-ray diffraction [17] (Fig. 1).

Complexes of amino acids with Pt(II) of various stoichiometries and formulae isolated in the solid phase and characterized with various physicochemical methods until 1975 have been described earlier [12]. Later, similar complexes with the amino acids β-alanine, phenylalanine and β-phenylalanine [18–20] of formulae *trans*-$K_2[Pt(\beta\text{-ala})_2X_2]$, *trans*-$[Pt(\beta\text{-ala})X_2]$ ($X = Cl^-$, NO^{2-}) and *trans*-$K_2[Pt(Phala)_2Cl_2]$ were described. Complexes of this type are prepared in alkaline solution according to the reaction

$$K_2PtCl_4 + 2H_2NCHRCOO^-K^+ \rightarrow \textit{trans}\text{-}K_2[Pt(H_2NCHRCOO)_2Cl_2] + 2KCl \quad (1)$$

This reaction produces not only the trans isomers with the amino acids L-norvaline and L-isoleucine but a mixure of various products from which the isolation of the compounds *cis*- and *trans*-$[Pt(H_2NCHRCOOH)_2Cl_2]$ is possible [21].

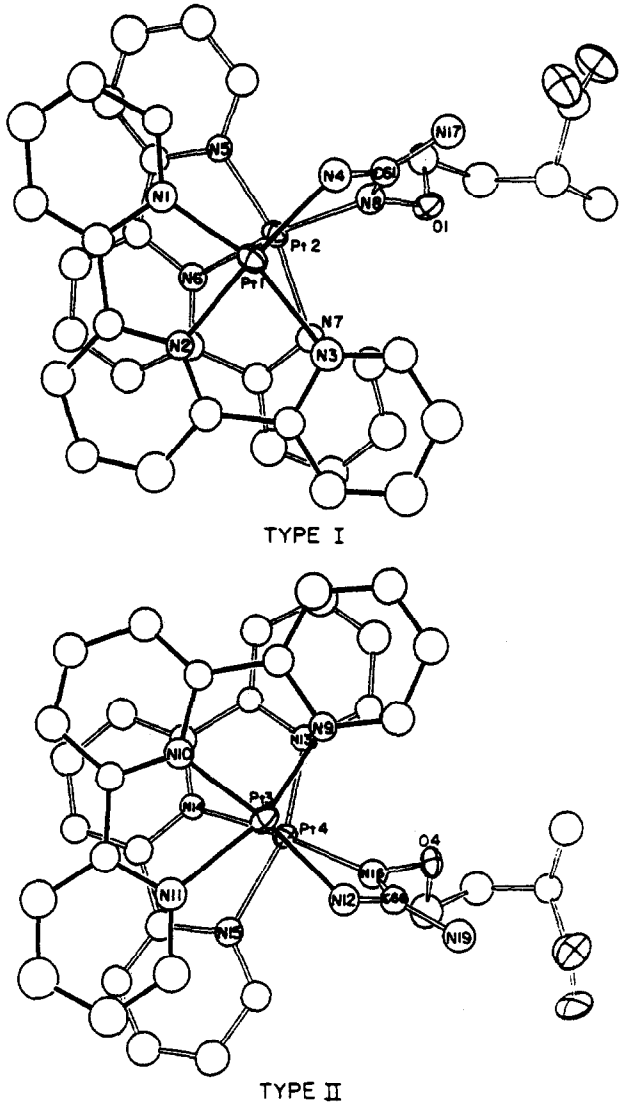


Fig. 1. Molecular structure of the two forms of the complex cation $[\{Pt(trpy)\}_2Can]^{3+}$ (from ref. 17).

The structures of the glycine complex *cis*-$[Pt(glyH)_2Cl_2]$ and of the two isomers $[Pt(NH_3)(glyH)Cl_2]$ [22–25] as well as of the complex with alanine, *trans*-$[Pt(ala)_2Cl_2]$ [26] were determined by X-ray diffraction. These compounds are square planar and the Pt–N bond length (of the amino acid) varies from 1.99 to 2.14 Å. In compounds with trans geometry, the Pt–NH_2 bond is stronger than in the cis compounds since the trans effect of Cl^- is larger than N.

The alanine conformation around the N–C bond in the above complex is seen

in Fig. 2. The carboxylate group is in a trans position to the metal ion, while the methyl group is in a gauche position. This conformation precludes Pt(II)–carboxylate interactions.

Differential thermal analysis (DTA) of monodentate complexes of the type *cis*-$[Pt(amacH)_2X_2]$ (where amacH = glyH, alaH and $X = Cl^-$, Br^-, I^-) with the amino acid $-NH_2$ coordinated show that heating to a temperature higher than 155°C in the solid state causes their isomerization to the corresponding trans species [27]. Similar thermal studies, however, on glycine complexes led to contradictory results [28,29]. More particularly, a mixture [29] of *cis*-$[Pt(N\text{-}glyH)_2Cl_2]$ and glycine in a ratio 1:2 reacts at 125°C in the solid state to form a stable compound of formula $[Pt(N\text{-}glyH)_2(O\text{-}gly)_2]$. (It was claimed that the trans isomer reacts in an analogous manner at 170°C.) On the other hand, the complex $[Pt(N\text{-}glyH)_4]^{2+}$ dissociates at 120°C to yield *trans*-$[Pt(N\text{-}glyH)_2Cl_2]$ and glycine [29].

A series of complexes of the type $[Pt(NH_3)_2(amac)]^+$ were characterized with ^1H and ^{13}C NMR spectroscopy in aqueous solution, where amac is glycine or its *N*-methyl substituted derivatives and proline and pipecolic acid [30,31], to investigate amino acid conformations. The energy difference between the various rotamers (Fig. 3) was calculated to be 0.4–1.5 kcal mol^{-1}. The predominant rotamer depends on the nature of the amino acid and is determined by steric factors present in each case. Thus, for glycine ($R_1 = R_2 = R_3 = H$) rotamer II is preferred, for alanine ($R_1 = R_2 = H$, $R_3 = CH_3$) rotamer III, for sarcosine ($R_1 = CH_3$, $R_2 = R_3 = H$) rotamer I, for (R,R)-N-methylalanine ($R_1 = H$, $R_2 = R_3 = CH_3$) rotamer II, etc.

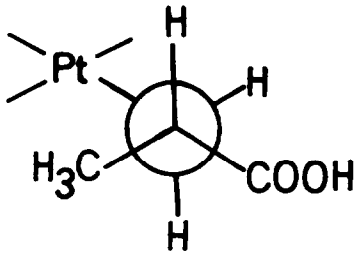


Fig. 2. The amino acid conformation in the complex *trans*-$[Pt(L\text{-}alaH)_2Cl_2]$.

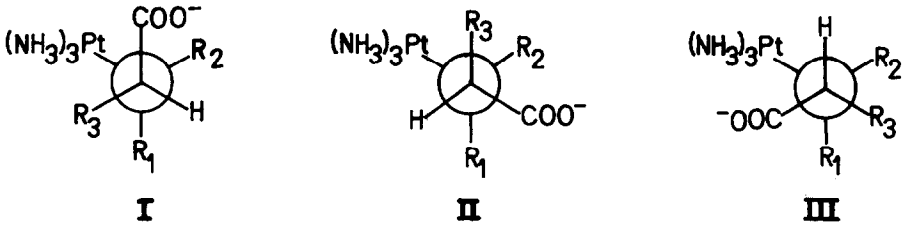


Fig. 3. The three possible rotamers around the N–Cα bond, of an N coordinated to Pt(II) amino acid.

[30,31], as a result of steric hindrance between the $(NH_3)_3Pt(II)$ group and the methyl or carboxylate groups of the ligand.

The antitumour compounds of Pt(II), *cis*-diaminodichloroplatinum(II), cyclobutane-1,1-dicarboxylato-diaminoplatinum(II) and diaminoethylmalonatoplatinum(II), react under conditions similar to biological conditions with the amino acids glycine and L-histidine, producing complexes with Pt–N bonds, as shown in Fig. 4. The various products were isolated and identified by electrophoresis [32–34] and their structures were investigated with ^1H and ^{13}C NMR.

The complexes $[Pt(en)Cl_2]$ and *cis*-$[Pt(NH_2OH)_2Cl_2]$ react with glycine in the same manner, producing the 1:2 product analogous to compound(II) of Fig. 4 [35,36]. The trans isomer of the second compound was only isolated in the 1:1 ratio *trans*-$[Pt(NH_2OH)_2(gly)Cl]$ [35].

One more compound of histidine with Pt(II) was prepared by oxidation of

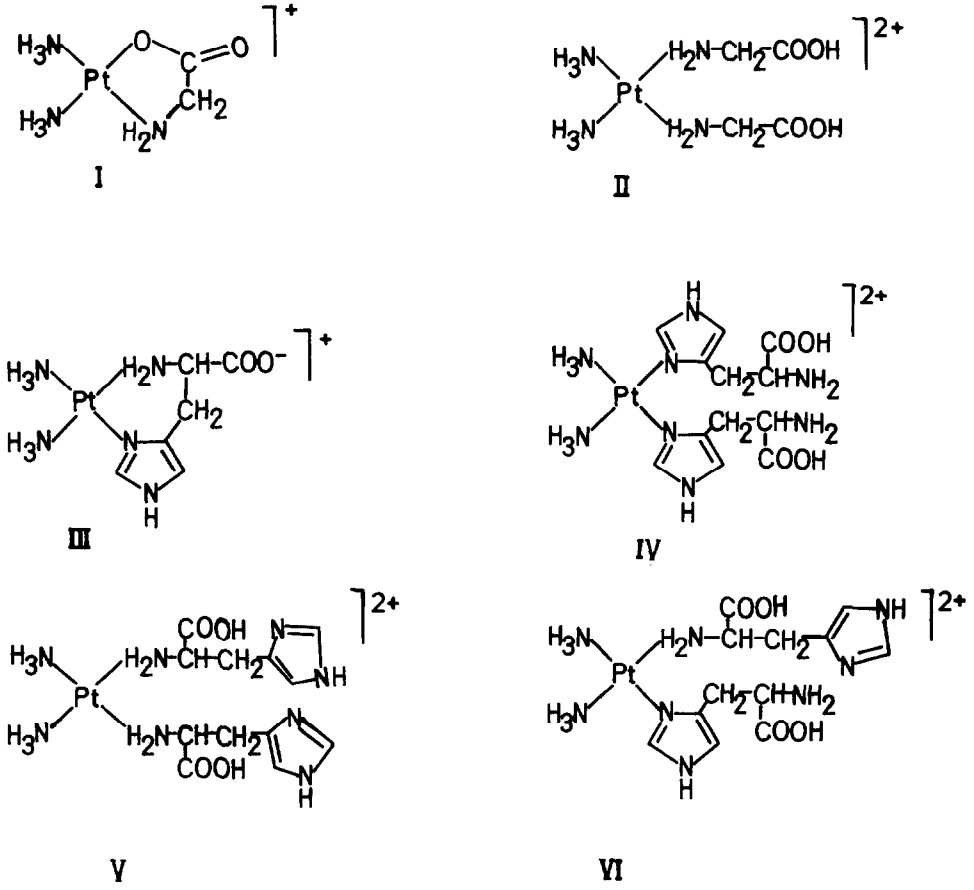


Fig. 4. Structures of the products formed by reaction of $(NH_3)_2Pt^{2+}$ with glycine and L-histidine under conditions similar to biological conditions.

metallic Pt by atmospheric oxygen in an aqueous solution [34]. In this product, corresponding to the formula *trans*-$[Pt(hisH)_2]^{2+}$, the amino acid coordinates in a chelate fashion through the amino group and the nitrogen atom of the imidazole ring, forming a five-membered ring.

More recently, the interaction of L-histidine and *N*-acetyl-L-histidine with the monofunctional species $[(dien)Pt(OH_2)]^{2+}$ and $[(trpy)Pt(OH_2)]^{2+}$ in aqueous solution was studied in detail [37]. The monodentate ligands coordinate through the amino group (only in the case of L-histidine) or the imidazole N(1) or N(3) atoms, but other modes of coordination are also possible, depending on the reaction conditions.

The absolute configuration of amino acids monodentately coordinated through the amino group in Pt(II) complexes has been studied by circular dichroism [38–41]. In the case of complexes *trans*-$[Pt(amacH)_2(thio)_2]Cl_2$ (amacH = L-alaH, L-nvalH, L-tyrH and L-hproH, thio = thiocarbamate), their spectra depend on the solvent used and the pH of the solution due to the preference of certain rotamers in each case. In DMF solutions, the protonated form of the carboxylate group is favoured, while in aqueous solutions, the percentage of this form strongly depends on pH. It was proposed that, in aqueous solutions, rotamer **a** of Fig. 5 predominates due to hydrogen bond formation between the carboxylate group and the amino acid and the amino group of the neighbouring thio ligand. In addition, in the **b** and **c** rotamers steric hindrance is also expected between the thio ligand and the R group [40].

In contrast, the nature of the solvent (C_2H_5OH, HCl, DMF) does not influence the CD spectra in the case of the complexes *cis*- and *trans*-$Pt(amacH)_2$ (amacH = L-alaH, L-nvalH, L-ileu, D-leu) [39].

Of particular interest are the proline complexes, given that nitrogen coordination makes this atom asymmetric. The optical isomers R_N and S_N give different CD spectra. Thus, reaction (2) produces a racemic mixture and reaction (4) selectively produces the S_N isomer. Reaction (3) takes place with retention of the absolute configuration of the complex since the chelate proline of the reactant can only be found as the S_N isomer [38,42,43]. In alkaline solution, however, opening of the chelate ring takes place with inversion of the absolute configuration. As a result, in the product of reaction (4), proH is found as the R_N isomer.

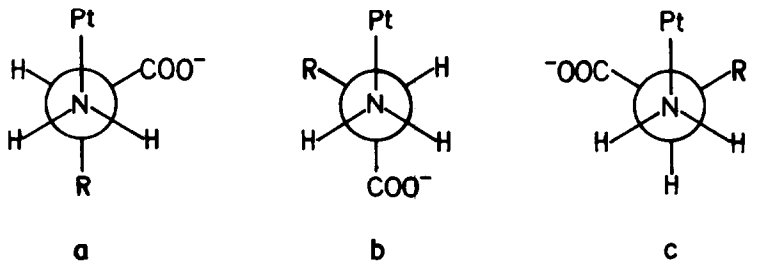


Fig. 5. Rotamers of the coordinated amino acids in *trans*-$[Pt(amacH)_2(thio)_2]Cl_2$.

$$K[Pt(pro)Cl_2] + proH \rightarrow trans\text{-}[Pt(pro)(proH)Cl] + KCl + HCl \quad (2)$$

$$trans\text{-}[Pt(pro)_2] + HCl \rightarrow trans\text{-}[Pt(pro)(proH)Cl] \quad (3)$$

$$trans\text{-}[Pt(pro)_2] + 2SC(NH_2)_2 \rightarrow trans\text{-}[Pt(pro)_2(SC(NH_2)_2)]$$
$$\rightarrow trans\text{-}[Pt(proH)_2(NH_2)_2SC)_2]Cl_2 \quad (4)$$

The structure of the analogous complex of 4-hydroxyproline, *trans*-[Pt(hpro)$_2$(SC(NH$_2$)$_2$)$_2$], has been determined by X-ray diffraction [41] (Fig. 6). The complex has a square planar geometry with a small deviation of 0.11 Å of Pt(II) from the average plane of the coordinated N and S atoms. The Pt–N bond length is 2.07 Å and the pyrrolidinic ring has an envelope configuration as in the free ligand and in its chelate complexes with Pt(II). The orientation of thiourea with its plane perpendicular to the coordination plane of platinum is also noticeable.

The ability of complexes of Pt(II) with amino acids to react stereoselectively was examined for the methyl ester of valine (valOMe) [44]. Thus, reaction (5) presents stereoselectivity, which was proposed to be due to interaction between the ligands in the intermediate product of trigonal bipyramidal configuration.

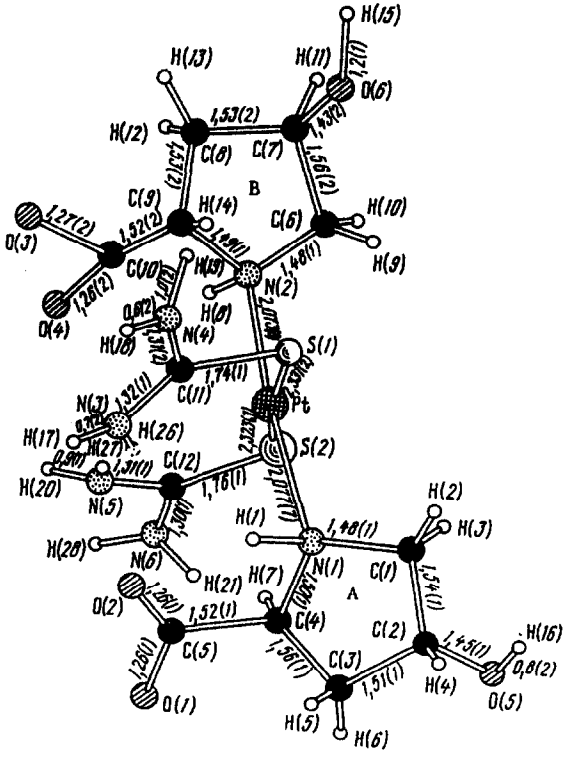
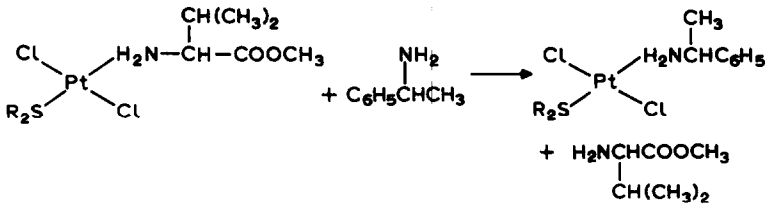


Fig. 6. Structure of the complex *trans*-[Pt(hpro)$_2$(SC(NH$_2$)$_2$)$_2$] (from ref. 41).



(5)

As an example, the *trans*-[$(R_2S)PtCl_2$(S-valOMe)(R-1-PhEtAm)] intermediate, with R-1-PhEtAm = R-1-phenylethylamine is favoured over the *trans*-[$(R_2S)PtCl_2$(R-valOMe)(R-1-RhEtAm)] because in the first there is less steric hindrance between the isopropyl group of valOMe and its neighbouring ligand R-1-PhEtAm. Consequently, while the reactant complex of (5) is a racemic mixture, in the product (free valOMe), the S isomer is preferred by a factor of 1.1 to 1.3. This factor, which measures the stereoselectivity of the reaction, results from the rate equations $-(d[R]/dt) = K_{RR}[R][A]$ and $-(d[S]/dt) = K_{SR}[S][A]$, where [R], [S] and [A] are the concentrations of *trans*-[$(R_2S)PtCl_2$(R-valOMe)], *trans*-[$(R_2S)PtCl_2$(S-valOMe)] and of the non-coordinated R-1-PhEtAm, respectively, and is equal to $K_{SR}/K_{RR} = [\log([S]/[S]_0)]/[\log[R]/[R]_0)]$.

Recently [45], complexes of formulae PtL(HL)Cl, $Pt(HL)_2Cl_2$, and $[Pt(HL)_2(NH_3)_2]Cl_2$ (HL = 1-phenylalanine) were prepared and characterized with IR, UV, CD and ^1H NMR spectra. The complexes were found to complete effectively with HL in the aminoacylation of transport RNA (tRNA) catalyzed by phenylalanyl-tRNA synthetase. They can be used in the inhibitory suppression of the key enzymes of protein synthesis.

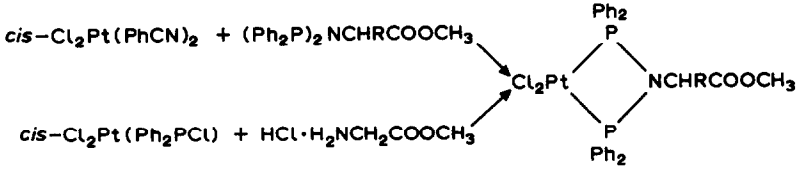
The isolation of amino acid complexes is possible, with the ligand coordinated only through the amino acid, by using amino acid esters. Complexes of Pt(II) and other related metal ions with modified amino acid esters (e.g. esters of *N*-chloro-α-amino acids [46], α-chloromethyl-amino acids [47], 1-amino-1-cyclopropancarboxylic acid [48], *N*-aminomethylglycine [49], and α-phenylglycine [50]) have been isolated and characterized.

Beck and his co-workers [13,51–56] have shown that platinum(II) and palladium(II) complexes of amino coordinated α-amino acids or their derivatives can be used as effective protecting groups for reactions on the ligands, including the synthesis of peptides. Castillo et al. [57] synthesized peptide complexes of Pt(II) and Pd(II) based on reaction (6) using a polymer containing a carbodiimide group (M = Pd(II), Pt(II)). Compounds of the latter type were described by Beck [13].

$$MCl_2(NH_2CH_2COOH)_2 + 2NH_2CHRCOOMe \xrightarrow[\text{DMF. } CH_2Cl_2]{\text{polymer 1}} MCl_2(NH_2CH_2CONHCHRCOOMe)_2 + \text{polymer 2} \quad (6)$$

More recently, Beck and co-workers [58], with the aim of preparing Pt(II) complexes with steroidal hormones to achieve a selective transport to cancerous

cells, prepared complexes of Pd(II) and Pt(II) by reactions of amino-coordinated amino acids and the steroids 3-(2-aminoethoxy)estrone, 3-(2-aminoethoxy)estradiol, 17α-amimethyl estradiol and 3-ol-17 amino-estrane of the general formulae *trans*-$Cl_2Pt(GlyNHR)_2$, $Cl_2Pt[(Gly)_nNHR]_2$ and $Cl_2Pd(HisNHR)$ (R = steroid, $n = 1–3$), and *cis*-$Cl_2Pt(GlyOR)GlyOH$, *trans*-$Cl_2Pt(GlyOR)_2$ and $Cl_2Pd(HisOR)$ (R = derivatives of estrone, prednisolone, prednisone and testosterone). Only the complexes *cis*-Cl_2Pt[glyNH[estradiol-3-(2-aminoethoxy)ether]]$_2$ and *trans*-Cl_2Pt[glyNH[estrone-3-(2-aminoethoxy)ether]]$_2$ caused growth inhibition of hormone-dependent MCF-7 cells of the same order as DDP. Esters of *N,N*-bis(biphenylphosphino)amino acids coordinate in a chelate fashion through the two phosphorus atoms with Pt(II) [59] (reaction (7)).



(7)

Various Pt(II) complexes with peptides [60–63] were prepared by direct reaction of the peptide with a platinum salt. The reaction products of K_2PtCl_4 and *cis*-DDP with diglycine and triglycine, characterized in aqueous solution by ^{195}Pt NMR spectroscopy [61], involve coordination of the peptides through the amino and imino groups. Contrary to that which was reported by other researchers (see Sect. 2.2), no interaction of the carboxylate or the carbonyl groups of the peptides with the metal ion was observed. This, however, is due to the fact that such interactions are observed using relatively short reaction times (1 to 24 h) while in a period of a few days, the thermodynamically stable products are formed [60]. It was proposed that the products had monomeric structures (Fig. 7).

The corresponding trans isomers of complexes **III** and **V** of Fig. 7 with the dipeptide gly-gly have been isolated in the solid state [62]. With the dipeptide gly-ala analogues of **III** and **IX**, complexes were prepared together with the trans isomer of **IX** [63].

Ternary complexes of Pt(II) with nucleic acid derivatives and amino acids monodentally coordinated through the amino group have been used as models for the simultaneous interaction of the metal ion with DNA and proteins. Compounds of stoichiometry Pt(II):nucleoside:aminoacid = 1:1:1 were isolated with the amino acids glycine and alanine and various nucleosides but they were poorly characterized, with postulated formula *cis*-[Pt(nucleoside)(aminoacid)Cl_2] [64,65].

The ability of complexes of the type *cis*-[Pt(tba)(amacH)Cl_2] (tba = $(CH_3)_3CNH_2$, amacH = amino acid, coordinated through the amino group), prepared as possible anticancer agents analogous to *cis*-DDP, to react with the bases of guanine of DNA was examined [7,8] by the synthesis of compounds of the type *cis*-[Pt(tba)(amacH)(guo)$_2$]Cl_2 [66]. The structures of these complexes were studied

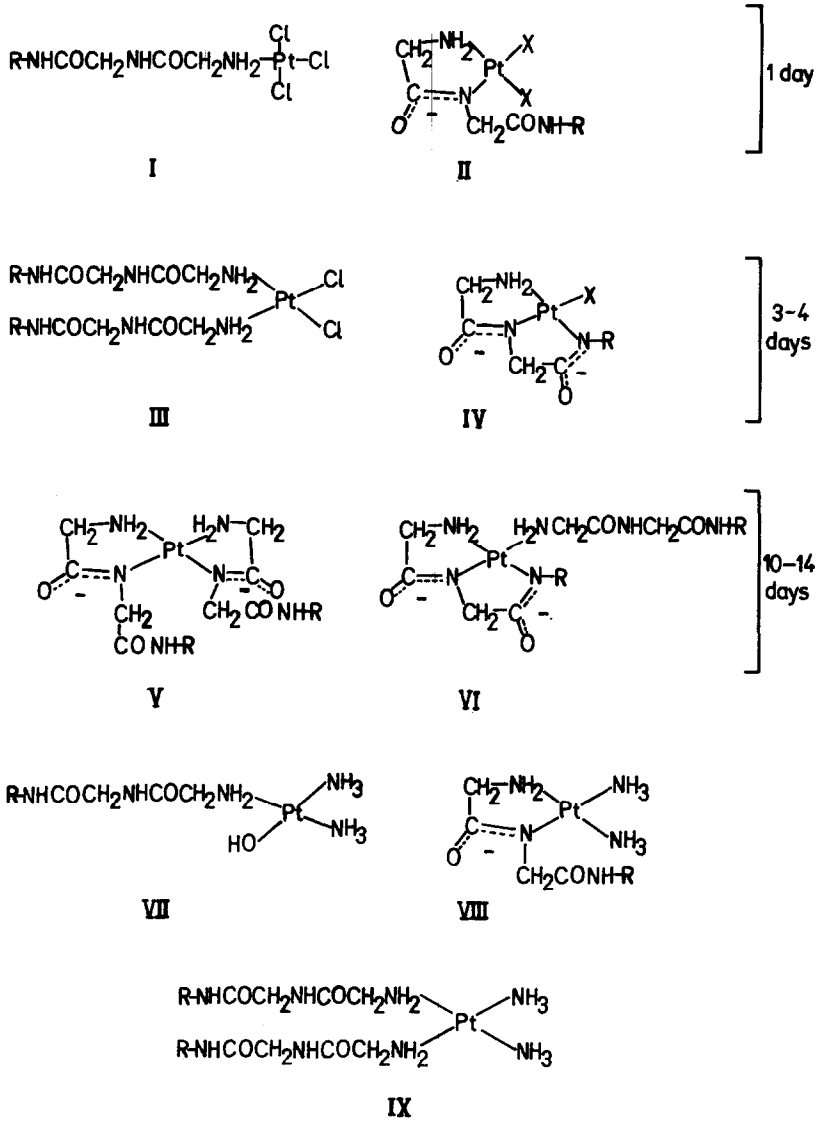


Fig. 7. Products of the reactions of the tripeptide gly–gly–gly with the salts K_2PtCl_4 and *cis*-$(NH_3)_2PtCl_2$ (R = $CHCOO^-$; X = Cl^-, OH^-). The charges on the complexes have been omitted.

by ^1H and ^{13}C NMR and CD spectroscopies. The two nucleosides coordinate through N(7) and have a head-to-head orientation. The parent complexes can therefore react with the guanine bases of DNA and possibly inhibit the replication of the latter. However, these complexes react to a lesser extent with DNA than *cis*-DDP [66].

Other ternary complexes of Pt(II), amino acids and nucleosides, prepared with

the aim of studying the more general Pt–DNA–protein interactions [67–69] include these of general formulae *cis*-$[(ino)_2Pt(amac)]Cl$, *cis*-$[(ino)_2Pt(amacH)Cl]Cl$ and *trans*-$[(guo)_2Pt(amacH)_2]Cl_2$ (ino = inosine, guo = guanosine and amacH = glycine, L-alanine, L-valine, L-isoleucine, L-phenylalanine and L-proline). The amino acids are NH_2 and COO^- chelated in complexes of the first type, while in the other two types, coordination occurs only through the NH_2 group. The nucleosides coordinate through N(7). The compounds *cis*-$[(ino)_2Pt(amacH)Cl]Cl$ were prepared by treatment of those with the chelated amino acids with an equivalent amount of HCl [67,68]. The *trans*-$[(guo)_2Pt(amacH)_2]Cl_2$ compounds [69], on the other hand, were prepared according to the reaction

$$K_2PtCl_4 + amacH \rightarrow K_2[Pt(amac)_4] \rightarrow \textit{trans}\text{-}[(amacH)_2PtCl_2] \downarrow \textit{trans}\text{-}[Pt(guo)_2(amacH)_2]Cl_2 \quad (8)$$

Interactions between the hydrophobic side chain of the amino acid and the nucleosides were detected in aqueous solutions of the complexes based on ^1H and ^{13}C NMR data. These are stronger in complexes with a trans geometry, near the bonding sites, where the amino acids are influenced by both nucleosides and contrary to what was observed with the cis analogues, where the stronger interactions occur further from the bonding sites [68,69]. The percentage of the ^3E sugar conformation of the nucleosides increases slightly in the ternary complexes. An increase is also observed in the anti conformation of the sugar of the nucleosides in the ternary complexes and is larger in the trans than in the cis analogues compared with the binary Pt-nucleoside. This was explained as the cause of toxicity of both *cis*- and *trans*-DDP, forming Pt–DNA–protein cross-links.

Intramolecular interactions of this type were also detected using ^1H NMR spectroscopy in aqueous solutions of ternary complexes of formulae *cis*-$[(NH_3)_2Pt(Nb)(amac)](NO_3)$, where Nb was 9-methylguanine (9-MeG) or 1-methylcytosine (1-MeC) and amac was an amino acid anion, coordinated through the $-NH_2$ group to Pt(II) [70]. Such interactions were found to be considerably weaker in the corresponding trans isomers [71]. In all cases, the rotamer distribution of the coordinated amino acids was not significantly different from the corresponding free amino acids.

The structures of the ternary complexes *cis*-$[(NH_3)_2Pt(gly)(1\text{-}MeC)]^+$ [70] and *trans*-$[(CH_3NH_2)_2Pt(gly)(1\text{-}MeC)]^+$ [72] were determined by X-ray diffraction (Fig. 8). In both species, the gly anion coordinates only through NH_2 and 1-MeC through N(3), and there are no intra- or intermolecular interactions between the ligands or between the ionized carboxylate group and the metal ion. This is in agreement with the behaviour of the compounds in solution. The arrangement of gly, however, in both crystal structures would exclude the analogous interactions even with the heavier amino acids if a similar arrangement for them is postulated.

Ternary complexes of Pt(II) with histidine derivatives and the nucleobases

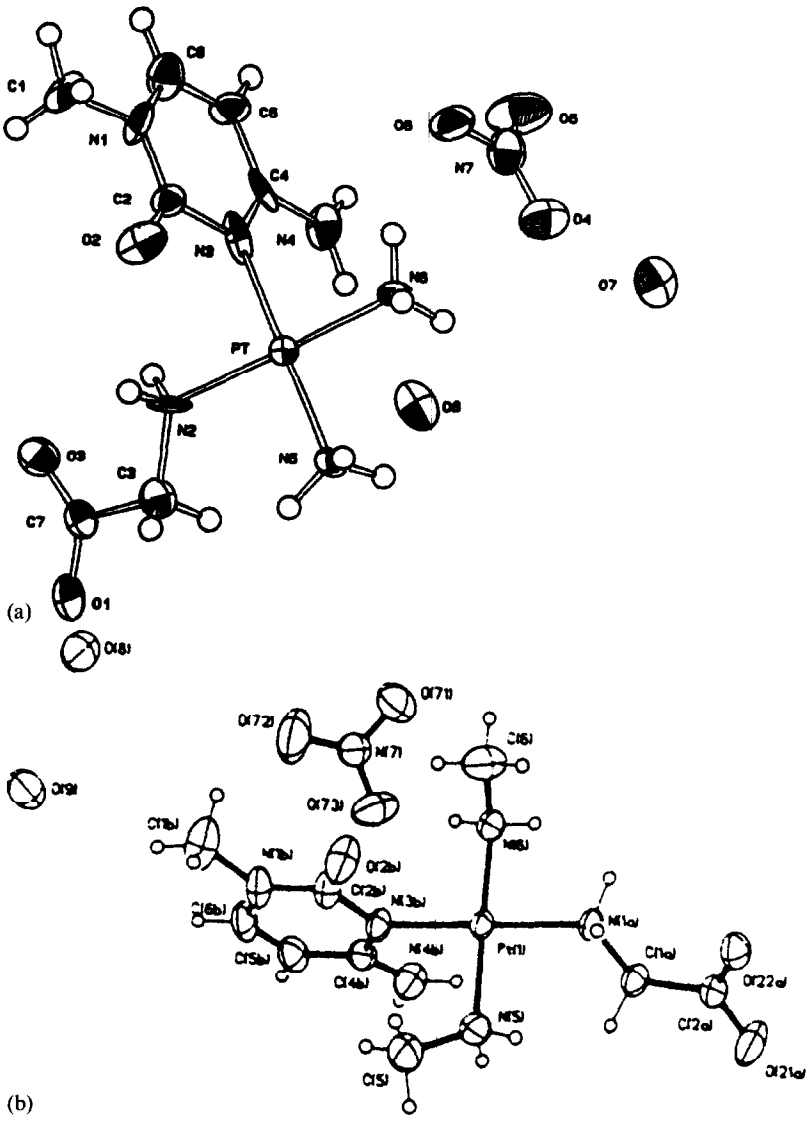


Fig. 8. Structures of the complexes (a) *trans*-$[Pt(CH_3NH_2)_2(1\text{-MeC})(gly)]^+$ [70] and (b) *cis*-$[Pt(NH_3)_2(1\text{-MeC})(gly)]^+$ [72].

1-MeC or 1-methyluracil (1-MeU) have also been isolated and characterized [37]. Depending on the amino acid binding site (imidazole N(1) or N(3) atoms) two linkage isomers are formed. The coordination of the amino acid also results in the stabilization of different tautomeric forms [37].

The synthesis of ternary complexes of Pt(II) and pyridine and glycine of cis

and trans geometry (formula $[Pt(py)(glyH)X_2]$, X = Cl, Br) has also been reported [73].

Other reports on monodentate NH_2 bound amino acids with Pt(II), refer to kinetics and mechanism of formation of a chelated ring [74–78]. The formation of such a chelate is achieved through two processes: (a) by direct substitution of the neighbouring ligand (halogen ion) by the ionized carboxylate group of the amino acid and (b) by substitution of the halogen ion by solvent molecules (H_2O) which are afterwards replaced by the ionized carboxylate group of the amino acid. It was proposed that route (b) is more favoured by an increase of the side chain of the amino acid, but this has not been proven unambiguously [74–78].

The synthesis of Pt(II) complexes were also reported with ethylenediamine-*N*,*N*-bis-acetic acid and 2-(2-amino-ethylamine)acetic acid [79,80], which may be considered as substituted glycine derivatives. Similarly, complexes with α,γ-diaminebutyric acid [81] bound by the metal ion through the NH_2 group are described. In addition, the formation of platinum blues with glutamine was reported [82]. These compounds have unknown structures (probably the amino acid bridges two metal ions through the skeletal and the side chain amino groups). Finally, mixed complexes of Pt(II) with glycine and ortho-substituted anilines were also reported [83].

The IR and Raman spectra of various complexes of amino acids with Pt(II), with the amino acid coordinated either monodentately through the NH_2 group or bidentately through both NH_2 and COO^- were examined and qualitatively assigned [84,85]. The $\nu^a_{COO^-} - \nu^s_{COO^-}$ difference [85], corresponding to the asymmetric and the symmetric stretching vibrations of the coordinated carboxylate groups, increases gradually with increase of the length of the aliphatic side chain of the chelated amino acids, following the order, gly < ala < 2-aba < val < nval. This shows that the Pt–O bond is more covalent in the above order, and also shows an increase in the stability of the chelated complex with increase of the length of the aliphatic side chain of the amino acid [85].

Treatment of the complex $[Pt(glyH)_2(gly)_2]$ with HX acids (X = halogen ion) causes liberation of two trans ligands [12,86] and the products formed are transformed to the bis-chelated complexes of cis or trans geometry (reaction (9)).

$$2[Pt(glyH)_2(gly)_2] + 4HX \rightarrow \textit{trans}\text{-}[Pt(glyH)_2X_2] + \textit{cis}\text{-}[Pt(glyH)_2X_2] + 4glyH \quad (9)$$

2.2 *Amino acid coordination through oxygen. Chelate complexes of amino acids, peptides and their derivatives with amino and carboxylate group coordination*

Complexes of Pt(II) with amino acids coordinated monodentately through the oxygen of the carboxylate group have not as yet been isolated in the solid state. Postulated complexes of this type with 1,2-diaminepropionic acid were not satisfactorily characterized [87], though such complexes are known to form in solution

[14–16,37]. On the other hand, the simultaneous coordination of the NH_2 and COO^- groups to form chelated complexes is very common. Such compounds are the bis-chelated complexes of the type *cis*- or *trans*-[Pt(amac)$_2$], which were prepared for the amino acids glycine, alanine, 2-aminobutyric acid, valine, asparagine, glutamic acid, proline, leucine, tyrosine, β-alanine [12], L-isoleucine, L-norvaline [21], L-phenylalanine (only the trans isomer) [20], γ-aminobutyric acid (only the trans isomer) [88], L-hydroxyproline (only the trans isomer) [42], as well as of their derivatives such as 1-amino-1-cyclopropane carboxylic acid [48]. Bis-chelate mixed complexes of L-proline with L-alanine, L-serine, L-valine, sarcosine [89,90] and of alanine with glycine, valine and 2-aminobutyric acid are also known [12].

Chelate complexes of the type [Pt(amac)X_2]$^-$ were isolated with the amino acids, glycine ($X = Cl^-$ [12,30,31], $X = NO_2^-$ [91]) and with alanine [30,31], sarcosine [12], L-proline [30,31], L-hydroxyproline [92], L-lysine [92,93], for $X = Cl^-$, as well as with the amino acid derivatives *N*-methylhydroxyproline [43], L-2,4-diaminobutyric acid [87], L-ornithine [87], L-pipecolic acid, *N,N*-dimethylglycine, *N*-methylalanine, *N,N*-dimethylalanine, *N,N*-dimethyl-L-2-aminobutyric acid and L-2-aminobutyric acid [30,31].

Complexes are also known with the general formula [Pt(amac)A_2]$^+$, with amac = glycine, L-alanine, L-2-aminobutyric acid, L-valine, L-nor-valine ($A = NH_3$ [94]), L-proline ($A = NH_3$ [95]), N-substituted derivatives of iminodiacetic acid ($A = NH_3$ [96]), $A_2 = 1$, 1-bis(aminomethyl)cyclohexane [97] or 1,2-diaminocyclohexane [98], as well as complexes of the type [Pt(amac)AX], with amac = alanine, valine and proline ($A = NH_3$, $X = Cl^-$) [12].

Complexes with ratio of Pt:amino acid = 1:2, where the one amino acid molecule coordinates as a chelate and the other monodentately through the amino group, are also known [12,18,19,74–78]. Such compounds correspond to the molecular formula [Pt(N,O-amac)(N-amac)X]$^-$.

The structures of the complexes *cis*-[Pt(gly)$_2$] [99,100], [Pt(gly)$(NO_2)_2$] [91], *cis*-[Pt(gly)(NH_3)Cl] [23], *trans*-[Pt(hpro)$_2$] [42], *cis*-[Pt(L-lys)Cl_2] [92], [Pt(mhypro)Cl_2]$^-$ (mhypro = anion of *N*-methyl-hydroxyproline) [43], *cis*-[Pt(gly)$(NH_3)_2$]$^+$, *cis*-[Pt(ala)$(NH_3)_2$]$^+$ and *cis*-[Pt(L-val)$(NH_3)_2$]$^+$ [94] were determined by X-ray diffraction. The N(amino acid)–Pt–O(amino acid) angle varies between 80 and 85° and is always smaller than the usual value of 90° due to the formation of the chelate ring. In complexes of glycine, Pt(II) and the coordinated atoms are found in the same plane while in the case of L-alanine and, to a larger extent, L-valine, there is a small tetrahedral distortion [94–97] causing the N and O coordinated atoms to lie up and down the coordination plane of Pt(II).

Structures of the ternary complexes of Pt(II) with α-methylbenzylamine (MBA) or pyrrolidone (pyr) and L-proline, with formulae *trans*-[(*N,N*)-[Pt(MBA)(L-pro)Cl]] or *trans*-[(*N,N*)-[Pt(pyr)(L-pro)Cl]] have also been determined [101,102]. No ligand–ligand interaction was observed.

In addition, crystal structures of 5-oxoprolines of Pt(II) with N,O coordination

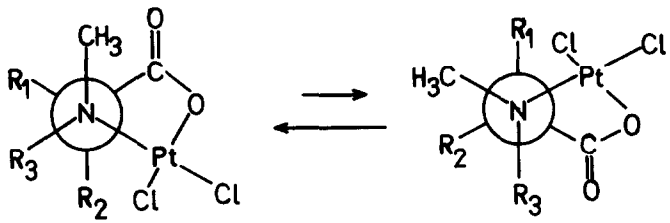
were recently reported for the compounds K[PtCl(oxo-5-prolinate(2^-)-O,N)(DMSO)](oxo-5-prolinate)·H_2O, [μ-(oxo-5-prolinate,N^1,O^5)Cl(DMSO)Pt]$_2$·H_2O and Na[Pt(oxo-5-prolinate,N,O)$_2$]·$2H_2O$ [103–105] as well as the crystal structure of *trans-d,l*-1,2-diaminocyclohexane(*N*-methyliminodiacetato)platinum(II) [98].

Amino acid coordination through the amino and the carboxylate groups results in modification of the relative amounts of the rotamers **t, g, h** around the C_α–C_β bond. The rotamers in which the aliphatic side chain of the amino acids are directed towards Pt(II) were found to dominate in aqueous solutions for the simple amino acids L-2-aminobutyric acid, L-norvaline and L-valine [94–97].

Optical rotatory dispersion (ORD) and circular dichroism (CD) data were collected for many chelate amino acid Pt(II) complexes [42,43,90,95,106–115] in both the solid state and in solution. The nature of the side chain of the amino acid influences the intensity of the bands in the CD spectra in the visible region. Increase in length of the amino acid side chain in the order leucine, valine, isoleucine implies increase in the intensity of d–d bands by a factor of 1.5 [109].

Isomers of chelate complexes of the type Pt(amac)Cl_2 were examined in aqueous solutions using ^1H and ^{13}C NMR spectroscopy (amac = anion of glycine and its derivatives, proline anion and anion of pipecolic acid) [30,31]. The envelope configuration is preferred for these chelated complexes. In the case of methyl-substituted glycine derivatives, rotamer **I** of Fig. 9 is favoured for steric reasons. Pipecolic acid coordinates in a chelate manner in two ways, forming cis or trans (Fig. 10) geometries, with the former being the more stable. For proline, only the cis configuration is possible in the chelated complexes.

Spectroscopic ^1H, ^{15}N and ^{195}Pt NMR data show that the first attack on Pt(II)



I II

R_1:	CH_3	R_2: H	R_3: H	meala
	H	CH_3	H	meala
	H	CH_3	CH_3	dmeala
	CH_3	CH_3	H	meaba

Fig. 9. Proposed rotamers of the chelate complexes of the amino acids *N*-methylalanine (meala), *N,N*-dimethylalanine (dmeala) and *N*-methylaminobutyric acid (meaba) with Pt(II) [31].

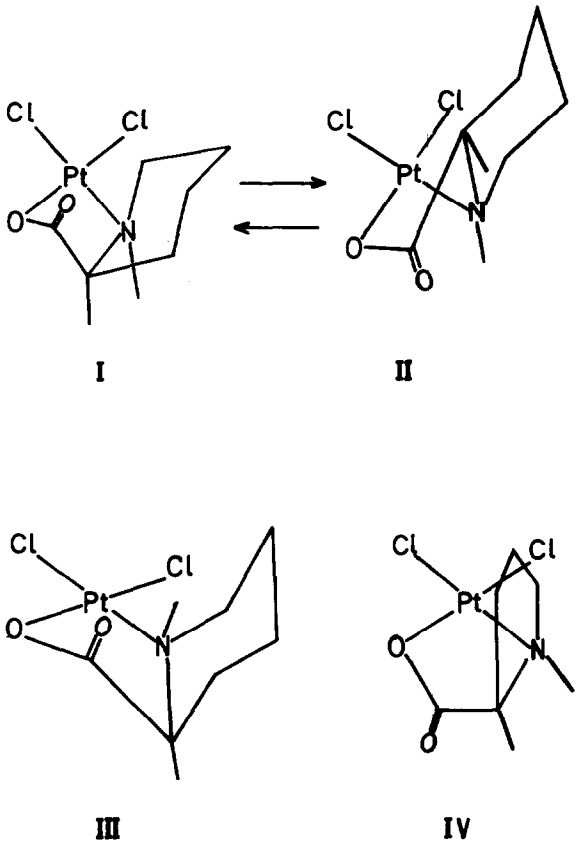


Fig. 10. Configurations of cis (**I, II**) and trans (**III**) isomers of the chelate complexes of pipecolic acid and the cis isomer (**IV**) of proline [30]. The charges on the complexes have been omitted for clarity.

takes place with the COO^- group of the amino acid in acidic solutions [14–16] or through the NH_2 group in basic solutions or in organic solvents such as DMSO [14–16,116,117]. In a second step, the thermodynamically more stable chelate (NH_2, COO^-) complex is formed, but the attack of Pt(II) by a second amino acid molecule is also possible. Such reactions for a series of aliphatic amino acids of type $NH_2(CH_2)_nCOO^-$ are shown in Fig. 11.

The chelate glycine complex *cis*-$[(Et_3P)_2Pt(gly)]^+$ has also been prepared by replacement of the two labile ligands of the complex *cis*-$[(Et_3P)_2Pt(OSO_2CF_3)Cl]$ by the amino acid [118].

Recently, a number of complexes of the general formula $[L_2Pt(N,O\text{-}(N\text{-acetyl})amac)]$, where L is substituted phosphine and *N,O*-(*N*-acetyl)amac is N-acetylaminoacidate^{2-} chelated through the imino and the carboxylate groups, has been prepared for the *N*-acetylated amino acids glycine, alanine, methionine and phenylalanine [119]. The *N*-formylglycine and L-proline

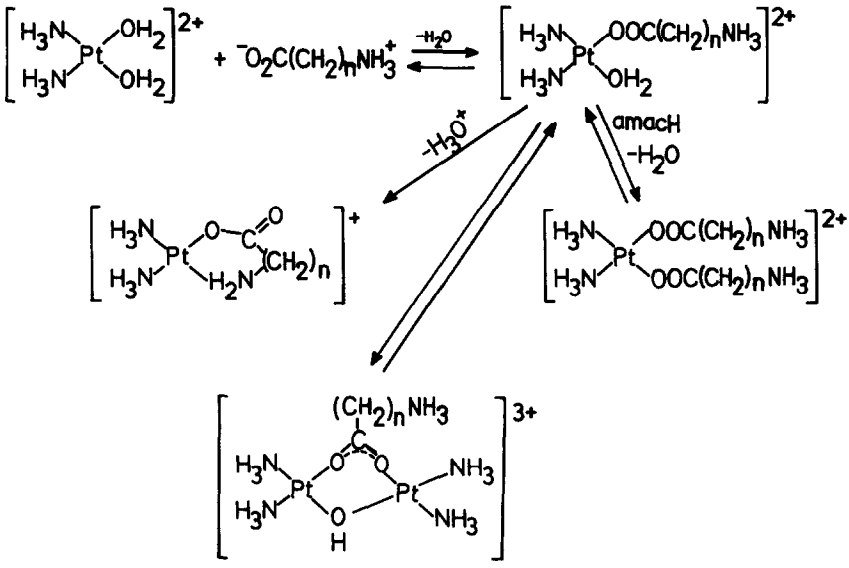


Fig. 11. Reactions of *cis*-$(NH_3)_2Pt^{2+}$ with simple amino acids.

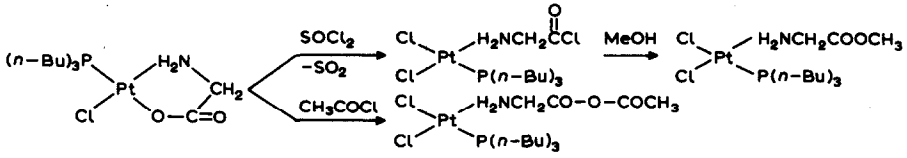
analogues of such complexes were also isolated in the same study and the crystal structure of [(dppe)Pt(*N,O*-acgly)] (dppe = $Ph_2P(CH_2)_2PPh_2$, *N,O*-acgly = *N*-acetylglycinate bound through the imino and the carboxylate groups) has been determined.

Kinetic studies [74–78,88,111,120–125] (including one polarographic study [125]) have been used to study chelate ring formation of Pt(II) complexes with various amino acids. Such reactions (being first order to the complex) are usually accelerated in aqueous basic solutions (in comparison with ethanolic solutions, for example). The mechanism proposed earlier for the formation of the chelated complexes was based on such kinetic studies. The experimental values of the rate constants for the two independent paths of the reaction vary between 10^{-5} and 10^{-3} M^{-1} s^{-1}, depending on the ratio of a mixture of two solvents (e.g. H_2O, CH_3OH:H_2O, dioxan, etc.).

Studies dealing with the thermodynamic [126] and thermal stability [127–129] of chelated complexes were also reported. The stability constants of a series of bis-chelate Pt(II) complexes with dicarboxylic acids (aspartic, glutaminic, etc.) were calculated based on the experimental pK values of their carboxylates [126]. The results ($\log K_{stab} = 10.0–13.9$) show that the chelated complexes of Pt(II) are more stable than those of Pd(II). The side chain of the coordinated amino acid does not significantly influence the value of $\log K_{stab}$ in the Pt(II) series of complexes examined.

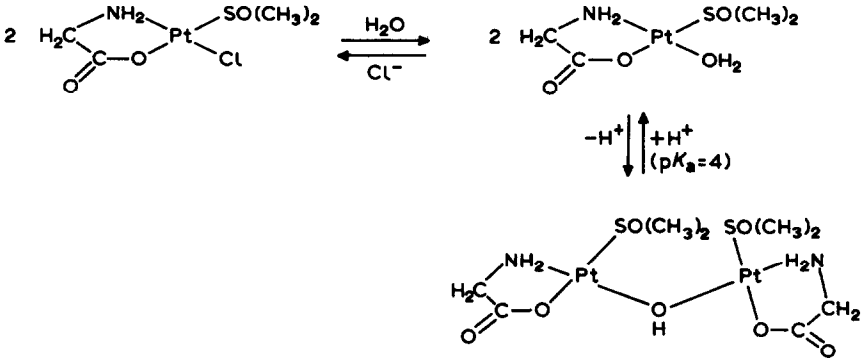
The thermal stability of chelate glycine complexes, with a Pt(II):gly ratio 1:1 or 1:2 was examined by thermogravimetric analysis (TGA) [127–129]. The chelates decompose at 270–300°C. In contrast, $H_2[Pt(gly)_4]$, with monodentate amino acid is converted to the bis-chelate complex *cis*-$[Pt(gly)_2]$ [127–129], at 220°C.

Hydrolysis of the Pt–O bond takes place in alkaline [130–132] and acid [67–69] solutions, resulting in opening of the chelate ring with monodentate NH_2 coordination. Opening of the chelate ring can also take place upon treatment with thionyl chloride [133] (reaction (10)). In this case, the amino acid is converted to an aminoalkyl halogenide or aminoacetyl ester in the product.



(10)

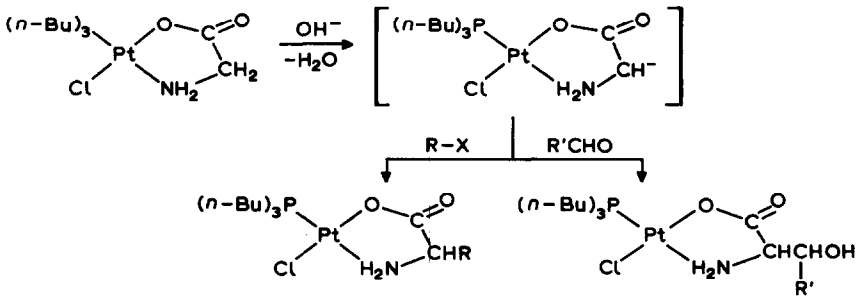
The formation of dimeric complexes is also observed in alkaline media for those compounds containing at least one labile ligand [134]. The rate of reaction for formation of the dimer of order $10^{-2}\,M^{-1}\,s^{-1}$ (pseudo-first-order constant) is 100 times larger than the rate of breaking it. The mechanism of its formation is proposed as follows.



(11)

In alkaline media, Pt(II) causes racemization of optically active amino acids [135]. At 120°C and pH = 8, the chelated L-alanine is converted to the racemic mixture 100 times faster than the free amino acid.

The Pt(II) chelated amino acids also undergo skeletal reactions. Reactions on the α position of the amino acid (only for glycine) with alkyl halogenides or aldehydes occurs (reaction (12)) [136].



(12)

Amidoacetals react in a similar fashion [137,138]. These compounds also react with the amino group of chelated glycine to form Schiff bases without changing the coordination of the organic ligand [137].

The only ternary complexes of Pt(II) with amino acids and nucleic acid constituents, with the amino acids coordinated in a chelate fashion, contain inosine and correspond to the formula *cis*-[Pt(ino)$_2$(amac)]Cl [67,68]. Analogous compounds of 2,2′-bipyridine (bipy) and 1,10-phenanthroline (phen) show antibacterial activity and cause growth inhibition in leukemia P-388 cells [139–144].

The scheme shown in Fig. 12 [134] was proposed for the formation of such ternary complexes, from reactants containing a ligand coordinated through sulphur (e.g. [Pt(amac)(DMSO)Cl]). It is important to mention the fact that purine, but not pyrimidine, nucleobases can replace chelated amino acids from complexes of formula *cis*-[Pt(NH$_3$)$_2$(amac)]$^+$ [145]. This may possibly show that the amino acids, peptides or their derivatives, or even proteins can be the transporters of anticancer compounds of Pt(II) to nucleic acids where they are bound. Such a possible mechanism for a chelated amino acid is shown in Fig. 13.

Reaction of chelated complexes of the type [Pt(amac)Cl$_2$]$^-$ (amac = anion of glycine, sarcosine and *N,N*-dimethylglycine) with DMSO in aqueous solution produces the isomeric ternary complexes *cis*-(*N,S*)- and *trans*-(*N,S*)-[Pt(amac)(DMSO)Cl] [146]. The formation of these complexes was investigated. Based on kinetic data, the mechanism shown in Fig. 14 was proposed [146]. In equilibrium, the cis isomer is favoured by a factor of 45 for the glycine derivative.

The variety of glycine interaction with Pt(II) also applies for the *N*-alkyl derivatives of this amino acid. Nevertheless, whenever more than one basic group is available, the formation of additional products is possible. Thus *N*-acetylglycine reacts at pH = 1 with *cis*-[(NH$_3$)$_2$Pt(H$_2$O)$_2$]$^{2+}$ first through the ionized carboxylate, which is the more nucleophilic group of the molecule [147]. In a second step, the amide nitrogen also coordinates and a five-membered ring forms [119,147].

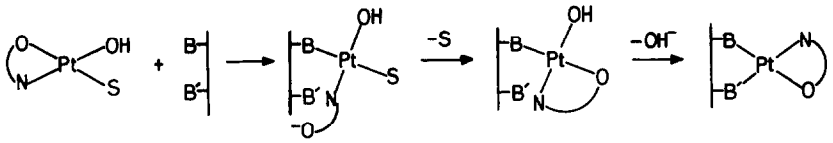


Fig. 12. A possible process for the formation of a ternary amino acid–Pt–nucleic acid complex.

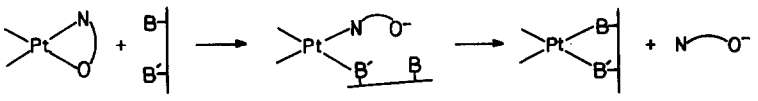


Fig. 13. A possible process for the formation of an endoclonic cross-link of Pt–nucleic acid through formation of the amino acid–Pt–nucleic acid complex [129].

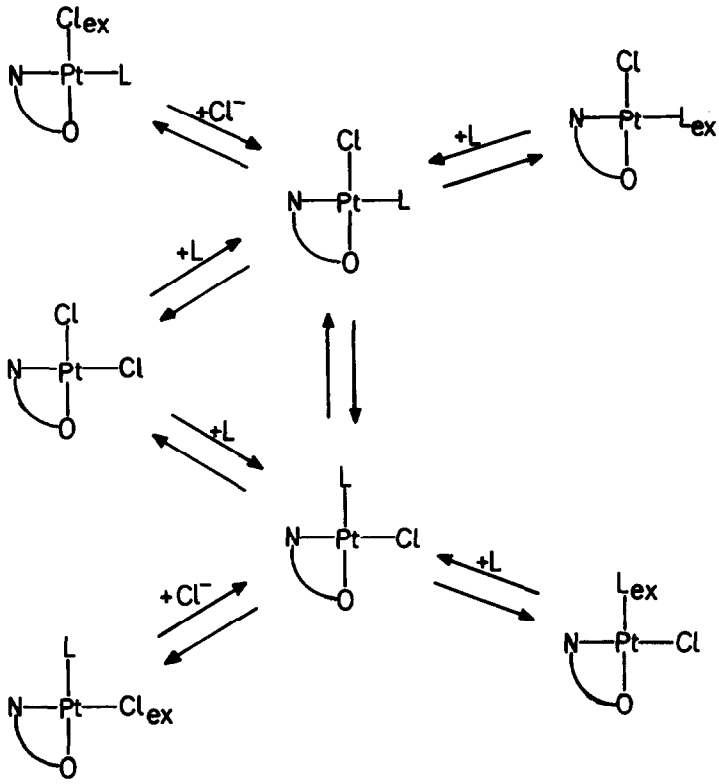
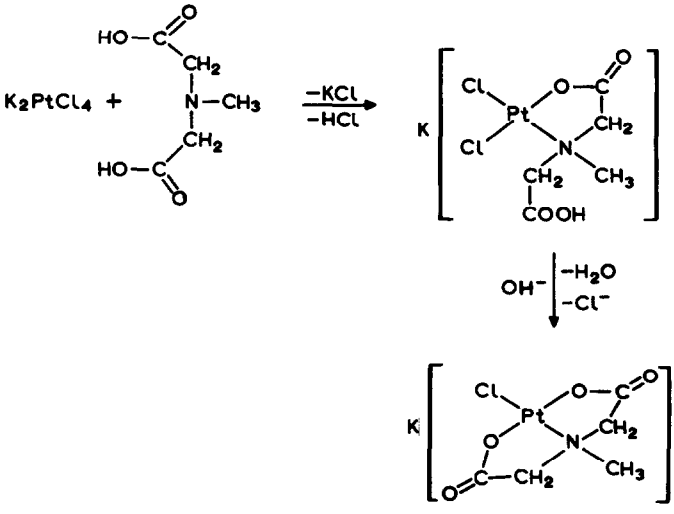


Fig. 14. A proposed general mechanism for substitution and isomerization reactions of the [Pt(amac)LC] complex.



(13)

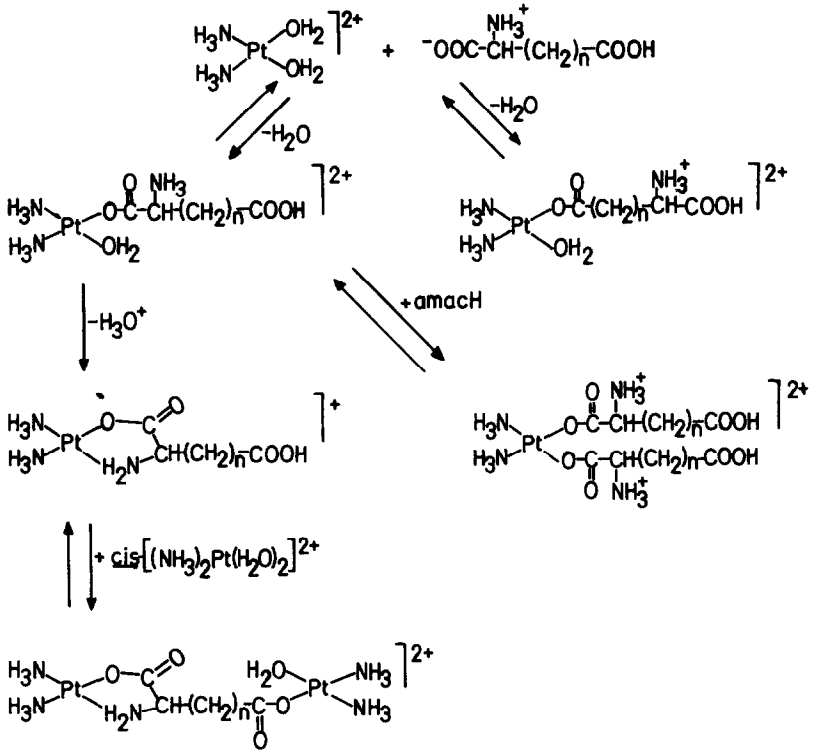
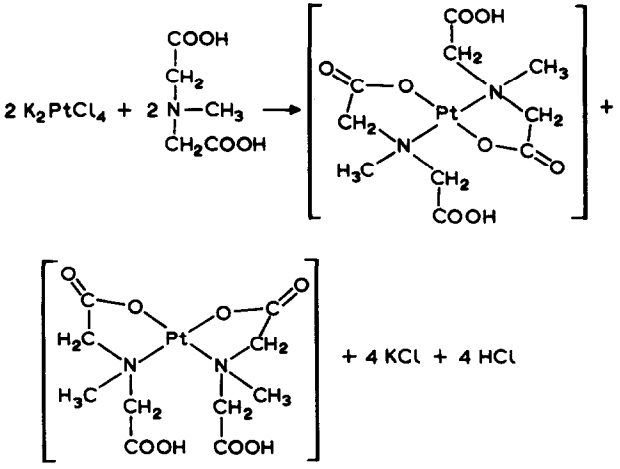


Fig. 15. Interaction of the hydrolysis products of cisplatin with aspartic ($aspH_2$, $n = 1$) and glutamic acid ($gluH_2$, $n = 2$) in aqueous solution.



(14)

(Methylimine)bis-acetic acid (*N*-carboxymethyl, *N*-methylglycine) reacts analogously with K_2PtCl_4 according to reactions (13) and (14) [148].

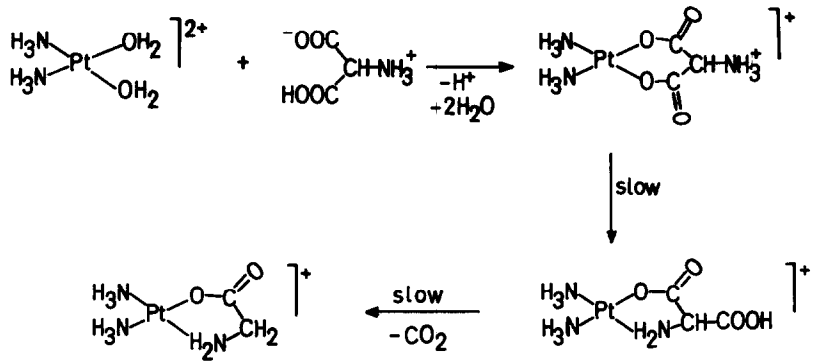


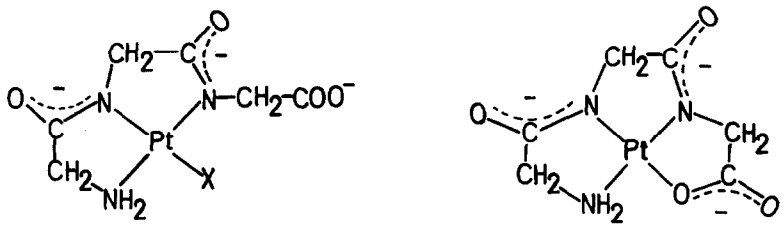
Fig. 16. Interaction of the hydrolysis products of cisplatin with 2-aminomalonic acid [149].

The reaction of *cis*-$[(NH_3)_2Pt(H_2O)]^{2+}$ with aspartic or glutaminic acid is shown in Fig. 15. At pH < 2, the α-carboxylate group coordinates preferentially and the products are analogous to those of glycine [14–16], though at pH = 4–5 both carboxylates react to the same extent [149]. In the presence of an excess of Pt(II), binuclear complexes are also formed with coordination of all the nucleophilic groups of the ligand. The 2-aminomalonic acid also coordinates in a chelate fashion through the two carboxylate groups (Fig. 16) while at pH < 2, a slow decarboxylation of the ligand was observed with the formation of the known chelate complex of glycine [14–16,149] as the final product. Complexes of Pt(II) with ligands which can be considered as *N*-bis-substituted derivatives of glycine were isolated in the solid phase [150,151]. In these compounds with the general formula [Pt(DACH)(IDA)], where DACH = 1,2-diamine-cyclohexane and IDA = substituted anion of imino-bis-acetic acid, the amino acid derivative chelates through oxygen and nitrogen or through the oxygens of the two carboxylate groups, forming less stable complexes [151].

Similar complexes were prepared by using hydrazides of aspartic and glutaminic acids [152], derivatives of 1-amino-1-cyclopropane-carboxylic acid [48] and *N*-glycoso-α-aminoacids [153]. The synthesis of a complex of *N*-(α-pyridinyl), *N*-carboxymethyl glycine with Pt(II), was also reported, claimed to correspond to the rare trigonal bipyramidal structure, which was not, however, proven unambiguously.

The tripeptide triglycine (gly-gly-gly) reacts with $[PtCl_4]^{2-}$ at pH = 6–7 with deprotonation of the amide nitrogens [154]. The tripeptide is tridentate in this way, by using all the available nitrogen atoms or tetradentate using the nitrogen atoms and the carboxylate group. The complexes formed correspond to the ratio metal ion : ligand = 1 : 1 and their proposed structures are shown in Fig. 17. The same tripeptide reacts with the hydrolysis products of cisplatin and coordinates monodentately with the carboxylate group or in a chelate fashion with the carboxylate oxygen and the nearby amide nitrogen [61]. The cisplatin–triglycine interaction follows the scheme in Fig. 18. The dipeptide coordinates in a monodentate fashion through the

amino or the carboxylate groups or it forms a chelate (using the carboxylate oxygen and the nearby amide nitrogen) in monomeric or dinuclear complexes. The structure of the dinuclear complex $[\{cis\text{-}(NH_3)_2Pt\}_2(gly\text{-}gly)]SO_4$ [61] is shown in Fig. 19.



I II

Fig. 17. Products of the interaction of triglycine (gly–gly–gly) with K_2PtCl_4: I, $[Pt\{(gly\text{–}gly\text{–}gly)\text{-}H_2\}X]^{2+}$ ($X = Cl^-$, OH^-); and II, $[Pt\{(gly\text{–}gly\text{–}gly)\text{-}H_4\}]$.

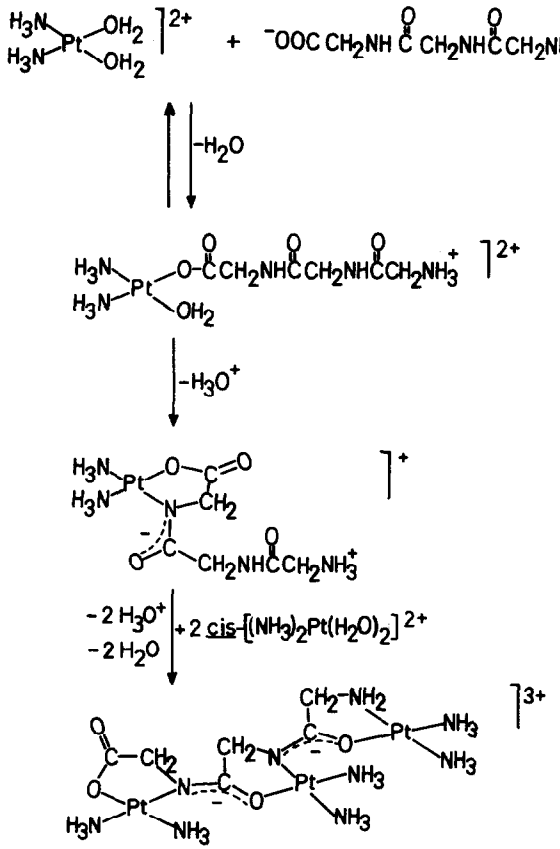


Fig. 18. Interaction of the hydrolysis products of cisplatin with triglycine in aqueous solution.

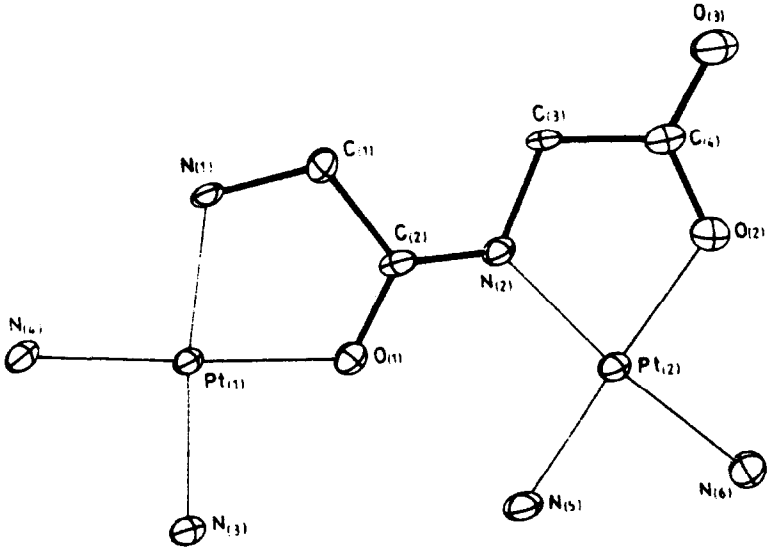


Fig. 19. Molecular structure of [{*cis*-$(NH_3)_2Pt\}_2$(gly–gly)](SO_4) (from ref. 61).

Multinuclear (^1H, ^{13}C and ^{195}Pt) NMR was used to study the effect of metal-centered stereochemistry on the stereoselectivity of coordination of prochiral olefinic alcohols [155]. Comparison of the equilibrium distribution of diastereomers of *cis*- and *trans*-(N,olefin) isomers for mixed complexes of formulae Pt(amino acid)(olefin)Cl (amino acid = glycine, α-aminobutyric acid, sarcosine and proline, olefin = allylalcohol, 3-buten-2-ol and 2-methyl-3-buten-2-ol(2-mb)), showed that the stereoselectivity of olefin coordination is not significant for any *trans*-(N,olefin) species. The *cis*-(N,olefin) isomers of *N*-chiral sarcosine and (S)-proline, however, showed substantial stereoselectivity $> 40/1$ for 2-mb. The structures of the preferred isomers *cis*-(N,olefin)Pt(sar)(2-mb)Cl and *trans*-(N,olefin)Pt(S-pro)(2-mb)Cl were also determined [155].

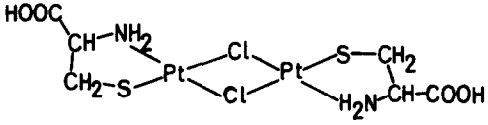
Various Pt(II) complexes of amino acids or their derivatives, COO^- and NH_2 chelated (or with two COO^- groups) were found to present some antitumour activity, but they were less active than cisplatin [9,10,95,96]. It is not known if the mechanism of the antitumour action of these complexes is similar to the one known for cisplatin today.

The interaction of asparagine or of various carboxylamides with K_2PtCl_4, as well as of tryptophane with the hydrolysis products of cisplatin at pH = 7, leads to the formation of platinum blues [156–158]. These are paramagnetic compounds of platinum formed by its partial oxidation in the starting complexes. The amino acid seems to coordinate at least as a bidentate through the carboxylate and the amino group (or of the imino group in the case of asparagine). These compounds are rather oligomers with bridging ligands, but their exact structures are not known. Other amino acids such as alanine [157] do not produce blue compounds under similar reaction conditions.

2.3 Coordination of sulphur-containing amino acids, peptides and their derivatives

Sulphur-containing amino acids (e.g. methionine and cysteine) react very easily with Pt(II) because of the great tendency of sulphur (soft Lewis base) to form bonds with this metal (soft Lewis acid). This fact, in combination with the larger trans effect of sulphur, results in a very different way for the interaction of sulphur-containing amino acids with Pt(II), compared with the other amino acids, which becomes very important for the biological behaviour of the platinum anticancer drugs.

Compounds in which the sulphur amino acid coordinates monodentately through sulphur ($[Pt(S\text{-}metH)_2(NH_3)_2]^{2+}$, $[Pt(S\text{-}cysH)_2Cl_2]$), bidentately through nitrogen and sulphur ($[Pt(N,S\text{-}metH)ClX]$ $(X = Cl^-, NH_3)$, $[Pt(N,S\text{-}metH)(NH_3)_2]^{2+}$, $[Pt(N,S\text{-}metH)_2]^{2+}$, $[Pt(N,S\text{-}CysH)_2]^{2+}$), monodentately and bidentately simultaneously ($[Pt(N,S\text{-}metH)(S\text{-}metH)]^{2+}$) and also, finally, tridentately ($[Pt(S,N,O\text{-}met)Cl]$), have been described [12]. For all the above complexes, dimeric structures were proposed. More recent infrared spectroscopic measurements, however, suggested the structures shown in Fig. 20 for Pt(II) cysteine complexes [159,160]. The infrared bands of the PtS_2O_2 group and of the bis-chelate complexes



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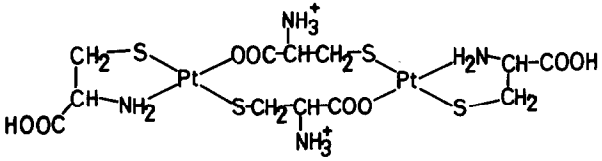

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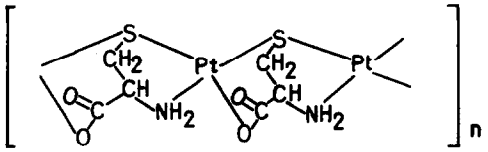


c

Fig. 20. Proposed structures of Pt(II) complexes with cysteine [159,160]: (a) $[Pt(N,S\text{-}cysH)Cl]_2$, (b) $[Pt(N,S\text{-}cysH)(\mu\text{-}O,S\text{-}cys)]_2$ and (c) $[Pt(N,S,O\text{-}cys)]_n$.

cis- and *trans*-[Pt(S,O-cysH)$_2$] have been characterized: $\nu_{Pt-S} = 380–400\ cm^{-1}$, $\nu_{Pt-O} = 540–571\ cm^{-1}$, and $\delta(PtS_2O_2) = 227–236, 160–175\ cm^{-1}$ [161–163].

$[PtCl_4]^{2-}$ reacts rapidly with cysteine to yield complexes with a metal ion:amino acid ratio of 1:1 or 1:2, for which dimeric or polymeric structures were suggested [162]. Later, it was found that, after a few days at 37°C, cisplatin forms a yellow amorphous solid with cysteine, corresponding to the empirical formula $Pt_6C_{21}H_{51}N_8S_5$, which is possibly polymeric, but without any specific structure suggested for it [164].

The interaction of $(Me_3P)_2PtCl_2$ or $(Me_3P)_2Pt(\mu\text{-}OH)_2Pt(PMe_3)_2$ with cysteine or *N*-acetylcysteine (accys) has been studied recently [165]. *N*-Acetylcysteine coordinates through the sulphur atom bridging two platinum ions, thus forming dimers with the formula $[(Me_3P)_2Pt(\mu s\text{-accys})_2Pt(PMe_3)_2]$. Treatment of the last complex with cysteine causes displacement of the bridging ligand by cysteine, which coordinates through N and S giving [$(Me_3P)_2$Pt(N,S-cys)] chelates [165]. The conversion of the dimer complex to the monomer chelate indicates the thermodynamic preference of the amino acid to coordinate through N and S forming stable five-membered chelate rings. It also suggests the possible use of such agents in releasing platinum bound to the sulphur atoms of proteins [165].

Except for the above-mentioned complexes prepared earlier, complexes of platinum with methionine and the dipeptides glycylmethionine (gly-metH) and α-alanyl-methionine (ala-metH) [166–169] were also prepared and characterized. X-ray spectroscopic studies show that the Pt–S bond strength is about equal in complexes with metH and ala-metH but smaller in those with gly-metH [166–169].

The interaction of Pt(II) with methionine in aqueous solution has recently been studied in detail [170,171]. The ligand primarily coordinates as a monodentate through the sulphur atom and chelates in a second step, binding through the amino group. The various products formed depend on the reaction conditions [170].

Certain Pt(II) compounds of methionine present biological activity. More particularly, the complex [Pt(S,N,O-met)Cl] with the amino acid tridentate possesses anticancer activity similar to cisplatin in the model biological system sarcoplasm reticulum (S.R.) [11].

The optical activity of complexes with a 1:1 ratio of Pt:methionine, was studied with circular dichroism and optical rotatory dispersion in aqueous solutions and in the solid state [172].

S-substituted derivatives of cysteine were also used for the synthesis of complexes with Pt(II) of the type $PtLCl_2$ (L = S-ethylcysteine or S-ethylcysteine sulphoxide) and their structures were determined by X-ray diffraction [173–175]. These monomeric complexes are chelates, with the ligand S,N coordinated, and the five-membered ring always has the λ configuration. Such chelates were also isolated in the case of S-alkyl and S-alkylaryl derivatives of cysteine, with platinum [176,177].

The *S*-oxide of methionine (metH-S-ox) was also found by X-ray diffraction, to chelate through sulphur and nitrogen with Pt(II) and to form a monomeric

compound of formula Pt(metH-S-ox)Cl_2 or through S,N and O, forming a dimeric compound of formula [Pt(metH-S-ox)]$_2$, where two nitrogen atoms bridge two metal ions and form a four-membered ring of Pt_2N_2 [178,179] (Fig. 21). The structure of the complex *cis*-dichloroethionine platinum(II) was also recently reported [180], involving simultaneous S,N coordination of the ligand with Pt(II).

The *N*-dithiocarboxyamino acids are interesting ligands, because they can be used for limiting the toxic side effects of the platinum anticancer drugs. Such compounds, known as detoxicants or rescuing agents, bind to the excess of platinum and eliminate it from the organism.

Complexes of platinum with *N*-dithiocarboxyamino acids of the general formula PtL_2 have been prepared and structurally characterized using spectroscopic methods [181,182]. The ligands chelate through their sulphur atoms and the complex contains the PtS_4 group. The thermal stability of such complexes was found to decrease with an increase in the aliphatic chain length of the amino acid used and follows the order Pt(glydtc)$_2$ = Pt(DL-aladtc)$_2$ = Pt(DL-valdtc)$_2$ = Pt(DL-leudtc)$_2$, where dtc = the dithiocarboxy group (CS_2^-) [182].

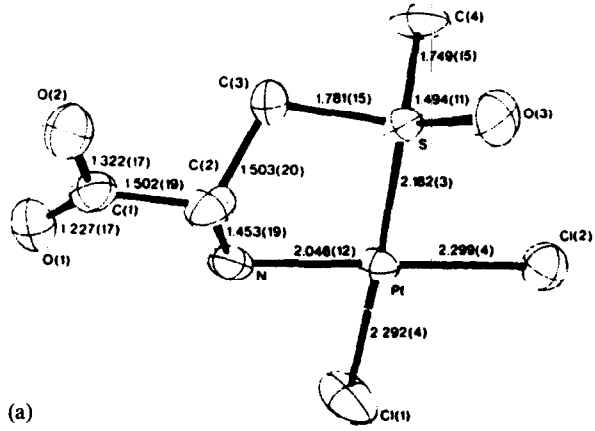
Interaction of the model tetrapeptide [Boc-Cys^1(SCH_3)-Ser^2-Ala^3-Cys^4(SCH_3)-$CONH_2$] with *cis*-Pt(en)Cl_2 was investigated using 1D- and 2D-NMR spectroscopy [183,184] with the aim of mimicking the metallothionein action and possibly discovering a rescue agent. It was found that *cis*-Pt(en)Cl_2 chelates to the tetrapeptide through its 1,4-S(CH_3) atoms, forming a 1:1 complex.

Compounds of formula $LPtCl_2$, where L = *S*-2-aminoethyl-L-cysteine, *S*-2-aminoethyl-DL-penicillamine and peptides containing a 2-aminoethylthio group, with the ligand chelated through sulphur and the neighbouring amino group exhibit anticancer activity [185–187].

The interaction of the carboxylate group of sulphur-containing amino acids with Pt(II) was also detected in aqueous solutions, but the compounds were not isolated in the solid state [188]. The interaction of the hydrolysis products of cisplatin with sulphur-containing amino acids in aqueous solution follows the reactions of Fig. 22 [188].

The monodentate, through sulphur coordination of the amino acid derivatives *N*-acetyl-L-methionine, *N*-acetyl-*S*-methyl-DL-cysteine and *S*-adenosyl-L-homocysteine also produces stable products [189–191]. Such complexes formed from the interaction of these ligands with K_2PtCl_4 possess two diastereomeric forms due to the asymmetry of the coordinated sulphur, which are converted the one into the other according to reaction (15). This transformation was studied by ^{195}Pt NMR spectroscopy and the energy of the process was estimated to be $\Delta G^* = 57–70$ kJ mol^{-1} [189,190].

Compounds such as *S*-adenosyl-L-homocysteine (Fig. 23) are worthy of mention, being nucleoprotein models which are cell constituents, and allow the study of an endocell antagonism for coordination to platinum of a nucleobase and a sulphur-containing compound. The complex [Pt(dien)Cl]$^+$ reacts preferentially with the



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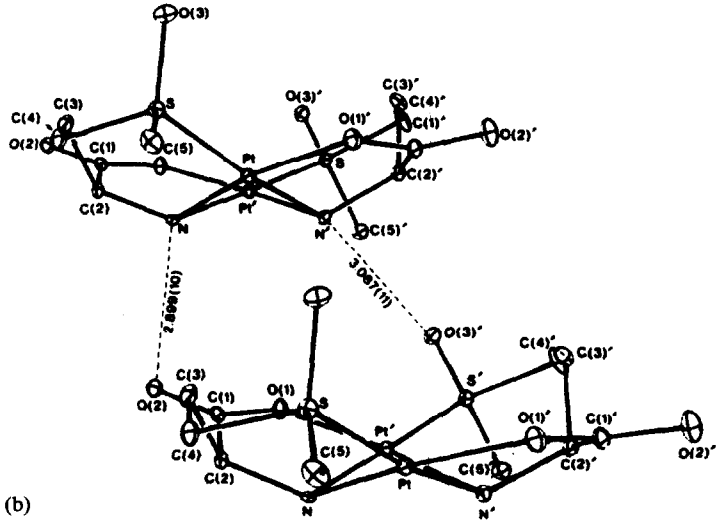

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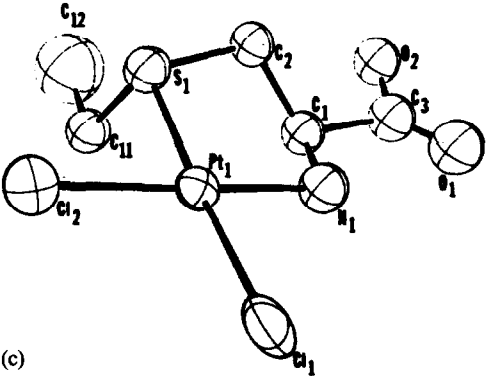


(c)

Fig. 21. Molecular structure of Pt(II) complexes with sulphur-containing amino acids. (a) *S*-oxide of methylcysteine (from ref. 173); (b) *S*-oxide of *S*-methionine (from ref. 179); (c) *S*-ethylcysteine (from ref. 175).

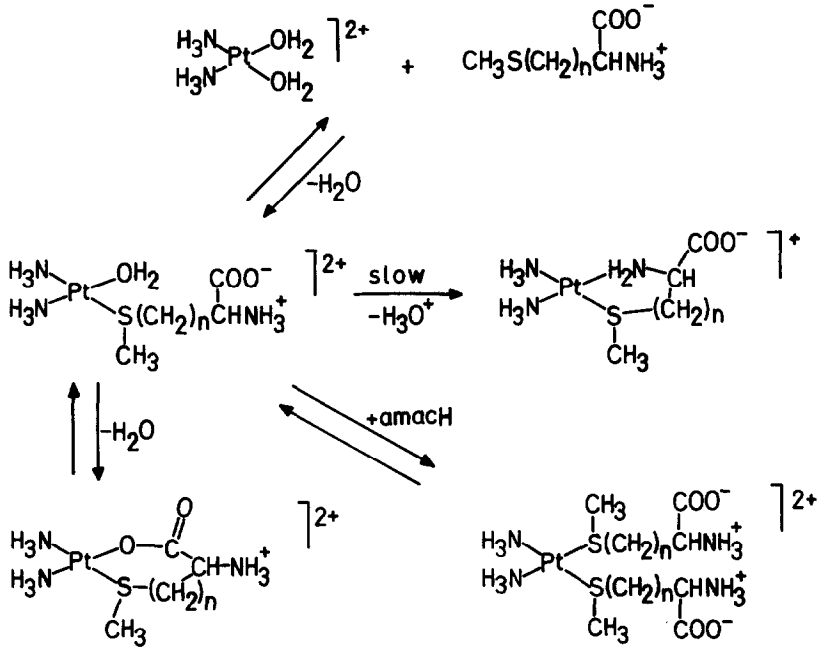
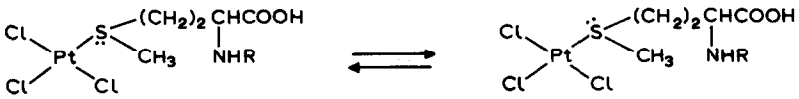


Fig. 22. Interaction of the hydrolysis products of cisplatin with the sulphur-containing amino acids *S*-methylcysteine ($n = 1$) and methionine ($n = 2$).



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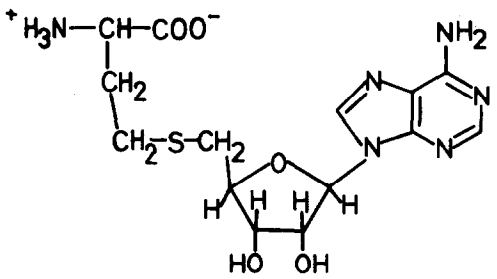


Fig. 23. Formula of *S*-adenosyl-1-homocysteine.

sulphur atom of this compound [191] in acid aqueous solutions (pH < 5), while under basic conditions (pH > 7), a rearrangement of the ligand takes place and it now coordinates in a monodentate fashion through the cysteine amino group. The products were characterized using ^{1}H and ^{195}Pt NMR spectra [191]. A dinuclear complex also forms with coordination of a $[Pt(dien)]^{2+}$ group with sulphur and of a second $[Pt(dien)]^{2+}$ group with the cysteine amino group. Such products were

never observed with either the sulphur-containing amino acids or their simple derivatives [11,159–173,178–182,192,193].

Only a few ternary complexes of Pt(II) with sulphur-containing amino acids and nucleosides were isolated and characterized by spectroscopic methods [177,180,194,195]. In these products of formulae $[PtL(nucl)Cl]$ or $[PtL(nucl)_2]^{2+}$ (L = cysteine methyl ester or its S-substituted derivatives and DL-ethionine), the amino acid is chelated through S and N atoms, while the nucleosides coordinate through N(7) and/or the purine N(1) or the pyrimidine N(3). The formation of such complexes under biological conditions [196] may prevent the formation of the proper cisplatin–DNA bonds that are responsible for the antitumour action of the drug.

The interaction of sulphur-containing peptides with platinum has scarcely been investigated. The reactions of *cis*-$[Pt(CH_3CN)_2Cl_2]$ with cyclo-L-methionyl-L-methionine [197] and of *cis*- and *trans*-DDP with glycylmethionine and *o*-alanylmethionine [198] give products with the dipeptide coordinated only through sulphur. The reaction of $Pt(H_2L)Cl_2$ (H_2L = glycyl-DL-methionine, α-DL-alanyl-DL-methionine) with H_2L, on the other hand, produced $[Pt(H_2L)_2]Cl_2 \cdot 2H_2O$ [199]. This reacted with Ag_2O to give $[Pt(HL)_2] \cdot nH_2O$ ($n = 1, 2$). The dipeptides were coordinated through S and the peptide N atoms.

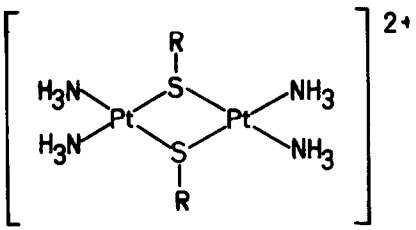
Burgeson and Kostic [200] studied the hydrolysis of unactivated amide bonds in peptides and other amino acid derivatives promoted by Pt(II) and Pt(IV) complexes containing chloro, aqua, iodo, ethylenediamine, 2,2′-bipyridine and 2,2′:6′,2″-terpyridine as ligands. The substrates studied were *N*-acetyl-L-cysteine, *S*-methyl-L-cysteine, *N*-acetyl-*S*-methyl-DL-cysteine, *N*-(2-mercaptopropionyl)glycine, *N*-acetylmethionylglycine, leucylglycine, reduced glutathione, *S*-methylglutathione and oxidized glutathione. The rate constants depend on the substrate, promoter, pH, ionic strength and chloride concentration. Hydrolysis is regioselective and occurs preferentially at the amide bond involving the carboxylic group of the platinated amino acid. K_2PtCl_4 reacts with cytochrome (from horse heart, having 104 amino acids [6]) and binds with the sulphur atom of methionine at position 65 [201]. Very stable protein–Pt(II)–protein cross-links are formed in this way, corresponding to the formula *trans*-$[Pt(cytochrome)_2Cl_2]$, with Pt(II) coordinating with two S atoms of the methionine molecules [201].

The tripeptide glutathione ($glutH_6$ = N-γ-glu-cys-gly-O = ▮ -$OOCCH(NH_3^+)$-$CH_2CH_2CONHCH(CH_2SH)CONHCH_2COOH$) is an important ligand for the study of the interaction of Pt(II) with biological molecules of proteinic nature. This tripeptide is not only a model for the sulphur-containing proteins, but it is also found in cell plasma in concentrations of 0.5–10 mM, and it was suggested [202,203] that it can bind Pt(II) complexes with toxic results (e.g. neuphrotoxicity, caused by the platinum anticancer drugs).

The reaction of $[Pt(dien)Cl]^+$ with glutathione produces the stable binuclear complex $[\{Pt(dien)\}_2(\mu\text{-S-glut}H_5)]^{3+}$ [202]. The reaction is second order, involving a direct nucleophilic attack of the tripeptide sulphur atom on platinum [204]. The

kinetic data also show that the tripeptide reacts with $[Pt(dien)Cl]^+$ faster than does 5′-guanosine monophosphate, but slower than it does with the hydrolized species $[Pt(dien)(H_2O)]^{2+}$ [204]. Cisplatin reacts analogously and produces the complex $[[(NH_3)_2Pt]_2(\mu\text{-S-glut}H_5)_2]$ (Fig. 24) in aqueous solutions according to NMR spectroscopic data [205]. The same behaviour of glutathione was also recently found in the study of its interaction with $(Me_3P)_2PtCl_2$ or $(Me_3O)_2Pt(\mu\text{-OH})_2Pt(PMe_3)_2$ in aqueous solution [165]. Coordination of the glutathione S atom labilizes, as in the case of the sulphur-containing amino acids [12], the ligand at the trans position, which is easily replaced by nucleophilic substituents [164,203,206,207]. This reaction also takes place under biological conditions [206,207] and can lead to the formation of the monomeric *trans*-$[Pt(N,S\text{-glut}H_5)_2]$ complex with bidentate tripeptide coordination through sulphur and the neighbouring amide nitrogen, forming a five-membered chelate ring [164].

To investigate possible products formed with *cis*- and *trans*-$[(NH_3)_2PtCl_2]$ and glutathione and their relation to the nephrotoxic behaviour of *cis*-DDP, Berners-Price and Kuchel [208,209] investigated the reactions of reduced glutathione with the above two complexes in aqueous solution and inside the human red blood cells with multinuclear NMR spectroscopy (^1H, ^{13}C, ^{195}Pt, ^{15}N, etc.). In the human red blood cells, from *trans*-DDP they identified the S-coordinated products *trans*-$[Pt(SG)(NH_3)_2Cl]$, *trans*-$[Pt(SG)_2(NH_3)_2]$ and possibly the S-bridged complex *trans*-$[\{(NH_3)_2PtCl\}_2SG]^+$, and also the mixed complex *trans*-$[Pt(SG)(S\text{-haemoglobin})(NH_3)_2]$ (GSH = reduced glutathione). *cis*-DDP on the other hand, possibly produced high-molecular-weight Pt:GSH and mixed GS–Pt–S (haemoglobin) polymers, exclusively coordinated through S, but with several different Pt–S and Pt–S–Pt environments.



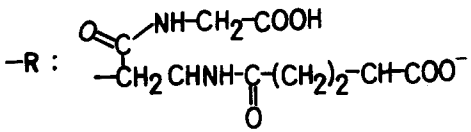


Fig. 24. Product of the reaction of *cis*-$[(NH_3)_2Pt(H_2O)_2]^{2+}$ with glutathione in aqueous solution [205].

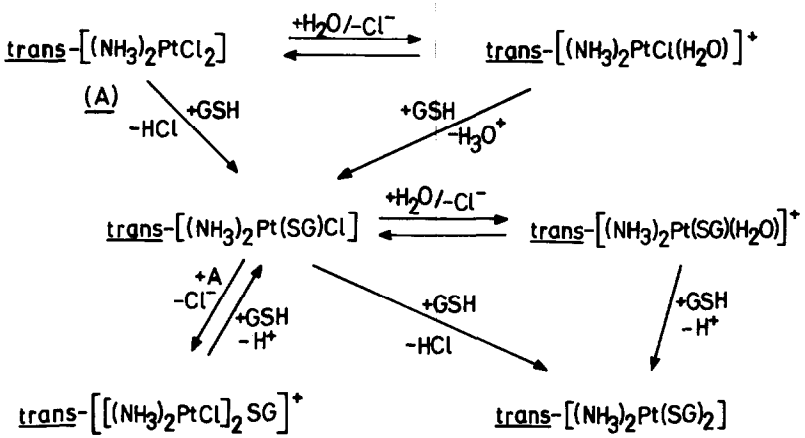


Fig. 25. Proposed scheme for the reaction of *trans*-$[(NH_3)_2PtCl_2]$ with glutathione (GSH).

The reaction of *trans*-$[(NH_3)_2PtCl_2]$ with GSH in aqueous solution follows the scheme (Fig. 25) involving S-coordinated glutathione [209].

Reedijk and co-workers [210], using the model adducts $[Pt(dien)GS]^+$, $[\{Pt(dien)\}_2GS]^{3+}$ and $[Pt(dien)GS\text{-}Me]^{2+}$ of complexes formed during the inhibition of the enzyme fumarase with *cis*-$[(NH_3)_2Pt(H_2O)_2](NO_3)_2$ (binding of an S-methionine site), found using NMR spectroscopy that the rescue agent sodium diethyldithiocarbamate (Naddtc) is a powerful regenerator of enzymatic activity. Thiourea was less active and sodium thiosulphate (STS) almost inactive.

Finally, complexes of the type [Pt(tridentate)Cl] [211] (tridentate = 2,6-pyridinecarboxylate, 2,2′:6′,2″-terpyridine and di(2-pyridyl-β-ethyl) sulphide) were used for stereoselective covalent modifications of proteins. This could be achieved by adjusting the steric properties of the tridentate ligand.

2.4 Organometallic compounds of platinum(II)-containing amino acids and their derivatives

Complexes of amino acids and peptides were prepared using Zeise salt $K[(C_2H_4)PtCl_3]\cdot H_2O$ as the starting material. Thus, the structure of the complex *trans*-(*N*-olefin)-$[Pt(C_2H_4)$ (β-ala)Cl] was determined by X-ray diffraction [212]. β-Alanine chelates through NH_2 and COO^- with the NH_2 group trans to C_2H_4. It was proposed that the formation of this complex is achieved according to reaction (16).

In aqueous solutions, isomerization of these complexes to the thermodynamically more stable *cis*-(*N*-olefin) analogues was observed [213].

The dipeptides L-valine-L-valine, L-valine-L-leucine and L-leucine-L-valine chelate with Pt(II) using all of their donor atoms [214]. The unusual structure of Fig. 26

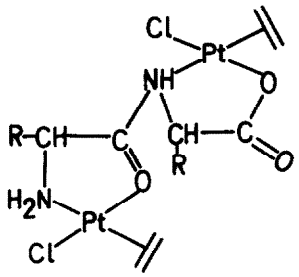
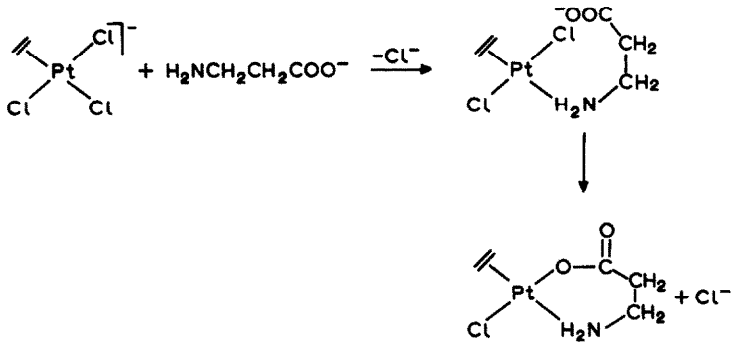


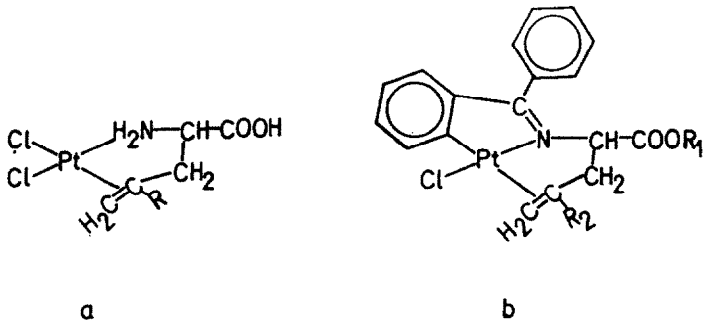
Fig. 26. Proposed structure of complexes of Zeise salt with dipeptides [214].



(16)

was proposed for the products formed [214] based on IR data and on preliminary X-ray diffraction results. The complete structure, however, has not yet been reported.

The attachment of an olefinic group to an amino acid increases the number of donor atoms of the derivative towards a metal ion. Thus, the organometallic compounds of Fig. 27 were isolated from the reaction of K_2PtCl_4 or $PtCl_2$ with *C*-allylglycine or with *N*-(diphenylmethyleno)-*C*-allylglycine ester. These compounds



a b

Fig. 27. Structures of Pt(II) complexes with (a) *C*-allyl glycine and (b) esters of *N*-(diphenylmethyleno)-*C*-allyl glycine [215].

were structurally characterized with spectroscopic methods and X-ray diffraction [215].

More recently [216], syntheses of the complexes $(R_3^1P)Cl_2Pt$(*C*-allylglycine ester) and $[(R_3^1P)Cl–Pt–NH_2CH(COOR^2)-CH_2–CR^3=CH_2]^+BF^-$ have been reported. Enolates (Nu^-) could be added to the coordinated C=C bond to give the γ-C-metallated α-amino acid ester complexes $(R_3^1P)(Cl)–Pt–NH_2CH(COOR^2)CH_2C(R^3)CH_2Nu$. In most cases, platination occurred stereoselectively, producing the five-membered metallocycles with CH_2Nu and $COOR^2$ in a trans position.

With the aim of studying the stereoselective reactions (enantioselective coordination of pro-chiral olefinic compounds), a number of complexes of the type olefin–Pt–amino acid were prepared [217–220]. The structures of the diastereomeric pairs of these complexes are shown in Fig. 28. The absolute configurations of the compounds were studied using CD and NMR spectroscopies.

3. PLATINUM(IV) COMPLEXES OF AMINO ACIDS, PEPTIDES AND THEIR DERIVATIVES

Complex compounds of Pt(IV) with amino acids and their derivatives are much fewer than those with Pt(II). This is due to (a) the difficulty in the preparation of such compounds due to the slower reaction rates of Pt(IV) complexes, (b) the more difficult isolation of the compounds formed since they are more soluble, and (c) the possibility for formation of more products, often diastereomers, the separation of which is not always easy.

However, the chemistry of Pt(IV) complexes with molecules of biological importance is interesting because (a) complexes of this metal ion show biological activity, (b) such compounds can be reduced to the corresponding Pt(II) species with the aid

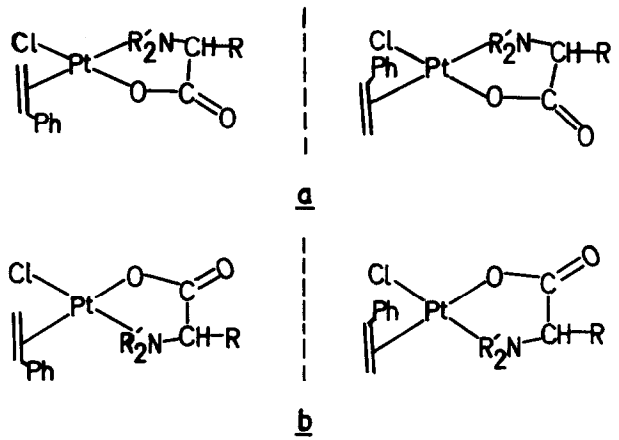


Fig. 28. Diastereomeric forms of (a) *trans*-(N,olefin) and (b) *cis*-(N,olefin) of Pt(II) complexes with olefins and amino acids.

of chemical or biological reducing agents, and (c) the variety of compounds that can be formed is very great and therefore their synthesis (after the necessary planning) and isolation are chemically useful.

For the above reasons, complexes of Pt(IV) with amino acids and their derivatives are prepared mainly by oxidation of the corresponding Pt(II) compounds and not by direct reaction of the ligand with Pt(IV) salts.

3.1 Amino acid coordination through nitrogen

Monodentate complexes of Pt(IV) with the amino acids alanine and glycine coordinated through the amino group were prepared [12,221]. In these compounds, the metal coordination sphere is completed with halogen ions and amines. They can undergo nucleophilic attack on the free carboxylate group of the amino acid with subsequent formation in one step of a chelate complex by substitution of a halogen ion [222–224]. The mechanism proposed for this reaction [223,224] involves the formation of a dinuclear chloro-bridged intermediate of Pt(II)–Pt(IV), as shown in Fig. 29. The formation constant of the chelate complex of Fig. 29 for glycine is of the order of 10^3 [222–224].

Complexes of Pt(IV) with glycine derivatives have also been prepared. For example, using an oxidative addition reaction, complexes of Pt(IV) with the glycine ethyl esters and of the dipeptides glycyl–glycine (gly-gly) and glycylcycloleucine (gly-cgly) were prepared [225] (reaction (17); L = glyOEt, gly-glyOEt and gly-cleuOEt).

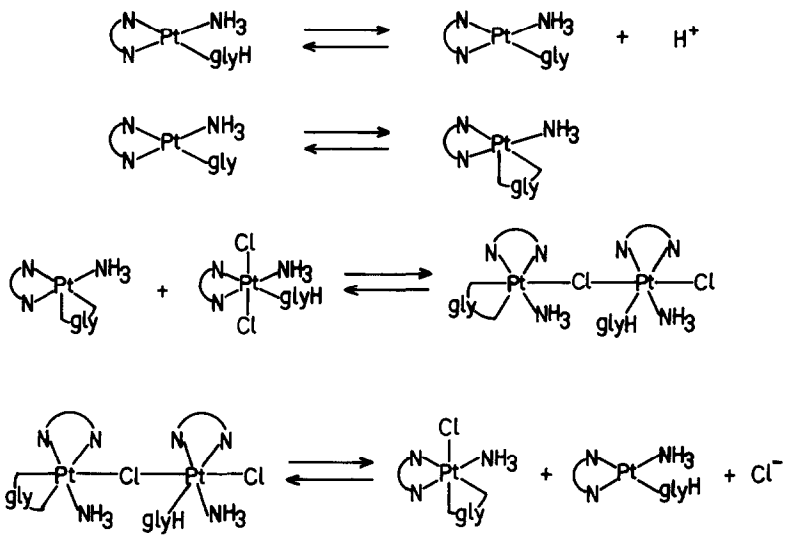
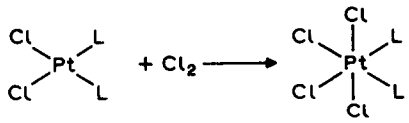


Fig. 29. Mechanism of oxidation of *trans*-$[Pt(en)(NH_3)(glyH)]^{2+}$.



(17)

The products of reaction (17) were characterized by spectroscopic methods (IR, NMR). The L substituent is monodentate through their amino groups.

L-2,3-diaminepropionic acid (*o*-(aminomethyl)glycine, L-Dap) has also been used as a ligand in complexes with Pt(IV) and coordinates in a chelate fashion through its two amino groups. The absolute configuration of the complexes [Pt(L-Dap)Cl_4], [Pt$(en)_2$(L-Dap)]$^{4+}$ prepared by oxidation of the complex [Pt(L-Dap)Cl_2] with chlorine, has been investigated [226]. From the complex with en, the diastereomeric forms $(+)_{312}$-[Pt$(en)_2$(L-Dap)] and $(-)_{320}$-[Pt$(en)_2$(L-Dap)] were separated by use of *d*-tartaric acid. The absolute configurations $\Delta(\lambda_{en}\lambda_{en}\lambda_{Dap})$ and $\Lambda(\delta_{en}\delta_{en}\lambda_{Dap})$ were correspondingly proposed based on the CD and ORD spectra of the complexes [226].

Compounds of Pt(IV) containing monodentate amino groups and dipeptides were prepared by oxidizing the corresponding Pt(II) species with H_2O_2, $KMnO_4$ or Cl_2 [227,228]. Reactions (18) and (19) (L = glycyl-glycine or glycyl-alanine) show the oxidation of the Pt(II) complexes with Cl_2.

$$trans\text{-}[PtL_2Cl_2] + Cl_2 \rightarrow trans\text{-}[PtL_2Cl_4] \quad (18)$$

$$trans\text{-}[PtL_2(NH_3)_2] + Cl_2 \rightarrow trans\text{-}[PtL_2(NH_3)_2Cl_2] \quad (19)$$

3.2 Amino acid coordination through oxygen. Chelate complexes with amino and carboxylate group coordination

Amino acid complexes monodentately coordinated through only the carboxylate group are not known. Formation of the complexes [Pt(*o*-glyH)$_2$(N-glyH)$_2Cl_2$]Cl_2 and [Pt(*o*-glyH)(N-glyH)$_2$(N,O-gly)Cl]Cl_2 by reaction of K_2PtCl_6 with glycine in the solid state has been reported [229], but they are ill characterized and their structure uncertain.

As with Pt(II), the most usual coordination involving a Pt(IV)–O bond, is formation of a chelate ring, with simultaneous amino and carboxylate coordination. Complexes of this type are known for glycine and alanine [12]. Thus, in a study of the formation of glycine chelate complexes (Sect. 3.1), *trans*-[Pt(en)(NH_3)(gly)X] (X = Cl^-, Br^-) was isolated [222–224].

Complexes of the iminodiacetic acid ((*N*-carboxymethyl)glycine) were prepared, on the other hand, by direct reaction of the ligand with K_2PtCl_6 in aqueous solution [148,230]. In the isolated products, the ligand is tridentate in a facial configuration:

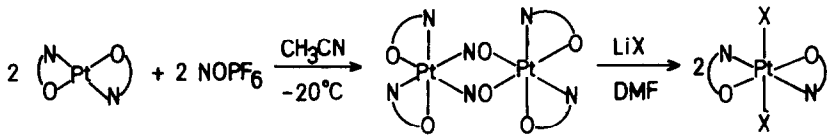


Fig. 30. Oxidation of trans-bis-chelate Pt(II) amino acid complexes, with $NOPF_6$ to the corresponding complexes of Pt(IV) [232] ($\widehat{NO} = H_2NCHRCOO^-$).

fac-K[Pt(ida)Cl_3], *fac*-[Pt(ida)$_2$] (IR, ^{1}H NMR). The latter complex is better prepared by oxidation of the Pt(II) complex Pt(idaH)$_2$ with H_2O_2 [148].

Complexes of Pt(IV) with EDTA (which can be considered as an *N*-substituted derivative of glycine) have been prepared by oxidation of the Pt(II) compounds [Pt(N,N-EDTAH$_2$)Cl_2] and [Pt(N,N,O,O-EDTA)] with Cl_2, but also by direct reaction of K_2PtCl_6 with Na_2(EDTAH$_2$) [231]. In the isolated compounds, the ligand is tridentate through the two nitrogen atoms and the oxygen of the carboxylate or tetradentate through the two nitrogen and the two carboxylate atoms.

The oxidation of the *trans*-[Pt(N,O-amac)$_2$] chelate complexes (amac = gly, ala and cleu) with $NOPF_6$ produces first a Pt(IV) product for which the dimeric structure shown in Fig. 30 was proposed [232]. This is converted to *trans*-[Pt(N,O-amac)$_2X_2$] by treatment with a lithium salt (LiX) (Fig. 30).

Similarly [233], the Pt(II)-N,O coordinated complex *trans*-PtL_2 (HL = L-hydroxyproline) when oxidized with Cl_2, $KMnO_4$ or H_2O_2 gave the Pt(IV) compounds $PtL_2Cl_2 \cdot nH_2O$, $PtL_2(OH)_2 \cdot H_2O_2$ and $PtL_2Cl_2 \cdot EtOH$. Oxidation with Cl_2 did not cause rearrangement of the L ligands, the Cl^- being added into trans axial positions.

3.3 *Sulphur-containing amino acids*

The only known complexes of Pt(IV) with sulphur-containing amino acids are those with methionine [234,235], polymethionine [236] and its ethyl ester [225]. The last of these corresponds to the formula [Pt(N,S-metOEt)Cl_4] and was prepared by interacting the hydrochloride salt of the ligand with the $[PtCl_4]^{2-}$ ion in alkaline media [225]. Oxidation of Pt(MtH)Cl_2 (MtH = methionine) by H_2O_2 produced [Pt(Mt)$_2$]X_2 ($X = NO_3^-$, $\frac{1}{2}PtCl_4^{2-}$, picolinate) with the ligand Mt^-, O,N and S coordinated [237].

Complexes of Pt(IV) with the dipeptides glycylmethionine and alanylmethionine, corresponding to formulae [Pt(LH)$_2Cl_4$] and [Pt(LH)Cl_3], have been prepared [234]. In the former, the dipeptide is bidentate through sulphur and the amide nitrogen, while the latter is tridentate through sulphur, the amino group and the amide nitrogen [234]. In these complexes, prepared by oxidation of the corresponding Pt(II) compounds with Cl_2 or $KMnO_4$, the dipeptide mode of binding is retained from the starting to the final products.

3.4 Organometallic compounds of platinum(IV)-containing amino acids and their derivatives

The only report, by Appleton and co-workers [231,238–244], involves a systematic study of the complexes formed between dimethyl- and trimethyl-platinum(IV) and amino acids and their derivatives. A large variety of products, many of which are given in Fig. 31, have been structurally characterized.

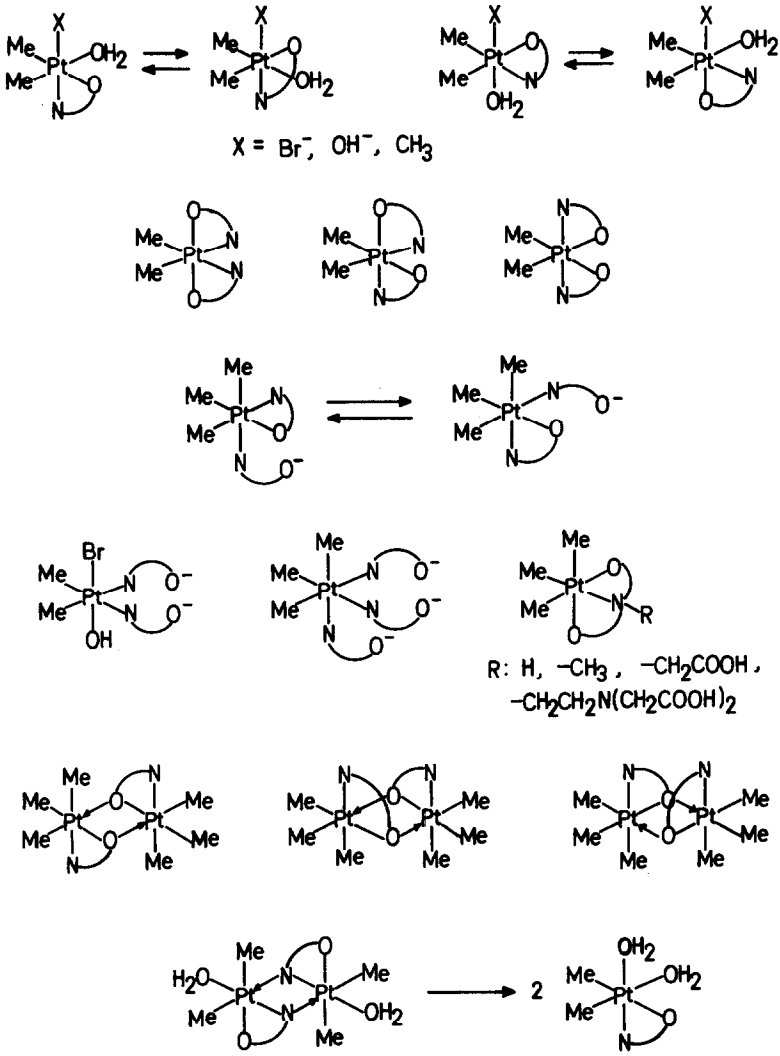


Fig. 31. Complexes of dimethyl and trimethyl platinum(IV) with amino acids and equilibria between the various isomers [231,238–244] (Me = CH_3, $\widehat{NO}$ = $H_2NCHRCOO^-$, $\widehat{ONO}$ = $^-OOCCH_2NRCH_2COO^-$). The charges on the complexes have been omitted for clarity.

nucleophiles. For the same reason, the methyl compounds of Pt(IV) show a large activity and easily react with the amino acids.

The pseudo-first-order rate constants for the isomerization shown in Fig. 31 (top) for $X = Br^-$ were determined by NMR lineshape analysis and were found to be in the range 3×10^{-6} to $1.7 \times 10^2\ s^{-1}$ [244].

4. CONCLUDING REMARKS

The interaction of platinum salts with amino acids, peptides and their derivatives results in the formation of a very large variety of compounds with the ligand coordinated either in a simple way (mono-, bi-, tri- or tetradentate) or bridging different metal ions resulting in the formation of oligonuclear compounds. The amino acids having aliphatic side chains or hydroxyl ions in the side chain, usually form chelated complexes through NH_2 and COO^- groups, but monocoordinate coordination only through NH_2 is also possible. Amino acids possessing a carboxylate group in the side chain can react in the same way as above, though the additional carboxylate group can also occasionally coordinate.

In the sulphur-containing amino acids, the sulphur atom is the preferred coordination site to Pt(II), but the activity of the NH_2 and COO^- groups may lead to simultaneous coordinations and the formation of oligomers or polymers.

The amide N and the peptide O atoms are also coordination sites for Pt(II) in peptide complexes [12].

Many complexes formed between amino acids–peptides and Pt(II) were prepared and studied as possible models for the more general interaction of proteins with the metal in vivo, while a number were screened as possible anticancer drugs without great success. Though the possibility for the preparation of new improved anticancer drugs based on platinum–amino acid complexes does not seem likely, undoubtedly the study of the interaction of the metal with amino acids and their derivatives may contribute to elucidation of the causes of toxicity of the platinum anticancer drugs.

The interaction of platinum with sulphur-containing amino acids and their derivatives may constitute the basis of the toxicity exhibited by platinum anticancer drugs. The study of such interactions is rather complex and leads to formation of various products. More research should be done in this area to understand the side effects of the platinum drugs.

The study of ternary platinum complexes with amino acids–peptides and nucleobases–nucleosides, etc., is interesting because it is expected to give information concerning the interaction of the metal with enzymatic systems and other biological processes to which peptides–proteins and/or DNA and RNA are taking part, and especially to elucidate the possible non-covalent interactions of the different macromolecules coordinated simultaneously with the same metal.

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