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Coordination Chemistry Reviews
166 (1997) 313–359

COORDINATION
CHEMISTRY
REVIEWS

Donor atom preferences in complexes of platinum and palladium with amino acids and related molecules

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Received 14 March 1997; accepted 16 April 1997

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PII S0010-8545(97)00047-7

Abstract

Amino acids present metal ions with a choice of potential donor atoms. The preferences for a particular donor atom for palladium(II) depends primarily on relative thermodynamic stabilities of the complexes formed, but for platinum thermodynamically less preferred complexes may be kinetically preferred, leading often to spontaneous conversion of a metastable complex into a thermodynamically preferred linkage isomer. Sizes of potential chelate rings often play a crucial role in determining donor atom preferences. On a more subtle level, when geometric isomers are possible with the same set of donor atoms bound to the metal, there may frequently be thermodynamic or kinetic preferences for a particular isomer depending on *trans* influences and *trans* effects of other ligands. These preferences are most marked when the *trans* influences of some of these ligands are very high, as in methylplatinum(IV) complexes. The review focuses on results obtained in the author's laboratory, and on related work of other groups. © 1997 Elsevier Science S.A.

Keywords: Platinum; Palladium; Amino acids; Donor atom; Linkage isomers

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1. List of abbreviations

(Acidic H-atoms are underlined in formulae. Atom numbering used in text is given where appropriate)

Hγaba	γ-aminobutyric acid, $^{+}N\underline{H}_3(CH_2)_3CO_2^-$
H_3acys	*N*-acetylcysteine, $CH_3C(O)N\underline{H}CH(CH_2S\underline{H})CO_2\underline{H}$
H_2acgly	*N*-acetylglycine, $CH_3C(O)N\underline{H}CH_2CO_2\underline{H}$
H_3achis	*N*-acetylhistidine, $CH_3C(O)N\underline{H}CH(CO_2^-)CH_2(C_3H_2N_2\underline{H}_2^+)$
H_2acmecys	*N*-acetyl-*S*-methylcysteine, $CH_3C(O)N\underline{H}CH(CH_2SMe)CO_2\underline{H}$
H_2acmet	*N*-acetylmethionine, $CH_3C(O)N\underline{H}CH(CH_2CH_2SMe)CO_2\underline{H}$
H_2aep	aminoethylphosphonic acid, $^{+}N\underline{H}_3(CH_2)_2PO_3\underline{H}^-$
Hαala	α-alanine, $^{+}N\underline{H}_3CHMeCO_2^-$
Hβala	β-alanine, $^{+}N\underline{H}_3(CH_2)_2CO_2^-$

$\mathrm{H_2amal}$	2-aminomalonic acid[a], $\mathrm{H_2N{-}CH(CO_2\underline{H})_2}$
$\mathrm{H_2amp}$	aminomethylphosphonic acid, $\mathrm{{}^{+}N\underline{H}_3CH_2PO_3\underline{H}^{-}}$
$\mathrm{H_2app}$	aminopropylphosphonic acid, $\mathrm{{}^{+}N\underline{H}_3(CH_2)_3PO_3\underline{H}^{-}}$
$\mathrm{H_2asp}$	aspartic acid, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})(CH_2CO_2\underline{H})}$
bpy	2,2′-dipyridyl, $\mathrm{(C_5H_4)_2}$
$\mathrm{H_2cys}$	cysteine, $\mathrm{{}^{+}N\underline{H}_3CH(CH_2S\underline{H})CO_2^{-}}$
Hdab	2,4-diaminobutyric acid, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})(CH_2)_2NH_2}$
dach	1,2-diaminocyclohexane, $\mathrm{C_6H_{10}(NH_2)_2}$
Hdap	2,3-diaminopropionic acid, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})CH_2NH_2}$
dien	diethylenetriamine, $\mathrm{HN(CH_2CH_2NH_2)_2}$
$\mathrm{H_2digly}$	*N*-glycylglycine, $\mathrm{{}^{+}N_{(1)}\underline{H}_3CH_2C(O_{(1)})N_{(2)}\underline{H}CH_2CO_{(2)}O_{(3)}^{-}}$
dmso	dimethylsulphoxide, $\mathrm{Me_2SO}$
$\mathrm{H_2edda}$	*N*,*N*′-ethylenediaminediacetic acid[a], $\mathrm{\underline{H}O_2CCH_2NH(CH_2)_2NHCH_2CO_2\underline{H}}$
$\mathrm{H_4edta}$	*N*,*N*,*N*′,*N*′-ethylenediaminetetraacetic acid[a], $\mathrm{(\underline{H}O_2CCH_2)_2N(CH_2)_2N(CH_2CO_2\underline{H})_2}$
en	ethylenediamine, $\mathrm{NH_2(CH_2)_2NH_2}$
Hetcys	*S*-ethylcysteine, $\mathrm{{}^{+}N\underline{H}_3CH(CH_2SEt)CO_2^{-}}$
$\mathrm{H_2glu}$	glutamic acid, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})(CH_2CH_2CO_2\underline{H})}$
Hgly	glycine, $\mathrm{{}^{+}N\underline{H}_3CH_2CO_2^{-}}$
Hglyam	glycinamide, $\mathrm{N_{(1)}H_2CH_2C(O)N_{(2)}\underline{H}_2}$
glyOEt	glycine ethyl ester, $\mathrm{NH_2CH_2C(O)OEt}$
HglyNOH	glycinehydroxamic acid, $\mathrm{NH_2CH_2C(O)N\underline{H}OH}$
GSH[b]	glutathione, $\mathrm{{}^{+}NH_3CH(CO_2^{-})(CH_2)_2C(O)NHCH(CH_2S\underline{H})C(O)NHCH_2CO_2H}$
$\mathrm{H_2his}$	histidine, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})CH_2(C_3H_2N_2\underline{H})}$
$\mathrm{H_2ida}$	iminodiacetic acid[a], $\mathrm{HN(CH_2CO_2\underline{H})_2}$
$\mathrm{H_4idmp}$	iminobis(methylenephosphonic acid[a], $\mathrm{HN(CH_2PO_3\underline{H}_2)_2}$
$\mathrm{H_3impa}$	*N*-(phosphonomethyl)glycine[a], $\mathrm{HN(CH_2PO_3\underline{H}_2)(CH_2CO_2H)}$
Hlys	lysine, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})(CH_2)_4NH_2}$
Hmecys	*S*-methylcysteine, $\mathrm{{}^{+}N\underline{H}_3CH(CH_2SMe)CO_2^{-}}$
Hmet	methionine, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})(CH_2)_2SMe}$
$\mathrm{H_2mida}$	*N*-methyliminodiacetic acid[a], $\mathrm{MeN(CH_2CO_2\underline{H})_2}$
$\mathrm{H_3nta}$	nitrilotriacetic acid[a], $\mathrm{N(CH_2CO_2\underline{H})_3}$
$\mathrm{H_6ntmp}$	nitrilotris(methylenephosphonic acid[a], $\mathrm{N(CH_2PO_3\underline{H}_2)_3}$
Horn	ornithine, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})(CH_2)_3NH_2}$
$\mathrm{H_2pen}$	penicillamine, $\mathrm{{}^{+}N\underline{H}_3CH(CO_2^{-})CMe_2S\underline{H}}$
RSH[b]	Thiolate ligand
sah	*S*-adenosyl-L-homocysteine (structure **135**)
sgh	*S*-guanosyl-L-homocysteine (structure **136**)
tpy	2,2′,6′,2″-terpyridine
$\mathrm{H_2uedda}$	*N*,*N*-ethylenediaminediacetate[a], $\mathrm{H_2N(CH_2)_2N(CH_2CO_2H)_2}$

[a] For simplicity, drawn in uncharged rather than zwitterion form.

[b] Overall charges are not shown for complexes with these ligands.

2. Introduction

Even the simplest amino acid, such as glycine, has a relatively complex coordination chemistry, in that it has the potential to bind to a metal ion monodentate through either nitrogen or oxygen, to form a five-membered *N,O*-chelate ring or a four-member *O,O'*-chelate ring, to bridge between two metal ions through N and O, or through the carboxylate oxygen atoms. For more complex amino acids, with more potential donor atoms, there are many more possibilities. Platinum and palladium form stable complexes with the *N*-, *O*- and *S*-donors commonly present in amino acids, with thermodynamic preference for *S*- and *N*-donors over *O*-donors. When an amino acid is presented with a metal complex containing several easily displaced ligands, the thermodynamically preferred product will usually be that in which the maximum number of chelate rings is formed – for example, a *N,O*-chelate ring for glycinate, *facial N,O,S*-tridentate coordination for methioninate with an octahedral metal ion. Of greater potential interest is the coordination mode which is adopted when the preferred geometry of the metal ion (e.g. square planar for Pt^{II}, Pd^{II}) is inconsistent with the preferred coordination mode of the ligand, or when the number of potential coordination sites is restricted to one or two. While the thermodynamic preference of the metal ion for a particular donor atom is a very important parameter in determining the choice of donor atom, at the pH of the experiment this donor atom may be protonated. The effect of chelate ring size may also be a factor in determining the coordination mode adopted. Even when the set of donor atoms used by the ligand is the same, there may be relatively subtle preferences for one geometric isomer over another when coordination sites differ because of differing *trans* influences of other ligands present.

The chemistry of amino acid complexes with the following metals has been reviewed (platinum metals [1], palladium [2], platinum [3]). This review does not attempt to cover the whole field of amino acid complexes with these metal ions, but focuses on situations where more than one potential coordination mode is possible. The major emphasis will be on results obtained from my laboratory in determining the preferred binding modes of amino acids and related molecules (such as aminoalkylphosphonates) to platinum and palladium, with reference to the work of others which places it in context. Some comparisons will also be made with related chemistry of other metal ions.

Because of the interest in the biological chemistry of platinum ammine complexes engendered by the anti-tumour activity of *cis*-$[PtCl_2(NH_3)_2]$ and analogues, ammines and amines have often been used as relatively non-labile ligands to block coordination sites on platinum(II) from access by the amino acid. When ligands of high *trans* effect (e.g. sulphur donors) bind to platinum(II), it is useful to use chelating amine ligands such as ethylenediamine (en) or diethylenetriamine (dien), and it is necessary to use such chelating ligands with palladium(II) because of the lability of monodentate ammine ligands [4]. In probing the response of the ligands to the *trans* influences of other ligands, di- and trimethylplatinum(IV) complexes have been used, because of the very high *trans* influence of methyl ligands and the robustness of the platinum–methyl bonds.

Most of the results summarised here are based on multinuclear NMR studies of aqueous solutions. This review will refer only in passing to these spectroscopic results. For details the reader is referred to the original articles.

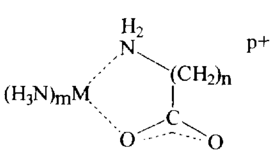
3. Complexes with amino acids $^{+}NH_3(CH_2)_nCO_2^-$

3.1. Complexes formed when one metal coordination site is available

3.1.1. Platinum(II) complexes

Reaction of $[Pt(NH_3)_3(H_2O)]^{2+}$ with glycine at pH 3 gave initially $[Pt(NH_3)_3(Hgly\text{-}O)]^{2+}$. Since glycine nitrogen (pK_a 9.8) is protonated under these conditions and the carboxyl group (pK_a 2.35) partially deprotonated, carboxylate oxygen is more available for reaction than the amine nitrogen. This complex was slowly converted into $[Pt(NH_3)_3(gly\text{-}N)]^+$ at ambient temperature. This reaction was inhibited by acid, but proceeded slowly even at pH 1.5. It could not be reversed. The kinetic product, with glycine *O*-bound, which is sufficiently stable to allow spectroscopic measurements, but which is ultimately converted to the thermodynamic product, has been termed "metastable". The isomerization reaction is intramolecular [5].

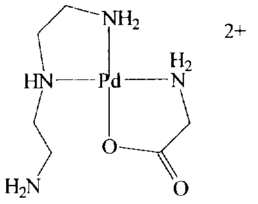
β-alanine has an additional methylene group. Its complex, $[Pt(NH_3)_3(H\beta ala\text{-}O)]^{2+}$, did not isomerise at pH 4.5, but there was slow formation of $[Pt(NH_3)_3(\beta ala\text{-}N)]^+$ in alkaline solution. For the γ-aminobutyric acid complex $[Pt(NH_3)_3(\gamma aba\text{-}O)]^+$ standing at pH 10 caused only slow displacement of the carboxylate-bound ligand by hydroxide [5]. The $-NH_3^+$ group of the coordinated amino acid is likely to be less acidic for the longer-chain ligands, but this is unlikely to cause the large differences in reactivity in solutions sufficiently alkaline for even a less acidic amine group to be deprotonated. With a five-coordinate intermediate **1** (M = Pt, $m = 3$, $p = 1$) for these isomerization reactions, unfavourable entropy of activation is a probable reason for the decrease in reactivity as n increases. Platinum(II)-hydroxide bonds are relatively inert. It is therefore not surprising that the reaction of $[Pt(NH_3)_3(OH)]^+$ with each of these amino acids near pH 10 produced $[Pt(NH_3)_3\{NH_2(CH_2)_nCO_2\}]^+$ only very slowly [5].



1

An analogous reaction between $[Pt(dien)(H_2O)]^{2+}$ and glycine gave initially $[Pt(dien)(Hgly\text{-}O)]^{2+}$, followed by isomerization to $[Pt(dien)(Hgly\text{-}N)]^{2+}$. The dinuclear complex $[(dien)Pt\text{-}NH_2CH_2CO_2\text{-}Pt(dien)]^{3+}$ was also formed, and was much more stable kinetically than $[Pt(dien)(Hgly\text{-}O)]^{2+}$ [6].

3.1.2. Palladium(II) complexes



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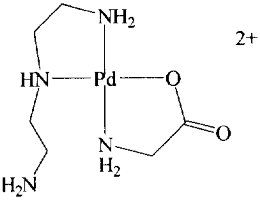


3

Reaction of $[Pd(dien)(H_2O)]^{2+}$ with glycine at pH 7.4 gave only $[Pd(dien)(gly\text{-}N)]^{+}$. At pH 3.6, this complex was in equilibrium with $[Pd(dien)(gly\text{-}O)]^{+}$, $[(dien)Pd\text{–}NH_2CH_2CO_2\text{–}Pd(dien)]^{3+}$ and the two isomers (**2**,**3**) of the complex with chelated glycinate and partially protonated dien. At pH 1.2, the proportions of species present changed, but $[Pd(dien)(Hgly\text{-}N)]^{2+}$ was still present. From the pH dependence of δ_C for the methylene carbon atom of $[Pd(dien)(Hgly\text{-}O)]^{2+}$, it was possible to estimate the pK_a value for deprotonation of the nitrogen atom in this complex as approximately 2.9. This represents a very large enhancement in acidity compared with zwitterionic glycine (pK_a 9.8) [6].

With the more labile palladium species, a metastable kinetic product is not observed, but the composition of the reaction mixture is determined entirely by equilibrium constants. With platinum, the *O*-bound glycine complex is observed as a metastable kinetic product, but equilibrium, even in acid, strongly favours *N*-bound glycine. The *O*-bound isomer is thermodynamically more stable relative to *N*-bound for Pd^{II} relative to Pt^{II}, reflecting a greater "hardness" for palladium.

3.1.3. Comparison with complexes of other metal ions

There are examples of linkage isomerism of coordinated glycine for other metal ions. Fujita *et al.* [7] prepared $[Co(NH_3)_5(Hgly\text{-}O)]^{3+}$, with glycine bound to cobalt through carboxylate oxygen, by reaction of $[Co(NH_3)_5(H_2O)]^{3+}$ with glycine in acid solution. The isomer with glycine bound through nitrogen could not be obtained by heating the complex with carboxylate bound [7]. Heating at pH 10 for 3 h gave no evidence for formation of $[Co(NH_3)_5(gly\text{-}N)]^{2+}$. Instead, the major products appeared to be complexes with glycinate chelated, following loss of ammonia [8]. Buckingham *et al.* [9] obtained this isomer by hydrolysis of the ester group of $[Co(NH_3)_5(\text{–}NH_2CH_2CO_2Et)]^{3+}$, which, in turn, was prepared by reaction of ethyl glycinate with $[Co(NH_3)_5\{OP(O^nBu)_3\}]^{3+}$ in tri-*n*-butyl phosphate solvent.

Chatterjee and Basak [10] prepared $[Rh(NH_3)_5(Hgly\text{-}O)]^{3+}$ in a similar way to the cobalt analogue. This complex was stable indefinitely in aqueous solution at pH 3.5, even when heated, but heating a solution for 3 h at pH 10 caused complete conversion to $[Rh(NH_3)_5(gly\text{-}N)]^{2+}$. Experiments with isotopically labelled glycine showed that there was no exchange of free and bound glycine in the course of the reaction [8]. This reaction must therefore occur *via* an intermediate **1** ($M=Rh$, $m=5$, $n=1$, $p=2$) in which both N and O of glycinate are bound to rhodium. The ability of the rhodium complex, but not the cobalt analogue, to undergo this reaction may reflect the greater tendency of rhodium(III) to undergo associative reactions compared with cobalt(III). The isomerization from *O*- to *N*-bound glycine or glycinate could not be reversed [8]. Under conditions where the glycinate complexes isomerised, $[Rh(NH_3)_5(\beta ala\text{-}O)]^{2+}$ did not react [8]. The greater decrease in entropy of activation involved in forming the intermediate **1** ($M = Rh$, $m = 5$, $p = 2$) when $n = 2$ compared with $n = 1$ is probably largely responsible for the difference in reactivity.

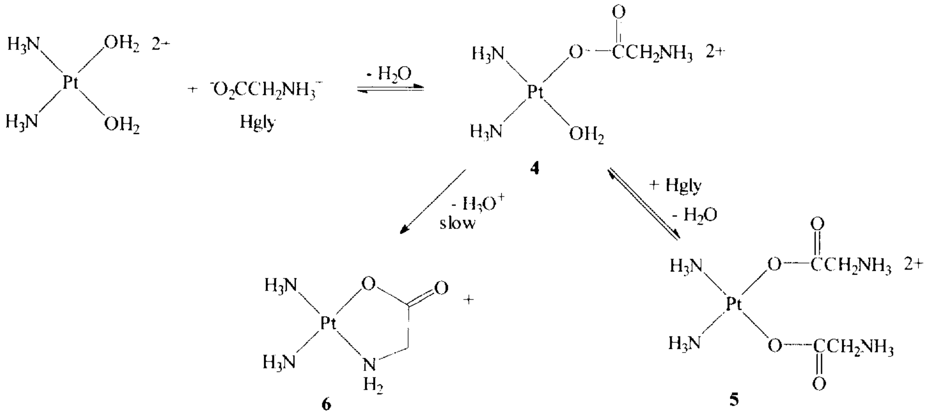
Diamond and Taube [11] prepared $[Ru(NH_3)_5(Hgly\text{-}N)]^{2+}$ by reaction of $[Ru(NH_3)_5(H_2O)]^{2+}$ with Na(gly), followed by acidification. Oxidation of this complex produced initially $[Ru(NH_3)_5(Hgly\text{-}N)]^{3+}$, which rapidly isomerized to $[Ru(NH_3)_5(Hgly\text{-}O)]^{3+}$ by an intramolecular mechanism. They estimated the half-life of $[Ru(NH_3)_5(gly\text{-}N)]^{2+}$ with respect to the isomerization reaction as 21 s. At $pH \geq 7$ there was an equilibrium between the isomers of $[Ru(NH_3)_5(gly)]^{2+}$, with the proportion of *N*-glycinato complex increasing at higher pH. There was no indication of any Ru^{II} complex with glycine *O*-bound in equilibrium with $[Ru(NH_3)_5(Hgly\text{-}N)]^{2+}$ in acid solution. The preference for the *O*-bound isomer for Ru^{III} reflects the "harder" character of the metal in the higher oxidation state.

3.2. *Complexes formed when two metal coordination sites are available*

3.2.1. *Platinum(II) complexes*

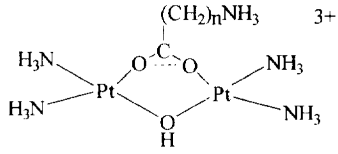
It has been well established that *N,O*-chelation is a characteristic coordination mode for glycinate bound to platinum(II). For example, Freeman and Golomb [12] determined the crystal structure of *trans*-$[Pt(gly\text{-}N,O)_2]$. It has also long been evident that the *N,O*-chelate ring could be readily cleaved by reaction with excess glycinate, to give complexes containing *N*-glycinate, or by reaction with HCl, to give complexes containing *N*-glycine. For example, reaction of $K_2[PtCl_4]$ with excess glycinate gives $[Pt(gly\text{-}N)_4]^{2-}$, which may be acidified to precipitate $[Pt(Hgly\text{-}N)_2(gly\text{-}N)_2]$ [13,14], and reaction of *cis*- or *trans*-$[Pt(gly\text{-}N,O)_2]$ with hot concentrated HCl gives the corresponding isomer of $[PtCl_2(Hgly\text{-}N)_2]$ [13]. The crystal structure of *cis*-$[PtCl_2(Hgly\text{-}N)_2]$ was determined by Baidina *et al.* [15].

Grinberg [16] and Gil'dengershel [17] showed that reaction of *cis*-$[PtCl_2(NH_3)_2]$ with glycinate gives $[Pt(NH_3)(gly\text{-}N,O)]Cl$ and (with excess glycinate) *cis*-$[Pt(NH_3)_2(gly\text{-}N)_2]$, and Pivcová *et al.* [18] confirmed that these products are obtained when the reaction is carried out under physiological conditions. However, reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with glycine gave initially a metastable complex with monodentate glycine bound only through carboxylate oxygen (**4**) which slowly underwent chelate ring closure to $[Pt(NH_3)_2(gly\text{-}N,O)]^+$ (**6**) [19,20] (Scheme 1). The reaction was slowed but not prevented by acid. In the reaction of *cis*-$[PtCl_2(NH_3)_2]$ with glycine, *cis*-$[Pt(NH_3)_2Cl(Hgly\text{-}O)]^+$ was not detected as an intermediate. A solution containing this species was obtained by addition of chloride to **4**, and slowly underwent ring closure. Since chloride is less labile than aqua, displacement of chloride from *cis*-$[PtCl_2(NH_3)_2]$ was the slowest step in the sequence of reactions leading to **6** [5].



Scheme 1.

There was no detectable reaction between *cis*-$[Pt(NH_3)_2(OH)_2]$ and glycinate at pH 12.8, but slow reaction occurred at pH 9–11, probably *via* traces of aqua complexes in equilibrium with the dihydroxo complexes. The initial product was *cis*-[Pt(NH_3)$_2$(gly-*N*)(OH)], which slowly underwent ring closure to [Pt(NH_3)$_2$(gly-*N,O*)]$^+$ (**6**) which, in turn, reacted with free glycinate to give *cis*-[Pt(NH_3)$_2$(gly-*N*)$_2$]. If acid was added to decrease the pH of a solution of *cis*-[Pt(NH_3)$_2$(gly-*N*)(OH)] to 6 (which would produce initially *cis*-[Pt(NH_3)$_2$(gly-*N*)(H_2O)]$^+$) ring closure to **6** occurred rapidly [20].



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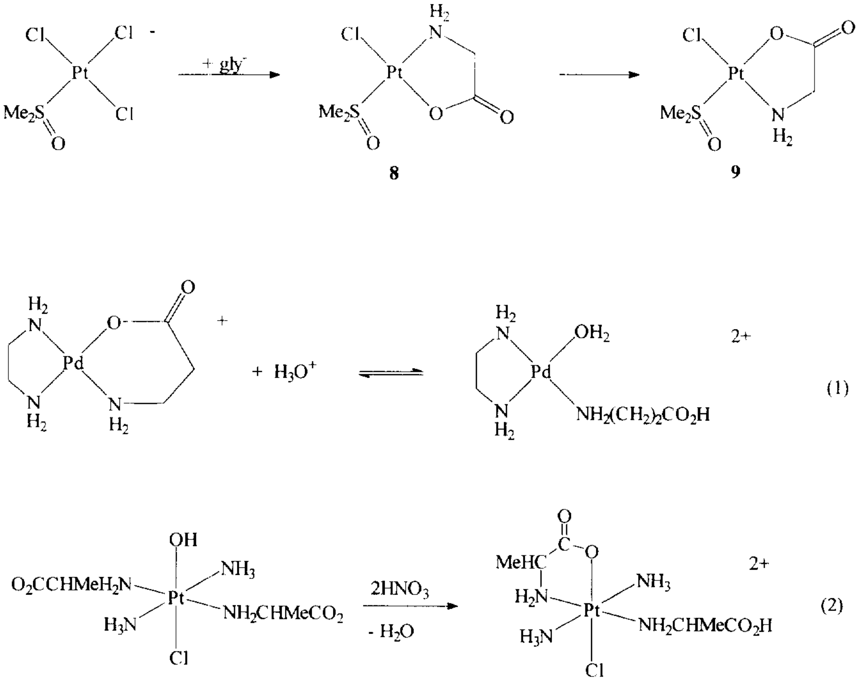
With the longer-chain amino acids β-alanine and γ-aminobutyric acid, the carboxylate-bound complex analogous to **4** was much more stable kinetically. At pH 5.5, heating at 80 °C for several hours was required to produce [Pt(NH_3)$_2$(βala-*N,O*)]$^+$, and prolonged heating at 90 °C to produce [Pt(NH_3)$_2$(γaba-*N,O*)]$^+$. In solutions from *cis*-[Pt(NH_3)$_2$(H_2O)$_2$]$^{2+}$ with these longer-chain amino acids that were allowed to stand at pH 5.5, there was present, in addition to the complexes with carboxylate-bound ligand analogous to **4** and **5**, a dinuclear complex with bridging carboxylate, **7** ($n=2$ or 3). There was only a trace of the analogous complex **7** ($n=1$) with in solutions obtained with glycinate [5]. The crystal structure of the acetate analogue, [{*cis*-Pt(NH_3)$_2$}$_2$(μ-O_2CCH_3)(μ-OH)](NO_3)$_2$ has been determined [21]. The effect of increasing chain length on ring closure from the *O*-bound complexes in this series paralleled the decrease, with increase in *n*, of the rate of ring closure in $[PtCl_2(\text{-}NH_2(CH_2)_nCO_2)_2]^{2-}$ [22].

Reaction of $[Pt(H_2O)_4]^{2+}$ with glycine at pH 3 gave $[Pt(Hgly\text{-}O)(H_2O)_3]^{2+}$ and *cis*- and *trans*-$[Pt(Hgly\text{-}O)_2(H_2O)_2]^{2+}$. If the pH of the solution was maintained at 3–4, there was slow precipitation of the isomers of $[Pt(gly\text{-}N,O)_2]$ contaminated by platinum(II) hydroxide [20].

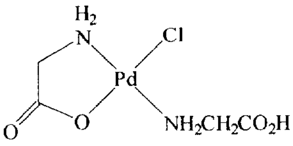
Erickson and Hahne [23] provided an example of the effects of the *trans* ligand on both kinetic and thermodynamic preferences for a particular isomer of a glycinate complex. Reaction of $[PtCl_3(dmso)]^-$ with glycinate gave initially the isomer **8** with N *trans* to dmso (Scheme 2). As dmso has higher *trans* effect than chloride, chloride *trans* to dmso was displaced by glycinate N, followed by ring closure. There was then slow isomerization to the thermodynamically more stable isomer, **9**. This thermodynamic preference is in keeping with the general rule [24] that the most stable isomer is that in which the ligand of weakest *trans* influence (in this case, glycinate O) is *trans* to the ligand of strongest *trans* influence (in this case dmso).



Scheme 2.

3.2.2. Palladium(II) complexes

As with platinum(II), *N,O*-chelated glycinate and *N*-bound monodentate glycine or glycinate are common coordination modes for glycine with palladium(II). For example, Baidina *et al.* determined the crystal structures of *cis*-$[Pd(gly\text{-}N,O)_2]\cdot 3H_2O$ [25], $K[PdCl_2(gly\text{-}N,O)]$ [26] and $[PdCl(gly\text{-}N,O)(Hgly\text{-}N)]$ (**10**) [27].



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In reactions of $[Pd(en)(H_2O)_2]^{2+}$ with amino acids, "metastable" kinetic products are not observed under normal conditions, but the reaction products are at equilibrium. The reaction with glycine at pH 4 produced the chelate complex $[Pd(en)(gly\text{-}N,O)]^+$. If no excess glycine was present, this complex remained stable up to pH 10, but at pH 12 the predominant species was $[Pd(en)(gly\text{-}N)(OH)]$. With excess glycinate near pH 10, $[Pd(en)(gly\text{-}N)_2]$ was formed. At pH 1, a small proportion of the complex with glycine bound through carboxylate oxygen, $[Pd(en)(Hgly\text{-}O)(H_2O)]^{2+}$, was in equilibrium with the diaqua complex and the chelate complex [28].

With β-alanine, the chemistry was overall analogous to that of glycine, with a slightly lower stability of the six-membered *N,O*-chelate ring relative to monodentate coordination. Thus, with no excess ligand, the chelate complex $[Pd(en)(\beta ala\text{-}N,O)]$ was dominant over the pH range 4–10, but at pH 10 (lower pH than for glycinate) $[Pd(en)(\beta ala\text{-}N)(OH)]$ began to form. With excess β-alanine in alkali, $[Pd(en)(\beta ala\text{-}N)_2]$ formed. At pH 2.5, the proportion of $[Pd(en)(\beta ala\text{-}O)(H_2O)]^{2+}$ relative to chelate complex was much higher than with glycine. As well, NMR peaks were broadened from the rapid ring-opening reaction (1), which was not observed with the glycinate analogue [28].

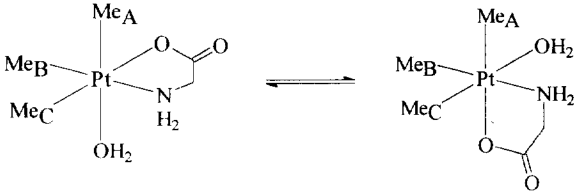
With γ-aminobutyric acid, at pH 7.9, and no excess ligand, the complex containing a 7-membered chelate ring, $[Pd(en)(\gamma aba\text{-}N,O)]^+$ was in equilibrium with the isomers of $[\{Pd(en)(\gamma aba\text{-}\mu\text{-}N,O)\}_2]^{2+}$, with the amino acid bridging between two Pd atoms. At pH 12, the major species was $[Pd(en)(\gamma aba\text{-}N)(OH)]$, but near pH 10 this species was in equilibrium with $[Pd(en)(\gamma aba\text{-}N)_2]$ and the hydroxo-bridged oligomers $[\{Pd(en)(\mu\text{-}OH)\}_n]^{n+}$ ($n = 2,3$). In acid solution (pH 2.4), $[Pd(en)(H\gamma aba\text{-}O)(H_2O)]^{2+}$ was the dominant species, in equilibrium with complexes with chelated and bridging γaba^- and $[Pd(en)(H\gamma aba\text{-}N)_2]^{2+}$ [28]. This chemistry is quite different from that of the glycine and β-alanine analogues, largely through the relatively low stability of the 7-membered chelate ring.

In the reaction of *cis*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ with glycine, the chelate complex $[Pd(NH_3)_2(gly\text{-}N,O)]^+$ formed initially. Slow subsequent reaction with protons released by the chelation gave the isomer of $[Pd(NH_3)(H_2O)(gly\text{-}N,O)]^+$ with ammine *trans* to glycinate oxygen (**11**), predicted to be more stable than the isomer with the *N*-donor atoms of higher *trans* influence mutually *trans*. A minor product was $[Pd((H_2O)_2(gly\text{-}N,O)]^+$ [28].

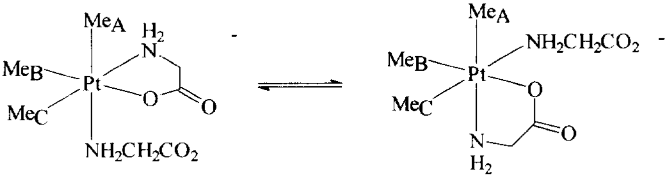
3.2.3. *Platinum(IV) complexes*

It has been well established, primarily through the work of Russian chemists [29–32] that glycinate and related amino acids such as α-alaninate form complexes with platinum(IV) in which the ligand is either *N,O*-chelated or *N*-monodentate. They also observed that chelate ring closure involving displacement of hydroxide does not easily occur in alkaline solution, but can occur when sufficient acid is present to partially protonate the coordinated hydroxide (e.g. reaction (2)). Davies *et al.* [33] obtained [Pt(gly-*N,O*)$_2$Cl$_2$] (all *trans*) by reaction of *trans*-[PtCl$_2$(H$_2$digly-*N*)$_2$] with hydrogen peroxide, and determined its crystal structure.

In methylplatinum(IV) derivatives, the coordination sites *trans* to methyl are labile, allowing substitution chemistry to occur readily. Reaction of *fac*-[PtMe$_3$(H$_2$O)$_3$]$^+$ with one mole glycinate gave [PtMe$_3$(gly-*N,O*)(H$_2$O)] [34]. When the solution was heated, a reaction occurred (reaction (3)) which interchanged Me$_A$ and Me$_C$ *trans* to water and carboxylate oxygen – i.e. the carboxylate oxygen migrated from one coordination site to another, while the amine nitrogen remained anchored *trans* to Me$_B$. Only at much higher temperatures did reactions occur which involved migration of coordinated nitrogen [34,35]. With an additional mole of glycinate, [PtMe$_3$(gly-*N,O*)(gly-*N*)]$^-$ was formed [34]. When this solution was heated, there was an interchange between chelated and monodentate glycinate (reaction (4)). Pt–O bonds were breaking, while the Pt–N bonds remained intact [34,35]. With more glycinate, *fac*-[PtMe$_3$(gly-*N*)$_3$]$^{2-}$ was formed [34]. In none of these solutions was there any evidence for complexes with *O*-bound monodentate glycine [34]. In each of reactions (3) and (4) enantiomers interconvert.



(3)

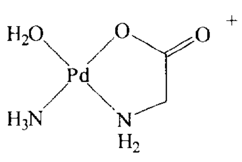


(4)

Analogous complexes were formed with α-substituted amino acids. For these complexes, reactions analogous to (3) and (4) interconvert diastereomers [36].

Concentration of solutions containing [PtMe$_3$(gly-*N,O*)(H$_2$O)] caused precipitation of a solid which was formulated as [{PtMe$_3$(gly)}$_n$] [34]. The α-alanine analogue was soluble in acetone. Molecular weight measurements and ^{1}H NMR spectra were consistent with a dimeric structure [36]. Structure **12** was proposed for these complexes [34,36], although alternative Pt–O–C–O–Pt bridging is also possible.

For dimethylplatinum(IV) complexes, the coordination sites *trans* to methyl are labile while those *cis* to methyl are inert. Reaction of *fac*-[PtMe$_2$Br(H$_2$O)$_3$]$^+$ with Na(gly) gave initially a product, **13**, with glycinate chelated *trans* to the methyl groups. Heating an aqueous solution caused irreversible isomerization to isomer **14**,



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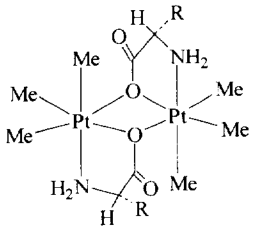
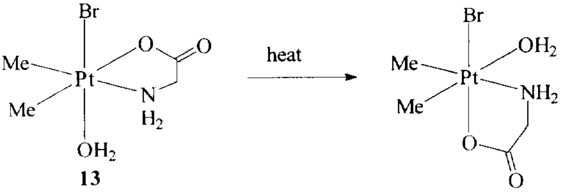


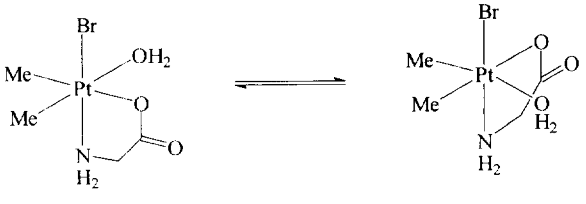
12

with glycinate oxygen *trans* to bromide. A third isomer, **15**, was prepared by reaction of $[\{PtMe_2Br(OH)\}_n]$ with glycine [37,38]. The thermodynamic stabilities of these isomers would be expected to be in the order **15** > **14** > **13**, as the most stable isomer would have the ligand of weakest *trans* influence (N > carboxylate O > H_2O) *trans* to methyl.

The isomerization from **13** to **14** (reaction (5)), since it involves an "inert" site *cis* to methyl has a rate constant that is smaller by a factor of approximately 10^8 than the analogous reaction involving "labile" sites *trans* to methyl (reaction (6)) (298 K) [36].



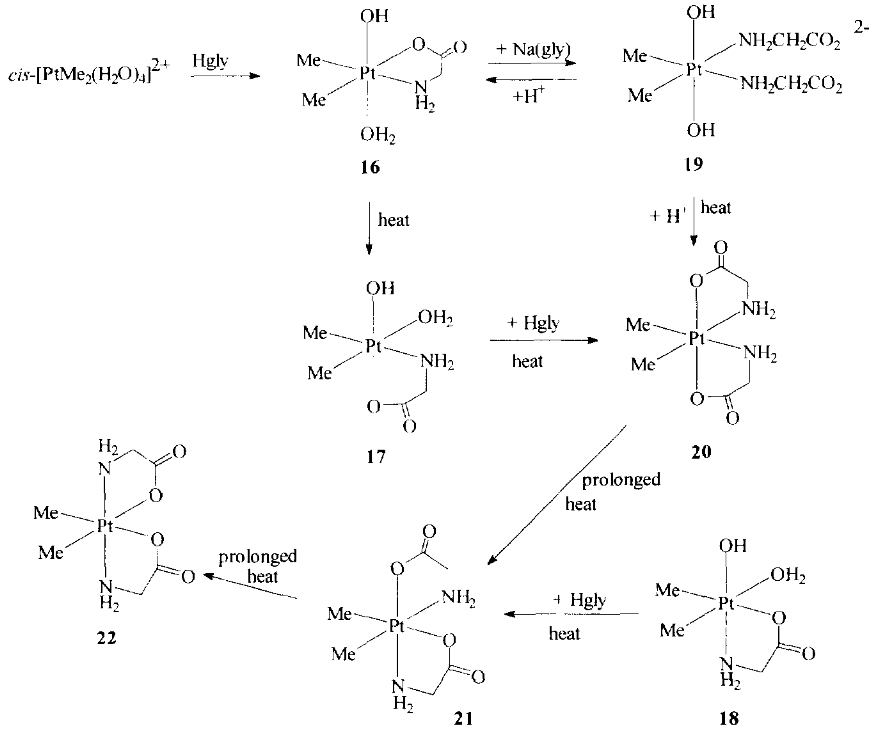
13 **14** (5)



15 (6)

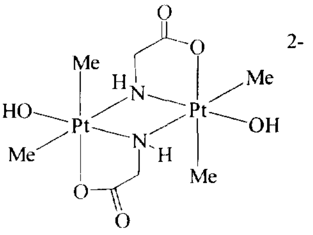
In analogous reactions (Scheme 3) *cis*-$[PtMe_2(H_2O)_4]^{2+}$ with glycine gave $[PtMe_2(OH)(gly\text{-}N,O)(H_2O)]$ (**16**), with glycinate chelated *trans* to the methyl groups. Heating caused isomerization to **17** [37,38]. The third isomer of $[PtMe_2(OH)(gly\text{-}N,O)(H_2O)]$, **18**, was not prepared directly from hydroxo and aqua precursors, but by reaction of the bromo analogue, **15**, with aqueous $AgNO_3$ solution [39].

Reaction of **16** with excess glycinate gave $[PtMe_2(OH)_2(gly\text{-}N)_2]^{2-}$ (**19**), which did not undergo chelate ring closure, but when the pH was decreased to 4.5 ring



Scheme 3.

closure to [PtMe$_2$(gly-*N,O*)$_2$] (**20**) was facile. Heating isomer **17** with glycine gave a second isomer of [PtMe$_2$(gly-*N,O*)$_2$], **21**, with one N-atom and one carboxylate oxygen *trans* to methyl. Prolonged heating of **21** gave a third isomer, **22**, with both N-atoms *cis* to methyl [37,40]. These reactions were irreversible, as expected if the order of thermodynamic stabilities is **22** > **21** > **20**. The structures of **20** [41] and **21** [42] were confirmed by X-ray crystal structure determination.



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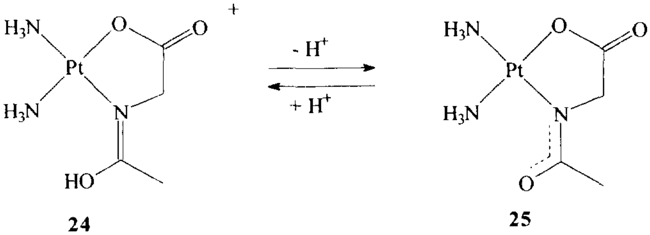
An attempt to prepare [PtMe$_2$(OH)(gly-*N,O*)(H$_2$O)] (isomer **18**) by heating the corresponding bromo complex **15** with NaOH solution led to the formation of a complex formulated as dinuclear, with bridging amido groups, **23** [39].

4. Complexes with glycine derivatives

4.1. Complexes with N-acetylglycine

The coordination of *N*-acetylglycine to transition metal ions was long thought to be limited to coordination through carboxylate oxygen [43]. Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with this ligand did initially produce the complex *cis*-$[Pt(NH_3)_2(Hacgly\text{-}O)(H_2O)]^+$. However, with standing, even in acid solution, a chelate complex $[Pt(NH_3)_2(Hacgly\text{-}N,O)]^+$ (**24**) formed. On addition of alkali, the coordinated ligand deprotonated to form $[Pt(NH_3)_2(acgly\text{-}N,O)]$ (**25**), most of which precipitated from solution (reaction (7)). The pK_a corresponding to this reaction was measured as 2.6. At pH > 9, there was a slow ring-opening reaction to produce *cis*-$[Pt(NH_3)_2(acgly\text{-}N)(OH)]^-$ [44].



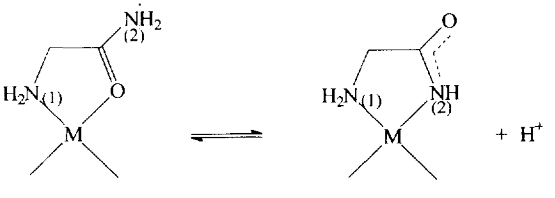
24 **25**

(7)

With $[Pd(en)(H_2O)_2]^{2+}$ only carboxylate binding was present at pH below 4. Between pH 7.0 and 10.5 the *N,O*-chelate complex [Pd(en)(acgly-*N,O*)] analogous to **25** was dominant, but weak peaks were present in NMR spectra that were assigned to dinuclear species with *N,O*-bridging. A major difference from the platinum analogue was the thermodynamic instability of a chelate complex with the amide group protonated, analogous to **24**, since the chelate complex formed only when the pH was high enough to deprotonate the coordinated amide. The pK_a was estimated as approximately 6, much higher than for the platinum analogue. At pH 12.2, the major species in solution was $[Pd(en)(OH)_2]$, but some $[Pd(en)(acgly\text{-}N)(OH)]^-$ was also present [45].

4.2. Complexes with glycinamide

With labile metal ions (e.g. Ni^{2+}, Cu^{2+}) the protonated $N_{(1)},O$-chelate complex **26** is in equilibrium with the deprotonated $N_{(1)},N_{(2)}$-complex **27** [43]. With relatively



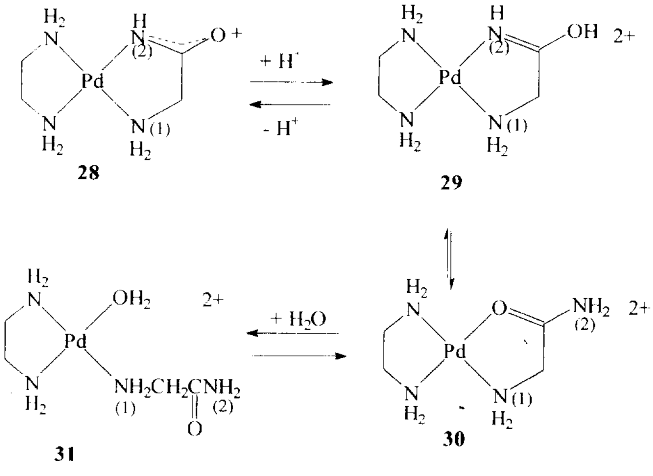
26 **27**

(8)

inert metal ions, the $N_{(1)},O$-chelate complex **26** may not be readily converted into the $N_{(1)},N_{(2)}$-complex **27**. For example, Buckingham *et al.* [46] showed that $[Co(en)_2(Hglyam\text{-}N_{(1)},O)]^{3+}$ does not isomerise to the $N_{(1)},N_{(2)}$-complex, and in alkaline solution there is rapid hydrolysis to give $[Co(en)_2(gly\text{-}N,O)]^{2+}$. They also showed [47] that intramolecular amidolysis of glycine ethyl ester in $[Co(NH_3)_5(glyOEt\text{-}N)]^{3+}$ leads to $[Co(NH_3)_4(glyam\text{-}N_{(1)},N_{(2)})]^{2+}$, which, once formed, is stable toward both isomerization to $N_{(1)},O$-chelate and hydrolysis.

With platinum(II), glycinamide behaves in a similar way to the Co(III) example above. There was no reaction between *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and glycinamide at pH 0.5, but at pH 5, $[Pt(NH_3)_2(Hglyam\text{-}N_{(1)},O)]^{2+}$ formed. There was no reaction with excess glycinamide at this pH, but at pH 7, *cis*-$[Pt(NH_3)(Hglyam\text{-}N_{(1)})_2]^{2+}$ formed. At pH 8–10, there was rapid hydrolysis of the $N_{(1)},O$-chelate complex to $[Pt(NH_3)_2(gly\text{-}N,O)]^{+}$ [48].

From a potentiometric study of the reaction of $[Pd(en)(H_2O)_2]^{2+}$ with glycinamide, Lim [49] proposed that a $N_{(1)},N_{(2)}$-chelate complex is formed, even in acid. From our multinuclear NMR study, $[Pd(en)(glyam\text{-}N_{(1)},N_{(2)})]^{+}$ (**28**) was the only species present at $pH > 3.5$. Below this pH, the protonated complex $[Pd(en)(Hglyam\text{-}N_{(1)},N_{(2)})]^{2+}$ (**29**) was in equilibrium with the $N_{(1)},O$-chelate complex $[Pd(en)(Hglyam\text{-}N_{(1)},O)]^{2+}$ (**30**) and the ring-opened aqua complex $[Pd(en)(Hglyam\text{-}N_{(1)})(H_2O)]^{2+}$ (**31**) (Scheme 4) [45]. The pK_a of **29** was estimated as 1.5 [44]. This is lower than Lim's estimate of 2.47 [49], which was based on the assumption that the protonated $N_{(1)},N_{(2)}$-chelate complex **29** would not exist.



Scheme 4.

4.3. *Complexes with glycinehydroxamic acid*

Davies *et al.* [33] prepared *trans*-$[Pt(glyNOH)_2]\cdot H_2O$ by reaction of $K_2[PtCl_4]$ with glycinehydroxamic acid. Reaction of this complex with HCl gave *trans*-$[PtCl_2(Hgly\text{-}N)_2].2H_2O$, whose crystal structure was determined by X-ray diffraction.

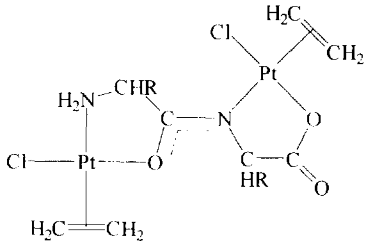
4.4. Complexes with oligo-peptides with non-coordinating side-chains

Wilson and Martin [50–52] showed that di- and tripeptides reacted with $[PdCl_4]^{2-}$ to form complexes in which the peptide nitrogen atoms coordinated, with deprotonation of the peptide groups.

With platinum(II) complexes where the availability of coordination sites was not restricted by the presence of other ligands, Volshtein and Motyagina [53] reported the preparation of the *N*-glycylglycine complex with the ligand bound through amine nitrogen ($N_{(1)}$), *trans*-$[PtCl_2(H_2digly\text{-}N_{(1)})_2]$. Mogilevkina *et al.* [54] reported that reaction of this compound with alkali gave $[Pt(Hdigly)_2]$. On the basis of IR spectroscopy, a structure with $N_{(1)},N_{(2)}$-chelate rings was proposed. Beck *et al.* [55] have determined the crystal structure of a complex containing *N*-glycylglycine ethyl ester bound through amine nitrogen, *cis*-$[PtCl_2(HdiglyOEt\text{-}N_{(1)})_2]$.

Schwederski *et al.* [56] used ^{195}Pt NMR to follow the slow reaction between $[PtCl_4]^{2-}$ and ^{15}N-labelled poly(glycine) peptides, and characterized a number of complexes containing the peptide bound through amine nitrogen and deprotonated peptide nitrogen atoms.

Nance and Frye [57] obtained dinuclear complexes of the type **32** by reaction of Zeise's anion, $[PtCl_3(C_2H_4)]^-$ with dipeptides. This structure was assigned on the basis of IR spectroscopy.



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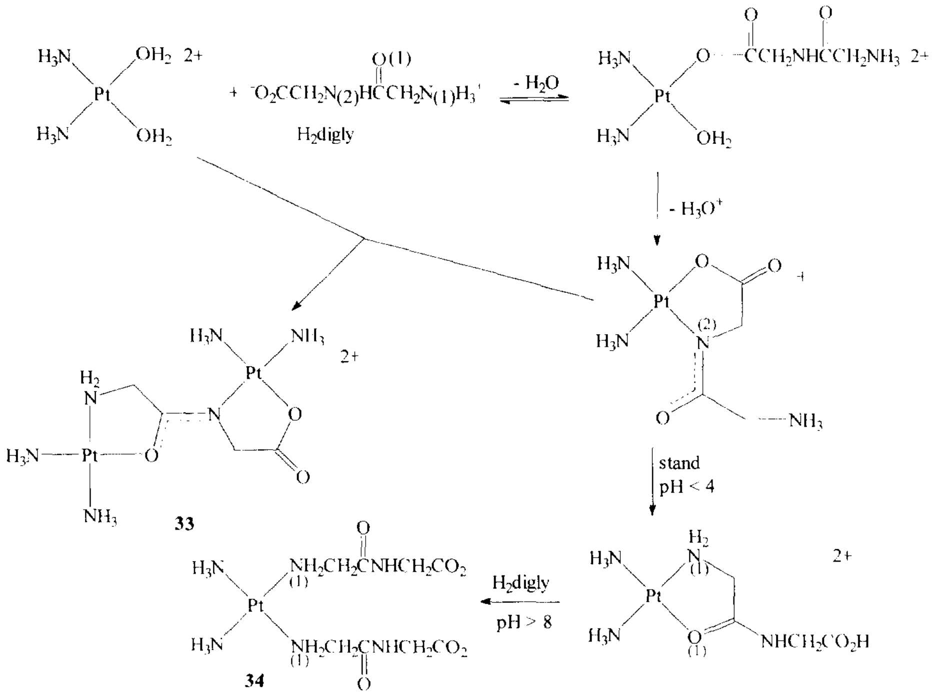
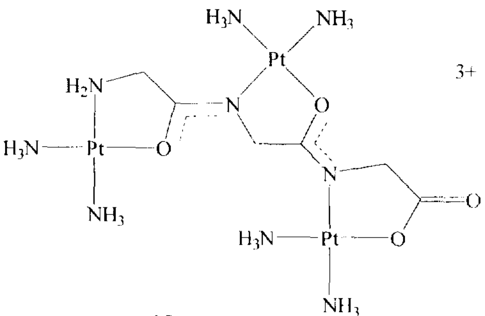
In our laboratory, the reaction between *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and *N*-glycylglycine was followed by multinuclear NMR [48]. Some of the species identified are shown in Scheme 5. The X-ray crystal structure was determined of the sulphate salt of the dinuclear cation **33**, which was eventually the major product at pH 4–6. No $N_{(1)},N_{(2)}$-chelate complex was observed in this study, but Schwederski *et al.* [56] did observe minor NMR peaks assigned to $[Pt(NH_3)_2(digly\text{-}N_{(1)},N_{(2)})]$ from reaction of *cis*-$[PtCl_2(NH_3)_2]$ with glycylglycine at $pH \geq 11$. The major species present was *cis*-$[Pt(NH_3)_2(Hdigly\text{-}N_{(1)})(OH)]$. *Cis*-$[Pt(NH_3)_2(Hdigly\text{-}N_{(1)})_2]$ (**34**) was a minor species unless excess glycylglycine was present.

Reaction between *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and *N*-(glycylglycyl)glycine produced salts which were formulated as containing the trinuclear cation **35** [48].

In the reaction between $[Pd(en)(H_2O)_2]^{2+}$ and glycylglycine (Scheme 6), the



Scheme 5.



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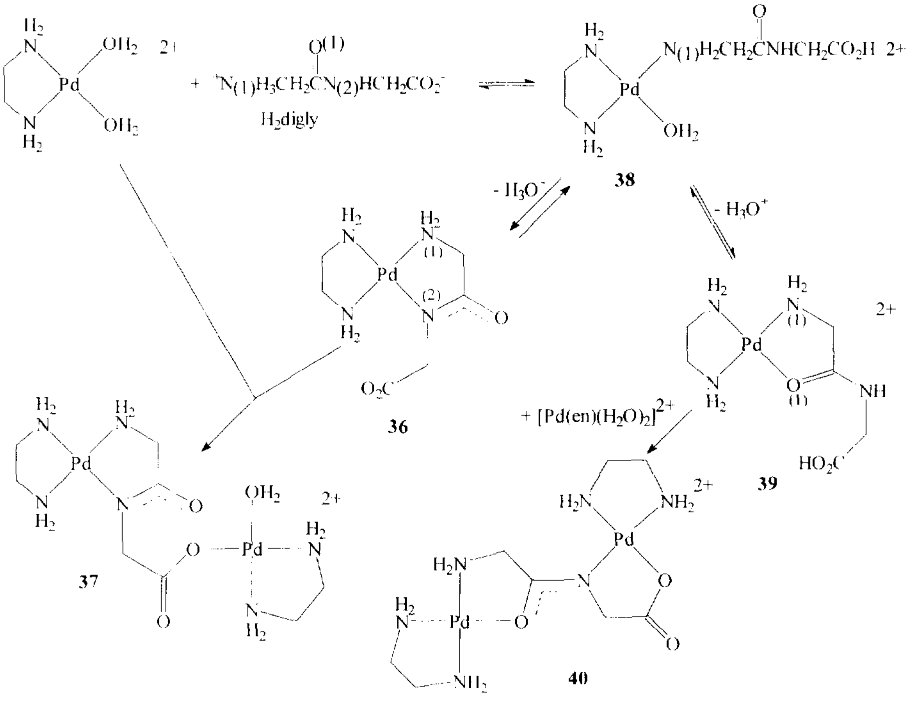
$N_{(1)},N_{(2)}$-chelate complex **36** or the adduct **37** were the major species present at pH > 2. At lower pH, **36** was in equilibrium with the $N_{(1)},O_{(1)}$-chelate complex **39** and the aqua complex **38**. A small amount of the dinuclear complex **40** was present in acid solution, but this did not become the dominant species as the analogue **33** did in the platinum system [45]. The glycylglycine complexes provide another example of quite different products obtained from reactions of Pd(II) and Pt(II) with similar ligand systems, arising from the greater lability of the palladium complexes.



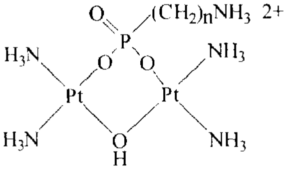
Scheme 6.

5. Platinum(II) complexes with aminoalkylphosphonic acids, $^{+}NH_3(CH_2)_nPO_3H^{-}$

Aminoalkylphosphonic acids are analogues of amino acids, the most obvious difference being that the phosphonic acid group is diprotic. Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with aminomethylphosphonic acid in strongly acidic solution (pH 1.5) gave initially a complex with the ligand bound only through phosphonate oxygen, *cis*-$[Pt(NH_3)_2(H_2amp\text{-}O)(H_2O)]^{2+}$, followed by slow chelate ring closure to $[Pt(NH_3)_2(Hamp\text{-}N,O)]^{+}$. The proton on the coordinated phosphonate group could be removed by addition of base (pK_a 2.5). From the ^{195}Pt–^{15}N coupling constants, the *trans* influences of both nitrogen and oxygen of the aminophosphonate ligand increased with this deprotonation [58].

Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with aminomethylphosphonate at pH 4 was more complex. The initial complex was again *cis*-$[Pt(NH_3)_2(H_2amp\text{-}O)(H_2O)]^{2+}$, and the chelate complex $[Pt(NH_3)_2(amp\text{-}N,O)]$ was the final product after long reaction times, but after 3 days reaction the major species was the dinuclear complex **41** ($n=1$). NMR peaks due to **42** were also detected; it appears likely that this species was an intermediate in the conversion of **41** into the *N,O*-chelate complex [58].

As with the amino acid analogues (Section 3.2.1, the chain length has a profound effect on the ease with which *N,O*-chelation occurs. Reaction of aminoethylphospho-



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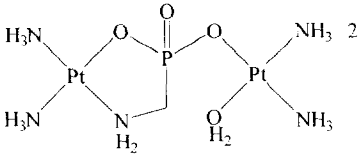

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nic acid with *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ in strongly acid solution (pH 1.5) gave *cis*-$[Pt(NH_3)_2(H_2aep\text{-}O)(H_2O)]^{2+}$. The chelate complex $[Pt(NH_3)_2(Haep\text{-}N,O)]^+$ formed slowly only when the solution was heated. With aminopropylphosphonic acid, *cis*-$[Pt(NH_3)_2(H_2app\text{-}O)(H_2O)]^{2+}$ formed at pH 1.5, but there was no further reaction, even with heating. At pH 4, each of these ligands formed dinuclear complexes **41** ($n=2,3$), but there was no further reaction to give chelate complexes [58].

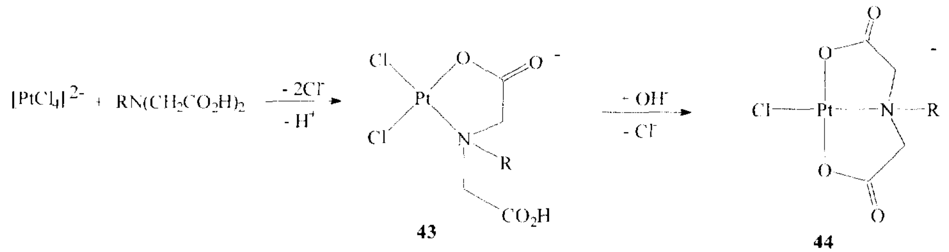
In the slow reaction between aminomethylphosphonate and *cis*-$[Pt(NH_3)_2(OH)_2]$ at pH 12.5, *cis*-$[Pt(NH_3)_2(amp\text{-}N)(OH)]^-$, $[Pt(NH_3)_2(amp\text{-}N,O)]$ and *cis*-$[Pt(NH_3)_2(amp\text{-}N)_2]^{2-}$ formed successively. With equimolar quantities of *cis*-$[Pt(NH_3)_2(OH)_2]$ and amp^{2-} initially, the solution ultimately contained equal concentrations of *cis*-$[Pt(NH_3)_2(amp\text{-}N)_2]^{2-}$, as would be expected if the amine group of amp^{2-} reacts with the Pt–O bond of the chelate complex more rapidly than with Pt–OH. The nucleophilicity of amine nitrogen decreases as increasing chain length removes the $-PO_3^{2-}$ group further from the amine group. Thus aep^{2-} did not react with *cis*-$[Pt(NH_3)_2(OH)_2]$ at pH 12.5, but slow reaction did occur at pH 11.5 (probably through traces of partially protonated complex) to give $[Pt(NH_3)_2(aep\text{-}N,O)]$, which did not react with more aep^{2-}. With app^{2-}, there was no reaction over the pH range 9–12 [58].

6. Complexes with iminodiacetate and derivatives

6.1. Platinum(II) complexes

Iminodiacetate has a strong preference for tridentate *N,O,O′-facial* coordination (see Section 6.3 which is not possible in a complex with square planar geometry. Smith and Sawyer [59] reported the preparation of K[Pt(L)Cl].2HCl (L = ida, mida) as compounds containing *meridional* tridentate ligand, with hydrochloric acid of crystallization. These compounds were shown to actually be the platinum(IV) complexes *fac*-$K[Pt(L)Cl_3]$, formed by aerial oxidation [60]. Reaction of $K_2[PtCl_4]$ with H_2L, with gentle warming, produced initially $[Pt(HL\text{-}N,O)Cl_2]$ (**43**) (Scheme 7), and with careful addition of base, *mer*-$[Pt(L)Cl]^-$ (**44**) formed [60]. Kortes *et al.* [61] subsequently showed that an analogous complex *mer*-$[Pt(Hnta\text{-}N,O,O')Cl]^-$ (**44**, R = CH_2CO_2H) formed with nitrilotriacetate. They proposed that there was a weak interaction between the "free" carboxylate group and the platinum atom when this carboxyl group was deprotonated.

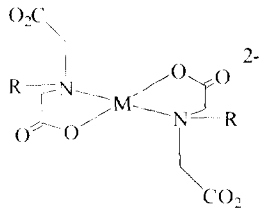
Smith and Sawyer [59] reported that reaction of $K_2[PtCl_4]$ with excess H_2ida



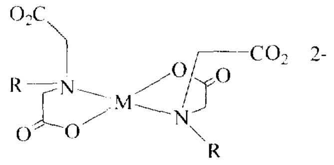
43 **44**

Scheme 7.

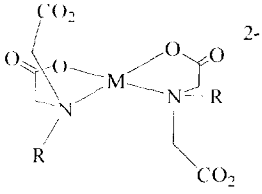
produced $[Pt(Hida)_2]$ which was water-soluble, but that the corresponding reaction with H_2mida gave an insoluble product. It was shown [60] that the mida complex they isolated was actually a platinum(IV) complex $[Pt(mida)_2]$. For $[Pt(Hida)_2]$, all of the four isomers **45**–**48** (M = Pt, R = H) interconvert in hot solution, but only the *trans* isomers **45** and **46** crystallize from solution. For $[Pt(Hmida)_2]$, only the *trans* isomers **45** and **46** (M = Pt, R = Me) were detected in solution [60].



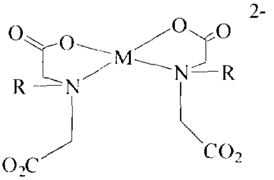
45 *trans anti*



46 *trans syn*

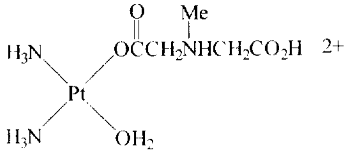


47 *cis anti*



48 *cis syn*

Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with H_2mida was shown by NMR to give initially the complex **49** with the ligand bound only through one carboxylate group, followed by chelate ring closure to form $[Pt(NH_3)_2(Hmida\text{-}N,O)]^+$ (i.e. structure **50** with carboxylate protonated) [20]. Hacker, Khokhar *et al.* [62] subsequently reported that diaminocyclohexane (dach) analogues [Pt(*R*,*R*-dach)(Rida)] (where Rida represents iminodiacetate with the substituent R on nitrogen) possessed high anti-tumour activity, and proposed a *O*,*O*′-chelate structure. Hoeschele *et al.* [63] prepared a number of these complexes, and found that there was no anti-tumour activity if they were pure. They also established that the structures of these complexes did correspond to **50** ($L_2 = R,R$-dach). Because of the asymmetry of the diamine ligand, the different configurations about nitrogen produce two diastereomers. Khokhar *et al.* obtained similar results for a series of complexes [Pt(*R,R*-dach)(Rida)] [64], and for a series [Pt(NH_3)$_2$(Rida)] (structure **50**, $L = NH_3$) [65], and subsequently confirmed structure **50** for [Pt(*dl*-dach)(mida)] by X-ray crystal structure determination [66]. Interaction between the "free" carboxylate group and the platinum atom for complexes with structure **50** in solution has been proposed [61,63,65], but there was no interaction of this type present in the solid state in this crystal structure.



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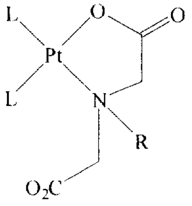

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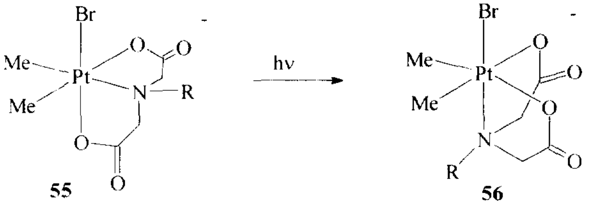
The reaction of $[Pt(H_2O)_4]^{2+}$ with H_2mida was studied, in the hope that this might lead to *mer*-[Pt(mida-*N,O,O'*)(H_2O)], as with the palladium analogue (see Section 6.2). The initial complex formed was $[Pt(H_2mida\text{-}O)(H_2O)_3]^{2+}$, with the ligand bound through one carboxylate oxygen. However, on standing, all ^{195}Pt NMR peaks disappeared, and the ^1H NMR spectrum showed a broad envelope, consistent with the formation of a complex mixture of oligomers, with mida bridging between Pt atoms [20].

6.2. Palladium(II) complexes

Smith and Sawyer [67] reported that reaction of an aqueous solution of palladium(II) nitrate with H_2L (L = ida, mida) produced *mer*-[Pd(L-*N,O,O'*)(H_2O)]. This finding has been confirmed by other workers [20,68]. With two moles H_2L, [Pd(HL-*N,O*)$_2$] was formed, with the *trans* geometry proposed. At high temperatures, there was exchange between coordinated and uncoordinated arms [67]. At low temperatures, only one set of peaks was observed, but, in the light of the results from the Pt(II) analogues (Section 6.1), it is likely that both *anti* and *syn* isomers (**45** and **46**, M = Pd) were present, with peaks from the different isomers not resolved in the relatively low-field ^1H NMR spectra then available. With nitrilotriacetic acid, [Pd(H_2nta)$_2$] was formed, with a similar structure (**45**, $R = CH_2CO_2H$). Again, there was exchange between coordinated and uncoordinated arms, with the Pd–O bonds labile and the Pd–N bonds relatively inert [67,69].

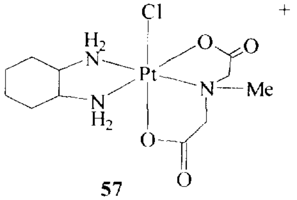
6.3. Platinum(IV) complexes

Reaction of *fac*-$[PtMe_3(H_2O)_3]^+$ with L^{2-} (L = ida, mida, Hnta) gave *fac*-[PtMe$_3$(L-*N,O,O'*)]$^-$ [34]. The initial product of reaction of "*cis*-$[PtMe_2(OH)_4]^{2-}$" with L^{2-} (L = ida, mida) was $[PtMe_2(OH)_2(L\text{-}N,O)]^{2-}$ (**51**), followed by slow chelate ring closure to *fac*-$[PtMe_2(OH)(L\text{-}N,O,O')]^-$ (**52**), which could be protonated to **53** (Scheme 8). Analogous reactions with *fac*-$[PtMe_2Br(H_2O)_3]^+$ produced ultimately *fac*-$[PtMe_2Br(L\text{-}N,O,O')]^-$ (**55**) with nitrogen, as expected, *trans* to a methyl group with high *trans* influence. Irradiation of **55** produced the thermodynamically more stable isomer with N *trans* to bromide, **56** (reaction (9)). On irradiation, the aqua analogue, **53**, isomerised much more slowly to **54** [70].



55 **56** (9)

The non-organometallic complexes *fac*-$K[PtCl_3(L)]$ were prepared by direct reaction of $K_2[PtCl_6]$ with HL^- (L = ida, mida) [60]. Xu and Khokhar [71] prepared a number of complexes [Pt(dach)(mida)Cl]Cl, with different isomers of dach, by chlorine oxidation of [Pt(dach)(mida)], and showed by crystal structure determination that [Pt(*R*,*R*-dach)(mida)Cl]Cl has the structure **57**.



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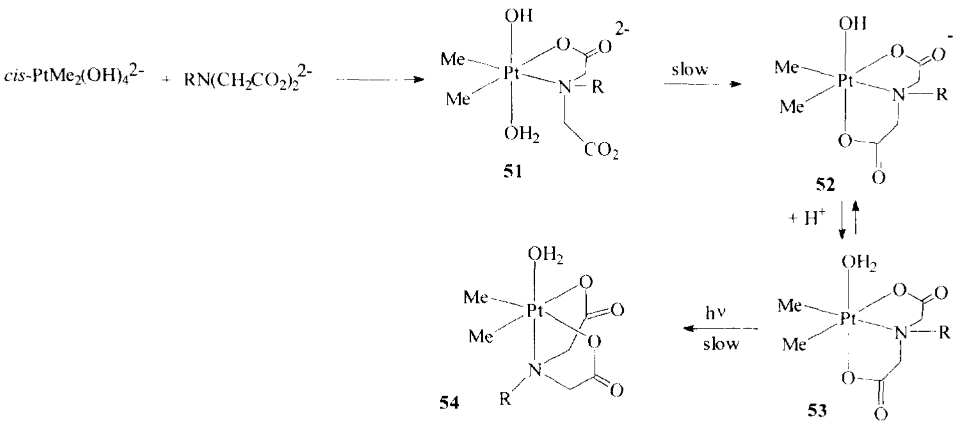
7. Complexes with iminodiphosphonates and derivatives

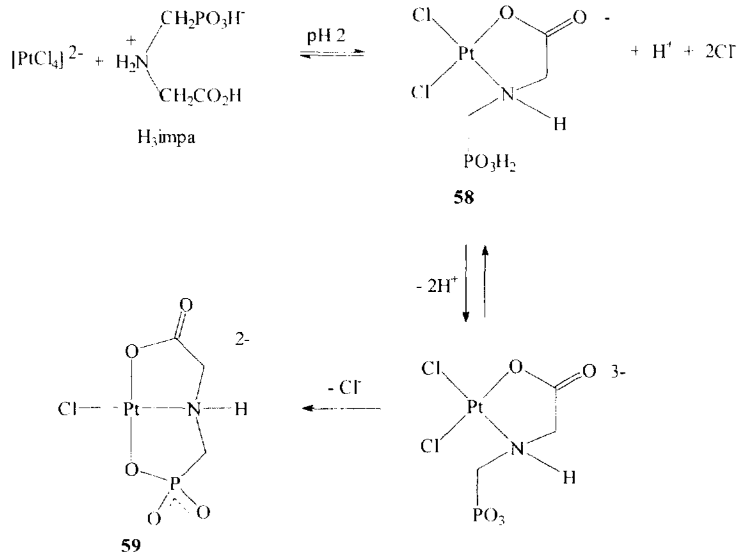
7.1. Platinum(II) complexes

Reaction of $[PtCl_4]^{2-}$ with iminobismethylenephosphonic acid (H_4idmp) at pH 1.5 gave $[PtCl_2(H_3idmp\text{-}N,O)]^-$, with one *N*,*O*-chelate ring. With pH increased to 6 and maintained at that value, *mer*-$[Pt(idmp\text{-}N,O,O')Cl]^{3-}$ slowly formed. Similar results were obtained with the *N*-methyl analogue [72]. Reactions between *N*-(phosphonomethyl)glycine ("glyphosate", H_3impa) and $[PtCl_4]^{2-}$ are outlined in Scheme 9. At pH 2, the product was **58** with the carboxylate group, but not the phosphonate group, involved in a chelate ring. At higher pH, the complex **59**, with ligand tridentate *meridional* formed [72].

In the reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with $RN(CH_2PO_3H_2)_2$, the initial product was *cis*-$[Pt(NH_3)_2(\text{-}OP(O)(OH)CH_2NHRCH_2PO_3H_2)(H_2O)]^{2+}$, with the



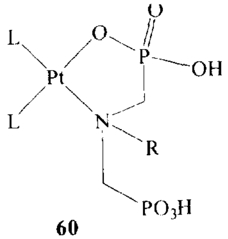
Scheme 8.



Scheme 9.

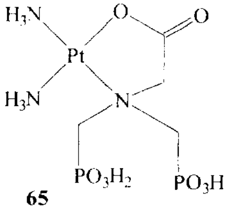
ligand bound only through phosphonate nitrogen, followed by chelate ring closure to **60** (L = NH_3; R = H, Me, $-CH_2PO_3H_2$) [72]. Sawada [73] contrasted the final reaction products for diammineplatinum(II) with those for bis(ethylenediamine)cobalt(III) complexes where an 8-membered *O,O′*-chelate ring was obtained [74].

In the reaction of glyphosate with *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ (Scheme 10), the phosphonate oxygen coordinated first to give **61**, followed by chelate ring closure to **62**, with the protonated phosphonate group bound. With standing in acid, there was



60

slow isomerization to **63**, with carboxylate bound. When the solution was made alkaline, there was slow isomerization to **64**, with deprotonated phosphonate bound, the stable form in alkaline solution. From ^{195}Pt–^{15}N NMR coupling constants, the order of *trans* influence, and presumably Pt–O bond strengths for the three oxygen-donor groups here is $-OC(O)^- \geq -OPO_3^{2-} > -OP(O)(OH)^{2-}$. The clear thermodynamic preference for carboxylate-bound ligand in acid solution is expected from the greater strength of binding with carboxylate compared with protonated phosphonate. In the absence of a large *trans* influence difference between carboxylate and deprotonated phosphonate the thermodynamic preference for the latter in alkaline solution must reflect more subtle effects (e.g. solvation) [72].



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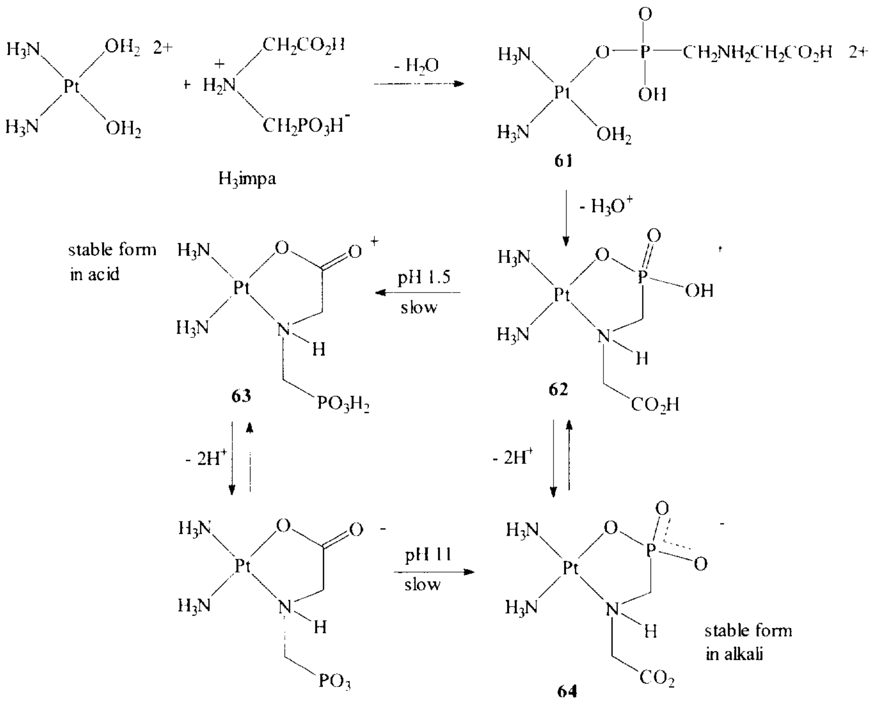
Keppler and his coworkers [75] have isolated and characterized a number of phosphonate complexes including complexes with structure **60** ($L = NH_3$ or $L_2 =$ *cis*-dach). The crystal structure was determined for **65**. A number of these complexes (e.g. $[Pt(NH_3)_2(H_4ntmp\text{-}N,O)]$ (**60**, $L = NH_3$, $R = -CH_2PO_3H_2$) were found to have high anti-tumour activity in mice, including high activity against bone malignancies. Bloemink *et al.* [76] showed that, in reactions of the nitrilotris(methylenephosphonate) complexes with oligonucleotides, the Pt–O bond is broken first, followed by the Pt–N bond.

7.2. Platinum(IV) complexes

With *fac*-$[PtMe_3(H_2O)_3]^+$ glyphosate formed a complex with the ligand coordinated *facially* through nitrogen, phosphonate oxygen and carboxylate oxygen. Some reactions of glyphosate with *cis*-$[PtMe_2(OH)_4]^{2-}$ are summarized in Scheme 11. As expected, the initial complex at pH 11 had impa^{3-} bidentate, but there was no preference for phosphonate (isomer **67**) over carboxylate coordination (isomer **66**). At pH 9.4, chelate ring closure could occur presumably because of the presence of traces of reactive aqua complex. At equilibrium, there was a 4:1 preference for isomer **68** with carboxylate *trans* to methyl over **69** with deprotonated phosphonate

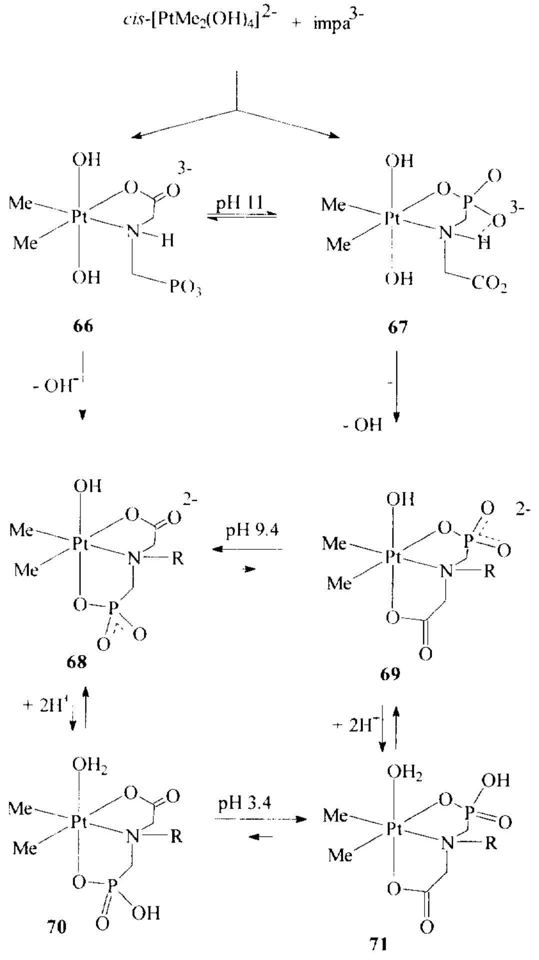


Scheme 10.

trans to methyl. If the most thermodynamically preferred isomer has the weakest donor atom *trans* to methyl, this indicates slightly stronger binding of deprotonated phosphonate over carboxylate. Addition of acid to decrease the pH to 3.4 caused protonation of the coordinated hydroxo and phosphonate ligands, and the preferred isomer now became **71**, with protonated phosphonate *trans* to methyl. This isomer crystallized from solution, and its structure was confirmed by X-ray crystal structure determination. This is consistent with protonated phosphonate being a weaker donor than carboxylate, as expected from the results with Pt(II) complexes discussed in Section 7.1 [77].

For the bromo analogues obtained by reaction of *fac*-$[PtMe_2Br(H_2O)_3]^+$ with glyphosate, the only isomer of $[PtMe_2Br(Himpa)]^-$ present at pH 2 was **72**, with protonated phosphonate *trans* to methyl, and the only isomer of $[PtMe_2Br(impa)]^{2-}$ present at equilibrium at pH 7.6 was **73**, with deprotonated phosphonate *cis* to methyl. At pH 5.7, near the pK_a value for coordinated phosphonate, both isomers were present at equilibrium in similar proportions. The structure of the silver salt of isomer **72** was determined by X-ray crystallography. As with the iminodiacetate analogue (Section 6.3 UV irradiation caused irreversible isomerization to the thermodynamically most stable isomer **74**, with nitrogen *cis* to the methyl groups. The crystal structure of a silver salt was determined [77].

Iminobis(methylenephosphonate) formed a less stable complex with trimethylplatinum(IV) than either iminodiacetate or glyphosate, and the Pt–O bonds



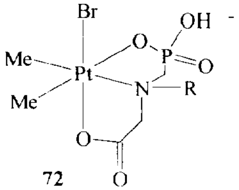
Scheme 11.

were more labile, with rapid exchange on the NMR time scale with aqua complexes. The only dimethylplatinum(IV) complexes obtained contained bidentate ligand. The relative instability of *facial* *N,O,O′*-coordination was ascribed to steric interaction between the phosphonate oxygen atoms in the coordinated ligand [77].

8. Complexes with amino acids with acid side chains

8.1. Aminomalonate complexes with platinum(II)

Gandolfi *et al.* [78] prepared a series of complexes with 2-aminomalonate, $[PtL_2(amal)]$ (L is an amine ligand) with significant anti-tumour activity claimed for a number of the complexes. They formulated these complexes as containing a



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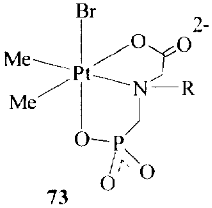

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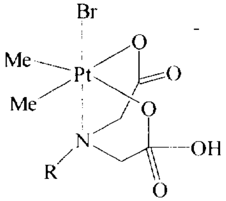

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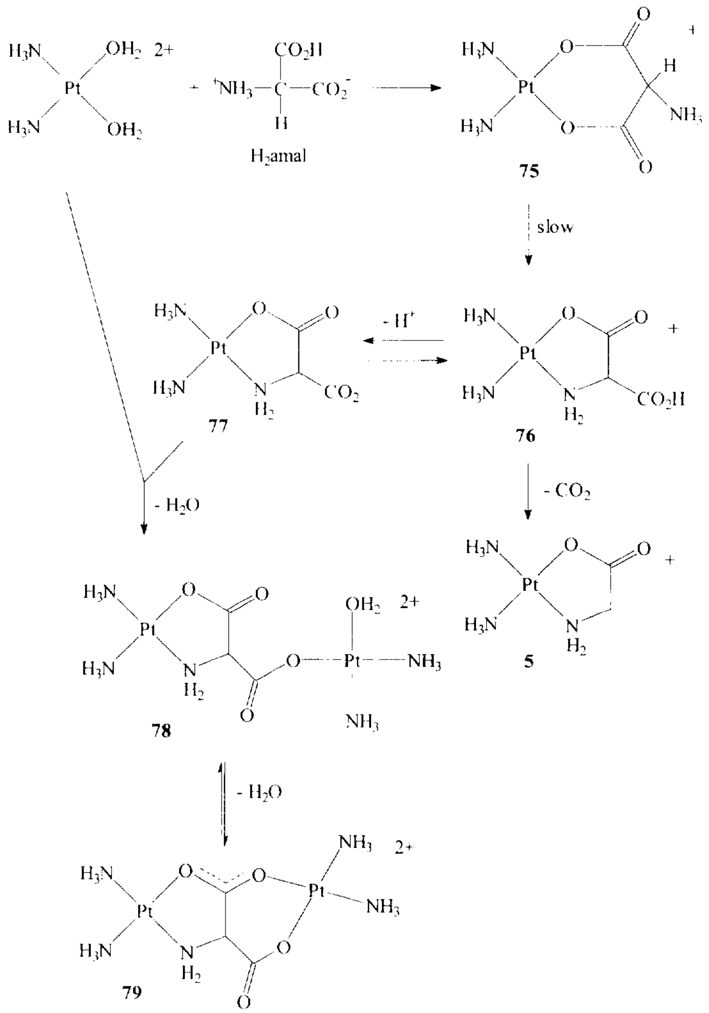
six-membered *O,O'*-chelate ring, with the amine group uncoordinated. The reactions between *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and aminomalonate were subsequently studied in this laboratory [79] and independently by Gibson *et al.* [80]. Reactions in acid solution [79] are summarised in Scheme 12. The initial product was the *O,O'*-chelate complex **75**, which slowly isomerised to the *N,O*-chelate complex **76**. When protonated, this complex was susceptible to decarboxylation to give $[Pt(NH_3)_2(gly\text{-}N,O)]^+$ (**5**), but the deprotonated compound **77** was more stable. Reaction of **77** with more *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ led to a complex **78** with platinum coordinated by the non-chelated carboxylate group, in equilibrium with **79**. The nitrate salt of **79**, $[\{Pt(NH_3)_2\}_2(amal)](NO_3)_2 \cdot H_2O$ crystallized from solution [79]. This is an example of "opportunistic" coordination of an oxygen atom which will normally be weakly binding, but is well-placed sterically to be part of a chelate ring. Near pH 5, NMR peaks were also observed which were assigned to **80**, analogous to **7** [79].

Gibson *et al.* [80] examined the compounds originally prepared by Gandolfi *et al.* [78], and found that they all contained *N,O*-chelate rings, analogous to **76**. Gibson *et al.* [80] also investigated the possibility of attaching a steroidal hormone "R" to a malonate group bound to platinum. When the linkage was through a methylene group, as in **81**, a *O,O'*-chelate complex was obtained cleanly. When the linkage was through an amide group, a mixture of the *O,O'*-chelate complex **82** with the *N,O*-chelate compound was obtained (formulated as having protonated amide by these authors, but under their reaction conditions more probably deprotonated, as in **83**).

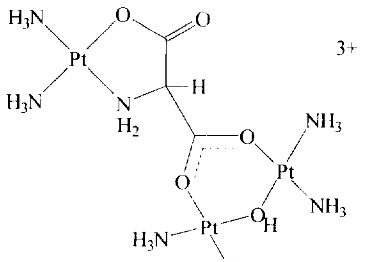
8.2. *Aspartate and glutamate complexes*

8.2.1. *Platinum(II) complexes*

In square planar complexes, the characteristic coordination mode of aspartate is through nitrogen and the α-carboxylate group, to form a five-membered chelate



Scheme 12.



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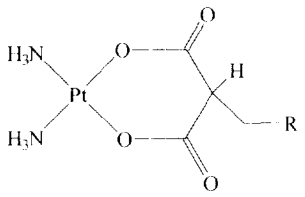

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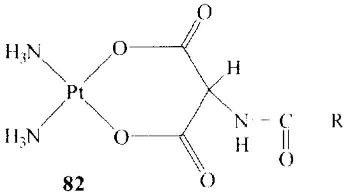

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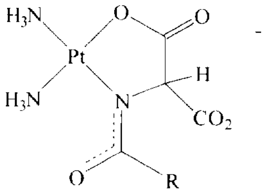

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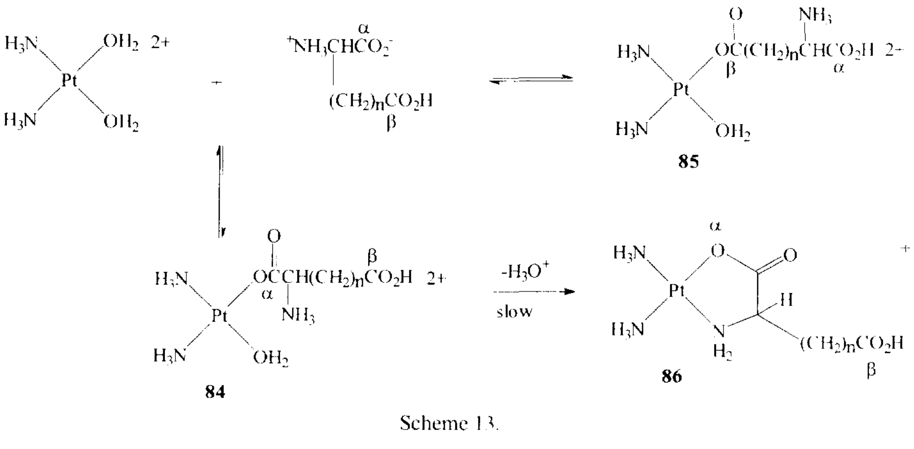
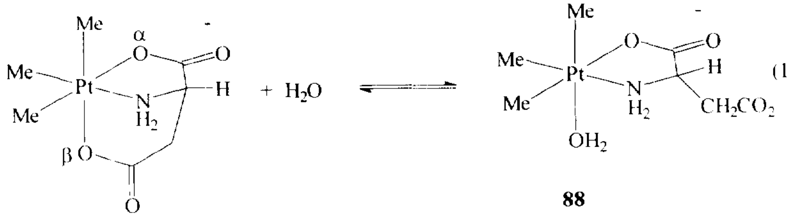
ring, as in [PtCl$_2$(Hasp-*N*,α*O*)]$^-$ and [PtCl$_2$(Hglu-*N*,α*O*)]$^-$ [14]. Reactions between *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ and aspartic and glutamic acids are summarized in Scheme 13 [79]. Since the acid dissociation constant for the α-carboxyl group is higher than for the other carboxyl, the α-carboxylate oxygen coordinated preferentially at low pH (1–2) to give **84**. Near pH 4, the isomer with the other carboxylate bound, **85**, was also formed. Chelate ring closure then slowly occurred, to give **86**, with a five-membered *N*,O_α-chelate ring. No complexes were formed with larger *N*,*O*- or *O*,*O*′-chelate rings. If excess *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ was added to a solution containing **86**, the deprotonated pendant carboxylate group of **86** coordinated to platinum [79].



Scheme 13.



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(10)

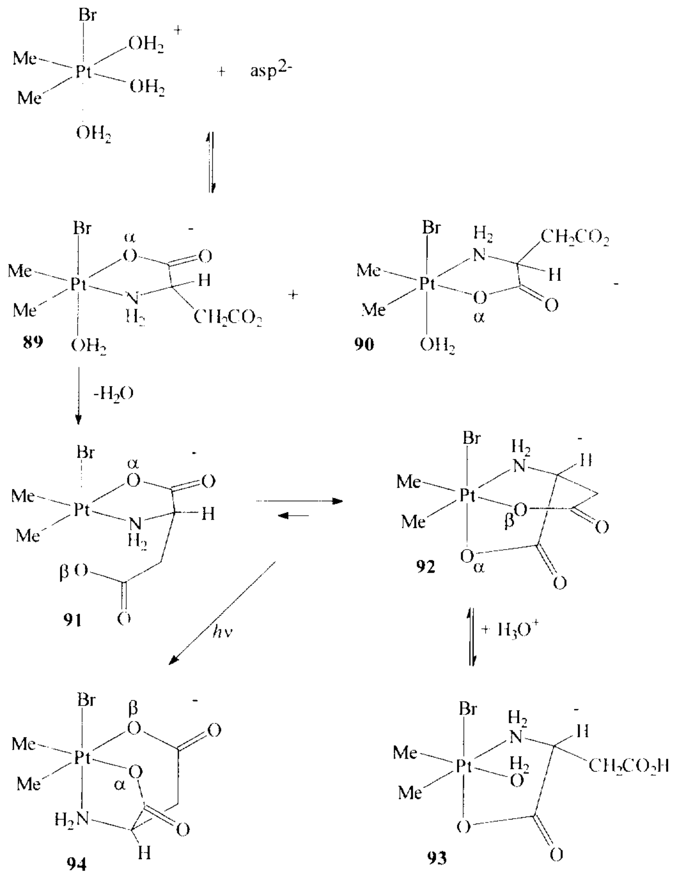
8.2.2. *Platinum(IV) aspartate complexes*

Reaction of *fac*-$[PtMe_3(H_2O)_3]^+$ with aspartic acid and sodium hydroxide in aqueous solution produced Na[PtMe$_3$(asp)]. NMR spectra indicated that there was a rapid (on the NMR time scale) equilibrium between the complex with aspartate coordinated tridentate, **87**, and a complex with aspartate bidentate, with water replacing β-carboxylate, **88** (reaction (10)) [81]. The initial product of reaction with *fac*-$[PtMe_2Br(H_2O)_3]^+$ was a mixture of the two isomers (**89** and **90**) of [PtMe$_2$Br(asp-*N*,α*O*)(H$_2$O)]$^-$ with nitrogen and α-carboxylate bound *trans* to methyl (Scheme 14). With standing, two isomers (**91** and **92**) of $[PtMe_2Br(asp)]^-$ with aspartate tridentate formed. Isomer **92**, with β-carboxylate *trans* to methyl was preferred over isomer **91**, with α-carboxylate *trans* to methyl, as expected if the Pt–βO bond is weaker than the Pt–αO bond in analogous complexes. Another indication of the relative weakness of the Pt–βO bond was the reaction of **92** with dilute acid to form the aqua complex **93**. An analogous reaction, involving cleavage of the Pt–αO bond, did not occur for isomer **91**. The thermodynamically most stable isomer of $[PtMe_2Br(asp)]^-$, **94**, with nitrogen *cis* to methyl, was obtained by UV irradiation of the mixture of isomers **91** and **92** [81].

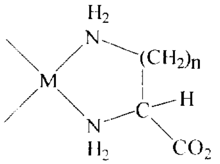
9. Complexes with amino acids with amine side chains

The possible ways by which bidentate coordination of an amino acid $NH_2CH(CO_2^-)(CH_2)_nNH_2$ may be achieved are: through two nitrogen atoms (**95**); and through *N*,*O*-chelation, with a five-membered chelate ring (**96**) expected to be thermodynamically more stable than a larger ring (**97**). Wilson and Martin [50] concluded from circular dichroism measurements on 2:1 amino acid complexes of palladium(II) that lysine ($n=4$) forms a five-membered *N*,*O*-chelate ring (**96**) while 2,3-diaminopropionic acid ($n=1$), 2,4-diaminobutyric acid ($n=2$) and ornithine ($n=3$) all bind through two nitrogen atoms (**95**). For the ornithine complex, the relative instability of the seven-membered *N*,*N*′-chelate ring is outweighed by the preference of palladium(II) for *N*- over *O*-donors, but the eight-membered *N*,*N*′-ring is not formed with lysine.

Altman and Wilchek [82] showed that K$_2$[PtCl$_4$] with 2,3-diaminopropionic acid at ambient temperature gave a mixture of the *cis*- and *trans*-isomers (**98** and **99**) of $[PtCl_2(H_2dap\text{-}O)_2]^{2-}$ (Scheme 15). Gentle heating gave the *N*,*O*-chelate complex



Scheme 14.



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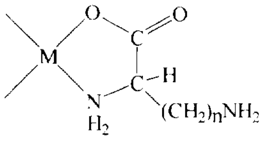

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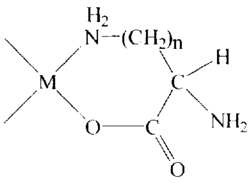

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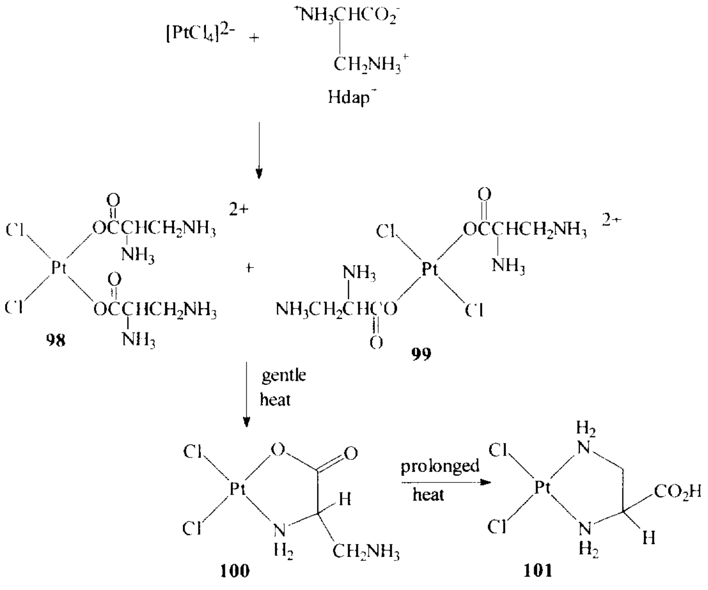
$[PtCl_2(Hdap\text{-}N,O)]$ (**100**), and prolonged heating the complex **101** with a five-membered *N,N'*-chelate ring. In analogous reactions with each of 2,4-diaminobutyric acid, ornithine and lysine, a *N,O*-chelate complex analogous to **100** was isolated by Altman *et al.* [83]. Prolonged heating of $[PtCl_2(Hdab\text{-}N,O)]$ caused isomerization to $[PtCl_2(Hdab\text{-}N,N')]$ (six-membered chelate ring), but analogous isomerization did not occur with the ornithine and lysine analogues to give complexes with seven- and eight-membered *N,N'*-chelate rings, respectively [83]. Bino *et al.* [84] determined the crystal structures of $[PtCl_2(Hdap\text{-}N,O)]$ (**100**) and $[PtCl_2(Hlys\text{-}N,O)]\cdot H_2O$.



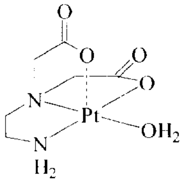
Scheme 15.

10. Complexes with ethylenediaminetetraacetate and analogues

10.1. Platinum(II) complexes

Liu [85] and Zheligovoskaya *et al.* [86] prepared the complex with *N,N'*-ethylenediaminediacetate, $[PtCl_2(H_2edda\text{-}N,N')]$, in which the ligand was bound only through the nitrogen atoms. Liu [85] also prepared $[Pt(edda\text{-}N,N',O,O')]$ in which the two carboxylate groups were also coordinated. Shepherd *et al.* [87] showed by ^1H NMR the presence of diastereomers with *R,S* or *RR*/*SS* configurations at the nitrogen atoms. At pH near 6, in the presence of chloride, one coordinated carboxylate was displaced to form $[Pt(edda\text{-}N,N',O)Cl]^-$ [87].

Zheligovoskaya *et al.* [86] also prepared the *N,N*-ethylenediaminediacetate complex $[PtCl_2(H_2uedda\text{-}N,N')]$. Shepherd *et al.* [87] prepared $[Pt(uedda)(H_2O)]$. On the basis of IR and ^{13}C NMR spectra, it was proposed that both carboxylate groups were interacting with platinum, to give a five-coordinate complex **102**.



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Two complexes have been well-characterized with *N,N,N′,N′*-ethylenetetraacetate [14,88], $[PtCl_2(H_4edta\text{-}N,N')]$ (**103**) and $[Pt(H_2edta\text{-}N,N',O,O')]$ (**104**).

10.2. Platinum(IV) complexes

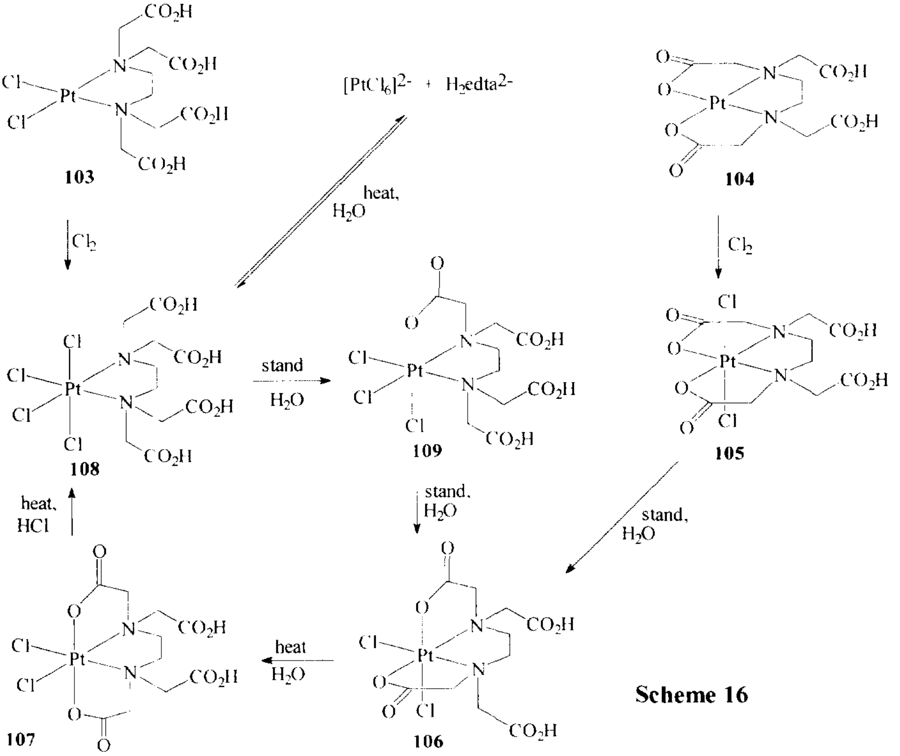
The reactions of platinum(IV) complexes with ethylenediaminetetraacetate [89] are summarised in Scheme 16. The Pt–N bonds are clearly more stable kinetically and thermodynamically than Pt–O bonds. The kinetic product of chlorine oxidation of **104**, $[Pt(H_2edta)Cl_2]$ (isomer **105**), isomerises to the less strained thermodynamically-preferred product **107**, *via* the intermediate **106**. The chelate ring closure reaction from $[Pt(H_4edta)Cl_4]$ (**108**) gives initially **109** as the product predicted from the *trans* effect order $Cl^- >$ N-donor. The kinetic product from the subsequent ring closure reaction, **106**, is predicted from the *trans* effect order N-donor > O-donor, but, with heating, the thermodynamically stable isomer **107** forms. No products with edta occupying more than four coordination sites were detected [89]. These reactions parallel some of those earlier reported by Liu [85] for edda complexes of platinum(IV).

The clear preference for N- over O-donors described above contrasts with the trimethylplatinum(IV) complexes formed with edta (**110**, **111**) (Scheme 17) [34] in which one or two $PtMe_3$ units are bound *facially* by N and two carboxylate O. This preference is presumably influenced by steric and strain effects.

11. Complexes with histidine and derivatives

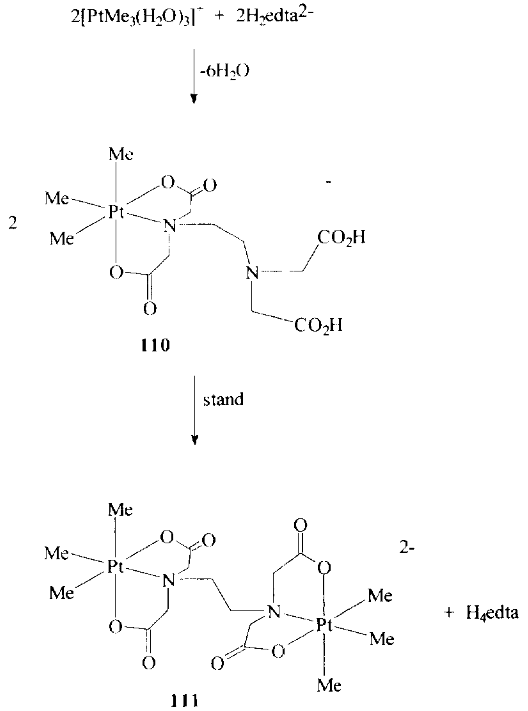
11.1. Platinum(II) and palladium(II) complexes with one coordination site available

Kostic *et al.* [90,91] showed that [Pt(tpy)Cl]Cl reacts selectively with imidazole side-chains in histidine-containing peptides and (provided that cysteine residues were blocked) proteins. The reaction of $[Pd(dien)(H_2O)]^{2+}$ with excess *N*-acetylhistidine (H_3achis) gave a pH-dependent equilibrium between the isomers of $[Pd(dien)(H_2achis)]^+$ with the ligand bound through imidazole N1 (**112**) and imidazole N3 (**113**) (M = Pd) [92]. Analogous species in equilibrium predominated in the reaction between $[Pd(dien)(H_2O)]^{2+}$ and histidine.

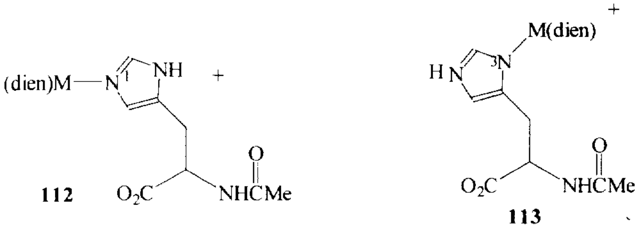


Scheme 16.

With $[Pt(dien)(H_2O)]^{2+}$, as expected, kinetic as well as thermodynamic factors affected the reaction products. Thus, reaction of $[Pt(dien)(H_2O)]^{2+}$ with excess *N*-acetylhistidine, with base added to increase the (D_2O) solution pD to 7.3, gave **112** and **113** (M = Pt), but, in the absence of added base, the initial product was **114**, in which carboxylate oxygen was bound, with slow isomerization to the imidazole-bound isomers. The reaction of $[Pt(dien)(H_2O)]^{2+}$ with histidine, with acid added to decrease the initial pD to 3.5, is shown in Scheme 18. Under these conditions, all of the histidine nitrogen atoms are protonated, so that the initial metastable product is carboxylate bound (**115**). Although complexes with imidazole nitrogen bound are clearly thermodynamically more stable than those with amine nitrogen bound, the amine nitrogen atom N_A may displace carboxylate oxygen by an intramolecular isomerization reaction analogous to those that occur with glycine (Section 3.1.1), so that **115** isomerises to **116**, with amine nitrogen bound. Although **116** is stable in acid solution, on standing at pH near 7, a further isomerization occurs to give **117**, with imidazole N3 bound. Imidazole N1 is less accessible to the metal in an intramolecular isomerization reaction, so $[Pt(dien)(H_2his\text{-}N1)]^{2-}$ does not form. Reaction of $[Pt(dien)(H_2O)]^{2+}$ with excess histidine, without added acid, gives both *N*1- and *N*3-bound isomers of $[Pt(dien)(H_2his)]^{2+}$. Both *N*1- and *N*3-bound linkage



Scheme 17.



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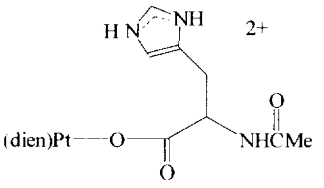

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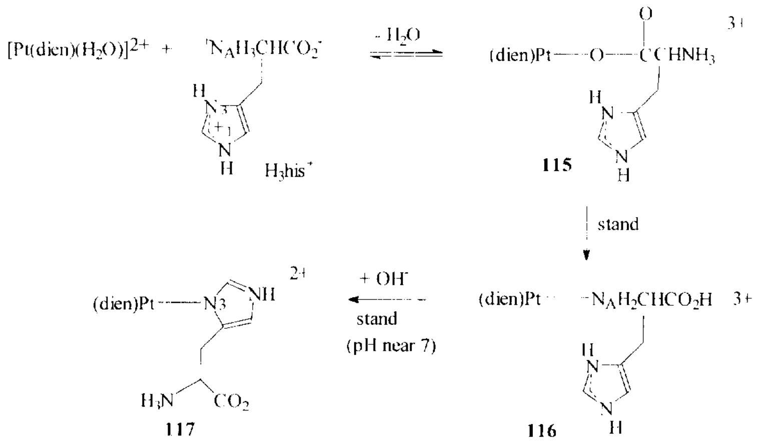
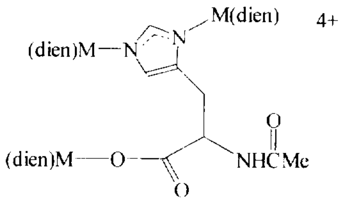
isomers were also shown to form when [Pt(tpy)Cl]Cl reacted with histidine or *N*-acetylhistidine [92].

With excess $[M(dien)(H_2O)]^{2+}$, in alkaline solution, it was possible to form complexes with *N*1,*N*3-bridging, (e.g. **118** with *N*-acetylhistidine, M = Pd, Pt) [92].



Scheme 18.



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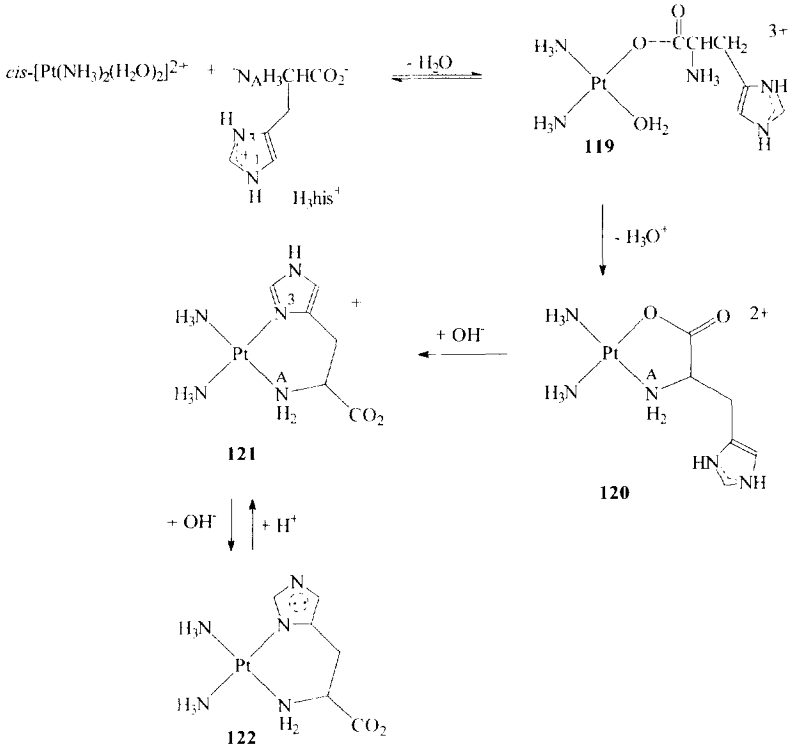
11.2. Platinum(II) and palladium(II) complexes with two coordination sites available

The characteristic coordination mode of histidine to platinum(II) and palladium(II) is chelation through amine nitrogen and imidazole N3 (e.g. in the crystal structure of [Pt(Hhis-N_A,$N3$)$_2$] determined by Baidina *et al.* [93], and in [Pd(en)(Hhis-N_A,$N3$)]$^+$ in solution studies by Pitner *et al.* [52]). Saudek *et al.* [94] identified the major product of reaction of *cis*-[PtCl$_2$(NH$_3$)$_2$] with histidine at 100°C, pH 7.3, as [Pt(NH$_3$)$_2$(Hhis-N_A,$N3$)]$^+$ (**121**). Minor products were formulated as containing two monodentate histidine ligands, bound through either N_A or N3.

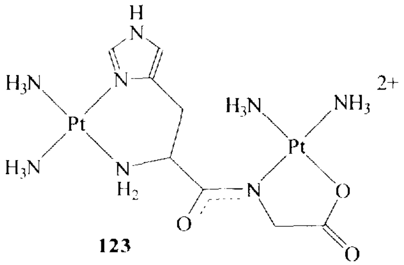
The reaction of *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ with histidine, with acid added to decrease the pH to 2–3 (Scheme 19) [95] gave initially **119**, with histidine-bound monodentate through carboxylate, followed by slow chelate ring closure to **120**, with the amine nitrogen atom (N_A) and carboxylate bound. This complex was stable in acid solution, but, on addition of alkali, to deprotonate the imidazole ring (pH 8–9), rapid irreversible isomerization occurred to the N_A,$N3$-chelate complex **121**. Addition of more base caused further deprotonation, of imidazole N1, to give **122** (pK_a 11.0 — significantly lower than 14.4 for free histidine) [95].

When the carboxyl function was blocked, as in histidine methyl ester or histidinamide, reaction with *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ gave slow formation of the N_A,$N3$-chelate complex. With histidylglycine, the terminal carboxylate bound first to platinum, then, slowly, a N_A,$N3$-chelate. With excess diammineplatinum(II), the



Scheme 19.

free carboxylate group was again bound, followed by chelate ring closure involving the peptide nitrogen atom, to give **123** [95].



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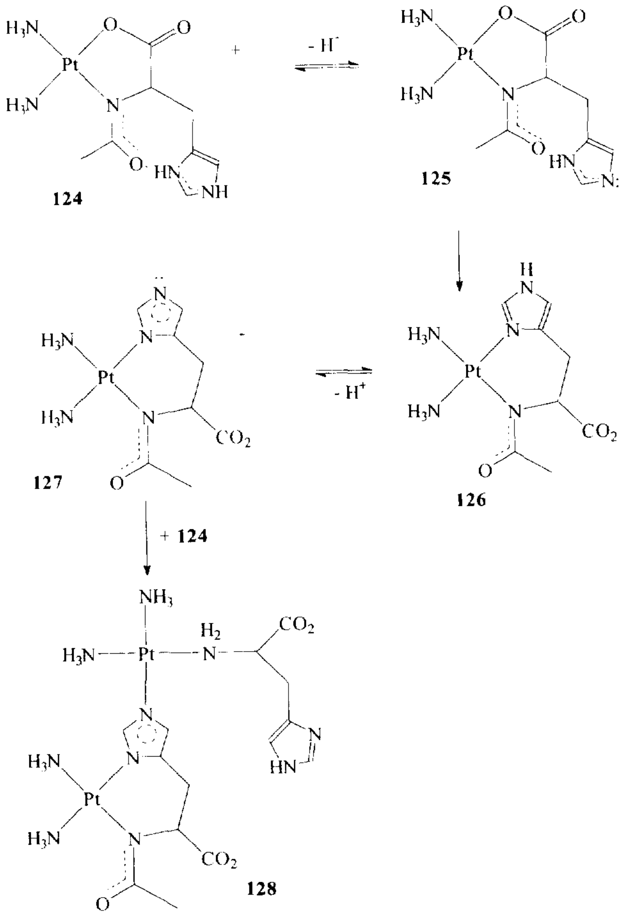
With *N*-acetylhistidine, carboxylate coordinated first, followed by chelate ring closure involving the amide N_A, to give $[Pt(NH_3)_2(H_2achis\text{-}N_A,O)]^{2+}$ (**124**). Possibly owing to hydrogen-bonding as shown in structure **124**, the pK_a value for deprotonation of the imidazole ring was much higher than for the histidine analogue (**120**). When a solution of **124** was allowed to stand near pH 10, the product was the dinuclear complex **128** (Scheme 20). At this pH, the N_A,*N*3-chelate complex **126** could form, but the remaining imidazole proton could also be removed to form **127**, allowing attack by deprotonated imidazole N1 on the Pt–O bond of unreacted **124**.

Analogous reactions occurred with carnosine (β-alanylhistidine), but reactions were more complicated with glycylhistidine, probably owing to the formation of chelate rings involving the terminal nitrogen atom. With carnosine, such chelate rings would be larger, and the terminal nitrogen atom did not become involved in coordination [95].



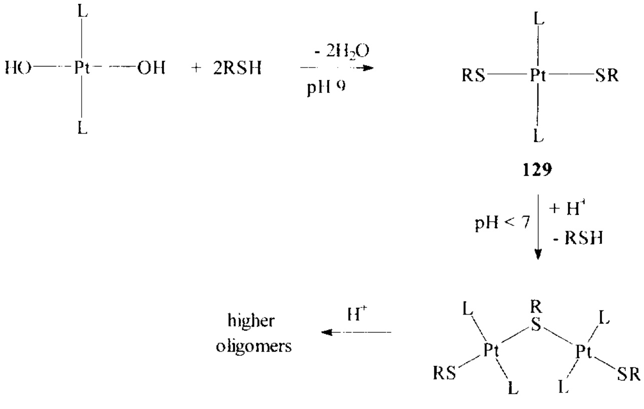
Scheme 20.

12. Complexes with thiolate amino acids and peptides

12.1. Platinum(II) complexes with one coordination site available

Lempers *et al.* [96] studied the reaction of glutathione (GSH) with $[Pt(dien)Cl]^+$. The reaction was pH-dependent. The product at $pH > 7$ was the mononuclear complex [Pt(dien)(SG)], but at pH < 7, a dinuclear complex with a thiolate bridge, [{Pt(dien)}$_2$(μ-SG)] was formed.

Berners-Price and Kuchel [97] studied the reaction of *trans*-[Pt(NH$_3$)$_2$Cl$_2$] with GSH under physiological conditions, and reported that *trans*-[Pt(NH$_3$)$_2$(SG)$_2$] was formed, with *trans*-[Pt(NH$_3$)$_2$Cl(SG)] an intermediate. In collaboration with Farrell's group [98], we have studied the reactions of GSH and the analogue *N*-acetylcysteine (H$_3$acys) (collectively represented as RSH) with aqueous solutions of *trans*-[PtL$_2$(ONO$_2$)$_2$] (L = NH$_3$, γ-picoline). As with the reactions of Pt(dien)$^{2+}$, the thiolate ligands were monodentate at high pH (9.0), to form *trans*-[PtL$_2$(SR)$_2$] (**129**), but at pH 7, this species was in equilibrium with [{(RS)PtL$_2$}$_2$(μ-SR)] (**130**) (Scheme 21). When L = NH$_3$ there was slow release of ammonia at pH < 5.



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Scheme 21.

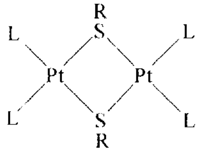
12.2. Platinum(II) complexes with two coordination sites available

Reaction of *cis*-[Pt(NH$_3$)$_2$Cl$_2$] with thiolate amino acids, such as glutathione or cysteine led ultimately to yellow solids which appeared to be polymeric [99–101].

Shanjin *et al.* [102] showed by ^{13}C NMR that only the thiol group of glutathione bound to platinum when *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ reacted with GSH. From our multinuclear NMR study [101] of the reactions between *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ and thiolate amino acids RSH (*N*-acetylcysteine, cysteine, homocysteine, glutathione) we concluded that the major product in each case was [{Pt(NH$_3$)$_2$(μ-SR)}$_2$]$^{2+}$ (**131**, L = NH$_3$). Broadening in ^{195}Pt, ^{13}C and ^{1}H NMR spectra was ascribed to an intermediate rate of inversion at the sulphur atoms. The NMR spectra obtained by Berners-Price and Kuchel [97] from the reaction of *cis*-[Pt(NH$_3$)$_2$Cl$_2$] with glutathione were also consistent with formation of products with bridging thiolate. These studies also showed that ammonia was readily lost, most quickly when the thiolate was cysteine whose N-atom is most available for *N*,*S*-chelate ring closure.

With the chelating ligand bpy present, cysteine (H_2cys), Kumar *et al.* [103] reported that [Pt(bpy)(Hcys-*N,S*)]$^+$ (**132**) formed. Mitchell *et al.* [104,105] showed that reaction of [Pt(bpy)Cl_2] with *N*-acetylcysteine or cysteine gave **131** (L_2 = bpy). The structure of the *N*-acetylcysteine complex was confirmed by X-ray crystal structure determination.

The structure **131** appears to be sterically hindered for penicillamine (H_2pen). Instead, in strongly acidic solution, the complex formed from reaction with *cis*-[$PtL_2(H_2O)_2$]$^{2+}$ (L = NH_3, 1/2(en)) was **133**, which slowly converted to **134** (more rapidly if alkali was added to assist in deprotonation of the amine group) [101].



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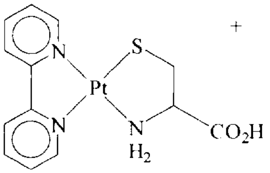

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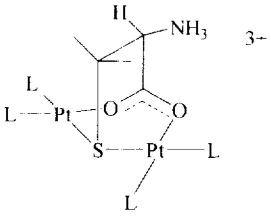

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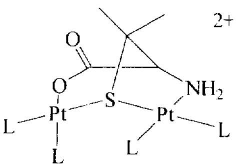

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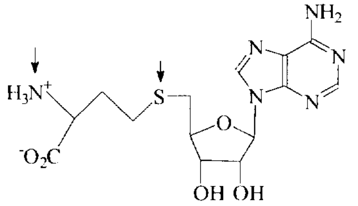
13. Complexes with thioether amino acids and peptides

13.1. Platinum(II) complexes containing thioether amino acids bound monodentate

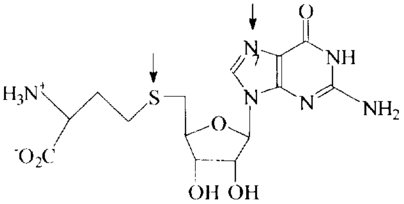
Kostic *et al.* [106,107] prepared complexes K[$PtCl_3$(L)], with L = *N*-acetyl-*S*-methylcysteine (H_2acmecys) or *N*-acetylmethionine (H_2acmet) bound through sulphur, and studied the inversion at sulphur by ^{195}Pt NMR.

Djuran *et al.* [108] found that reaction of [Pt(dien)Cl]$^+$ with *S*-methylglutathione gave a complex in which the peptide was bound to platinum only through sulphur, and Barnham *et al.* [109] showed that an analogous complex formed with methionine at low pH. However, Ratilla *et al.* [90] showed that [Pt(tpy)Cl]$^+$ will not react with thioethers because of steric hindrance.

Lempers and Reedijk [110] showed that *S*-adenosyl-L-homocysteine (sah, **135**) converted reversibly between binding to Pt(dien)$^{2+}$ through sulphur at low pH (< 5), and through the amine nitrogen at high pH (> 7). With excess [Pt(dien)Cl]$^+$, bridging occurred. The adenine nitrogen atoms of sah were not involved in coordination. Van Boom and Reedijk [111] showed that *S*-guanosyl-L-homocysteine (sgh, **136**) with $[Pt(dien)Cl]^+$ at pH between 2 and 6.5, gave initially a complex with sgh bound to $Pt(dien)^{2+}$ through sulphur, which converted spontaneously on standing to the complex with sgh bound through guanosine N7. With excess $[Pt(dien)Cl]^+$, *N*7,*S*-bridging occurred. At pH > 6.5, the amine nitrogen atom also became involved in coordination.



sah
135



sgh
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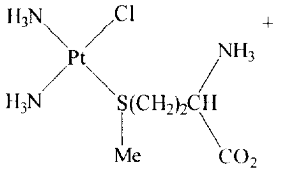
While *N*,*S*-chelated complexes are the most stable ultimate products from reactions of thioether amino acids with platinum(II) complexes having more than one coordination site available (see Section 13.2) intermediate complexes containing monodentate *S*-bound ligand may have some kinetic stability. Because monodentate thiothers are readily displaced by nucleophiles such as guanosine monophosphate, they may be important intermediates in the metabolism of platinum drugs [109]. Examples are *cis*-$[Pt(NH_3)_2Cl(Hmet\text{-}S)]^-$ (**137**), reported by Barnham *et al.* [112] as an intermediate in the reaction of *cis*-$[Pt(NH_3)_2Cl_2]$ with methionine, and **138**, produced by Barnham *et al.* [113] by reaction of the anti-cancer drug $[Pt(NH_3)_2(cbdca)]$ (carboplatin) with methionine. Acetylation of the amine nitrogen enhances kinetic stability of the complex with monodentate sulphur-bound ligand (e.g. in the complex [Pt(en)Cl(Hacmet-*S*)] reported by Barnham *et al.* [114]).

13.2. Platinum(II) and palladium(II) complexes containing thioether amino acids bound bidentate

Where two coordination sites are available, the thermodynamically most stable bonding mode for amino acids $NH_2CH(CO_2H)(CH_2)_nSR$ is *N*,*S*-chelation (e.g. crystal structure determinations for [Pt(Hmet-*N*,*S*)Cl_2] (Freeman *et al.* [115,116]),



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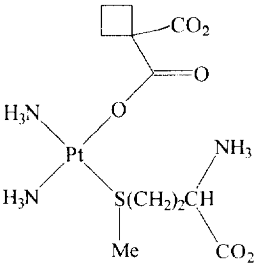

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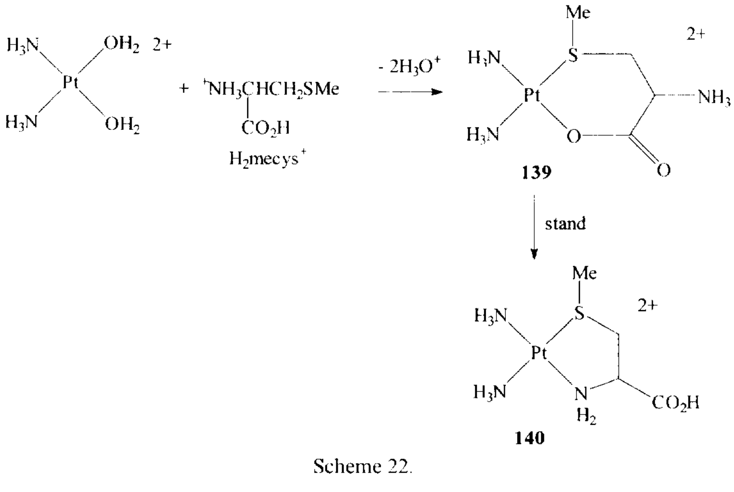
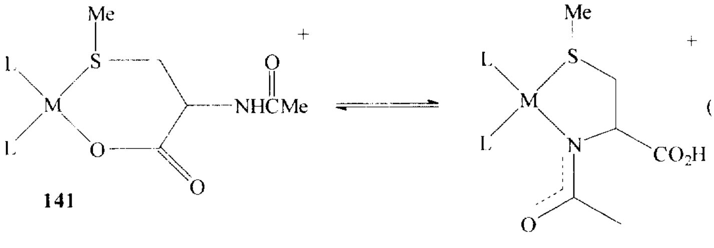
[Pt(Hetcys-*N,S*)Cl$_2$] (Theodorou *et al.* [117]) and [Pt(Hmecys-*N,S*)Cl$_2$] (Battaglia *et al.* [118])). Norman *et al.* [119] showed that the thermodynamically more stable geometric isomer (>90%) of [Pt(L-met-*N,S*)$_2$] is *cis*, as expected, since the less stable *trans* isomer would have the ligands of higher *trans* influence (the sulphur donors) mutually *trans*. Diastereomers were also observed owing to slow (on the NMR time scale) inversion at sulphur.

Reactions of *cis*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$]$^{2+}$ with *S*-methylcysteine in strongly acidic solution are summarised in Scheme 22 [120]. The initial product was the *O,S*-chelate complex **139**, which slowly isomerised to the *N,S*-chelate complex **140**. Analogous reactions with methionine were more complex, in that *cis*-[Pt(NH$_3$)$_2$(H$_2$met-*S*)$_2$]$^{4+}$ also formed, and loss of ammonia was much faster. These differences were probably related to the relative instability of the 7-membered chelate ring in [Pt(NH$_3$)$_2$(Hmet-*O,S*)]$^{2+}$. The conversion from *O,S*- to *N,S*-chelate complexes for both methionine and *S*-methylcysteine complexes was irreversible. Norman *et al.* [119] studied the reaction of [Pt(NH$_3$)$_2$(L-met-*N,S*)]$^+$ with excess L-methionine, showed that [Pt(met-*N,S*)$_2$] was the ultimate product, and identified a number of intermediates in the reaction.



Scheme 22.

Acetylation of the amine nitrogen atom slowed but did not prevent the formation of *N,S*-chelate rings, but also destabilized the *N,S*- chelate thermodynamically relative to *O,S*-, at least for *N*-acetyl-*S*-methylcysteine (H_2acmecys). Thus, reaction of *cis*-$[PtL_2(H_2O)_2]^{2+}$ (L = NH_3, 1/2(en)) with this ligand at pH 0.5 gave $[PtL_2$(Hacmecys-*O,S*)$]^+$, which, at pH 7 rearranged to $[PtL_2$(acmecys-*N,S*)]. There were four isomers of this complex, from slow inversion at sulphur, and slow rotation about the N–C (acetyl) bond [121]. When acid was added to decrease the pH to 3.1, an equilibrium was established between the isomers of $[PtL_2$(Hacmecys)] (Eq. (11), M = Pt), which, for L = 1/2(en) favoured the *O,S*-isomer **141** over the *N,S*-isomer **142** by the ratio 2:1. This change of pH caused protonation of the uncoordinated carboxyl group of the *N,S*-chelate complex (protonation of the amide group occurred in much more acidic solution), so that the shift in equilibrium appears to be due to relatively subtle changes in solvation. In more strongly acidic solution, the *N,S*-chelate complex again became the preferred isomer [121]. For the analogous palladium complexes (Eq. (11), M = Pd, L = 1/2(en)), the *N,S*-chelate complex [Pd(en)(acmecys-*N,S*)] predominated at pH 7, but at pH < 5, only the *O,S*-complex (**141**, M = Pd, L = 1/2(en)). That is, there was a lesser tendency for palladium to coordinate to N rather than O, than for "softer" platinum [121].



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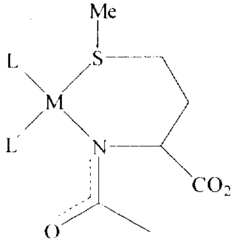
(11)

An *O,S*-chelate complex, $[PtL_2$(Hacmet-*O,S*)$]^+$ was also obtained in reactions of *cis*-$[PtL_2(H_2O)_2]^{2+}$ with *N*-acetylmethionine in acid solution, but reactions were more complicated, with greater proportions of *cis*-$[PtL_2(H_2$acmet-*S*$)_2]^{2+}$ and *cis*-$[PtL_2(H_2$acmet-*S*)$(H_2O)]^{2+}$ present, but at pH 7, $[PtL_2$(acmet-*N,S*)] (**143**, M = Pt, L = NH_3, 1/2(en)) was formed [114,121,122]. By contrast with the *N*-acetyl-*S*-methylcysteine analogue, the *O,S*- to *N,S*- conversion was irreversible when pH was decreased again. In the palladium system, [Pd(en)(acmet-*N,S*)] (**143**, M = Pd, L = 1/2(en)) predominated at pH 7, although 10% [Pd(en)(Hacmet-*O,S*)$]^+$ was also present. When the pH was decreased, the proportion of [Pd(en)(Hacmet-*N,S*)$]^+$ decreased relative to [Pd(en)(Hacmet-*O,S*)$]^+$ and [Pd(en)(Hacmet-*S*)$(H_2O)]^+$. Below pH 4.5, the *N,S*-chelate complex was no longer detectable [121]. This again illustrates the lesser preference for *N*-donors relative to *O*-donors for palladium(II) relative to platinum(II).

Freeman *et al.* [115,116] showed by X-ray crystal structure determination that the complex formed by reaction of $[PtCl_4]^{2-}$ has structure **144**.



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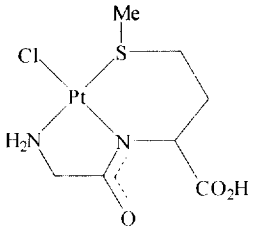

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Zhu and Kostic [123] showed that $[Pd(en)(H_2O)_2]^{2+}$ promoted the hydrolysis of peptide bonds in many peptides containing a thioether group. The mechanism clearly involves anchoring of the peptide to the metal through the thioether group, allowing the peptide bond to approach the metal centre.

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