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# Interaction of *cis*-$Pt(NH_3)_2Cl_2$ with Amino Acids. The Crystal Structures of *cis*-$[Pt(NH_3)_2(gly)](NO_3)$, *cis*-$[Pt(NH_3)_2(ala)](NO_3)$ and *cis*-$[Pt(NH_3)_2(val)](NO_3)$

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## Abstract

The reactions of *cis*-$Pt(NH_3)_2Cl_2$ with the amino acids of increasing aliphatic side chain glycine (gly), L-alanine (ala), 2-amino-butyric acid (2-abaH), L-norvaline (n-val) and L-valine (valH) were studied in aqueous solutions. Five new chelate complexes of the general formula *cis*-$[Pt(NH_3)_2(am\text{-}ac)](NO_3)$, with the amino acid coordinated through $-NH_2$ and $COO^-$, were isolated from these studies and characterized by elemental analysis, conductivity measurements, IR and $^1H$ NMR spectra. Furthermore, the crystal structures of three of these chelates, namely the ones of gly (**1**), ala (**2**) and val (**3**) were determined by X-ray diffraction techniques. The crystals belonged to the space groups $P2_1/n$, $P2_12_12_1$ and $C_2$ with unit cell parameters $a = 7.930(2)$, $b = 17.583(3)$, $c = 5.825(2)$ Å for **1**; $a = 13.097(2)$, $b = 5.616(2)$, $c = 12.704(2)$ Å for **2**; $a = 23.065(2)$, $b = 5.926(2)$, $c = 18.062(2)$ Å for **3**. Their refinements were carried out to final $R$ factors of 0.058, 0.063 and 0.069 for 1330, 1586 and 2266 reflections respectively. Treatment of the compounds with an equivalent amount of HCl acid produced the corresponding monocoordinated ($-NH_2$) complexes of the formula *cis*-$[Pt(NH_3)_2(am\text{-}acH)Cl](NO_3)$ which were rarely isolated, but detected with $^1H$ NMR spectra.

## Introduction

Amino acid complexes of Pt(II) and Pt(IV) have been known for a long time [1–6]. A large variety of compounds of Pt(II) with $NH_3$ and amino acids of the formulae: $Pt(am\text{-}ac)(NH_3)X$, $[Pt(am\text{-}ac)(NH_3)_2]X$, $Pt(am\text{-}acH)(NH_3)X_2$, $[Pt(am\text{-}acH)(NH_3)_3]X_2$, $[Pt(am\text{-}ac)(NH_3)_3]X$ and $M[Pt(am\text{-}ac)(NH_3)X_2]$, have been isolated and studied and the details are described in a review by Volshtein [7]. Gly compounds of *cis*-DDP (*cis*-$Pt(NH_3)_2Cl_2$, known also as cisplatin) have also been reported [6–9], together with $^1H$ NMR studies on complexes of Pt(II) and Pt(IV) with various amino acids and derivatives [8–15].

The amino acids are interesting ligands, not only because of their biological importance, but also for the large variety of complexes they may form with metals [7]. Furthermore, the investigation of the reactions of *cis*-DDP with amino acids may (i) contribute to a better understanding of the various reactions that the drug may undergo in the body with biologically important molecules and (ii) lead to the preparation of compounds with better antitumor properties than the parent *cis*-DDP compound. This was based on the idea that amino acids can carry Pt species through membranes [16]. It should be noted that Pt complexes of amino acids were previously reported to show some antitumor activity [17–19].

In an attempt to make the simplest models of DNA–protein crosslinks caused by *cis*- and *trans*-$Pt(NH_3)_2Cl_2$ [20], we have chosen to prepare and study ternary complexes of the named platinum salts with the simple amino acids (gly (glyH), L-ala (alaH), *S*(+)-2-amino-butyric acid (2-abaH), norvaline (n-valH) and valine (valH)), with increasing aliphatic side chain and the nucleobases 9-MeGua and 1-MeCyt. These reactions were carried out in two stages (i) the isolation of 1:1 compounds of *cis*-$Pt(NH_3)_2Cl_2$ with amino acids and (ii) the reactions of them with nucleobases to produce the ternary complexes.

In the present paper we report the results of the first stage of these studies, together with the crystal structures of three of the compounds isolated,

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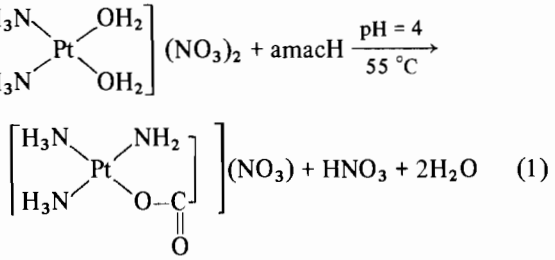
namely, *cis*-$[Pt(NH_3)_2(gly)](NO_3)$ (**1**), *cis*-$[Pt(NH_3)_2$-$(ala)](NO_3)$ (**2**) and *cis*-$[Pt(NH_3)_2(val)](NO_3)$ (**3**). The antitumor activity of the compounds against various tumors is under study.

## Results and Discussion

The preparation of the five new chelate ($-NH_2$, $COO^-$) complexes of *cis*-DDP and amino acids followed the scheme



$$\xrightarrow[55\ ^\circ C]{pH = 4} (NO_3) + HNO_3 + 2H_2O \quad (1)$$

Reactions of *cis*-DDP with gly are known to produce the 1:1 products in acidic media and 1:2 products in alkaline media [6]. A similar reaction of *cis*-$[(NH_3)_2Pt(H_2O)_2](NO_3)_2$ with gly, was studied by Appleton and Hall [9] and the 1:1 product, mono- or bidentate, was detected with $^1H$ NMR, the latter being favored at higher temperatures and pH.

Pivcová *et al.* [8] also reported the preparation of the 1:1 chelate complex of gly with *cis*-DDP, together with the detection of other possible products of the reaction. Their method was followed in the present case for the preparation of the gly chelate, but modifications of this were used for the preparation of the other amino acid chelates (see 'Experimental'). Various complexes of Pt(II) containing amino acids and $NH_3$ as ligands have also been reported [7], as described in the 'Introduction'.

The elemental analyses of the isolated complexes are in good agreement with the empirical formulae and are given in Table 1. The complexes are 1:1 electrolytes in aqueous solutions, as evidenced from the values of their molar conductivities, given also in Table 1.

Upon treatment of the products of reaction (1) with an equimolar amount of HCl, according to

$$cis\text{-}[Pt(NH_3)_2(am\text{-}ac)](NO_3) + HCl \longrightarrow cis\text{-}[Pt(NH_3)_2(am\text{-}acH)Cl](NO_3) \quad (2)$$

the corresponding monodentate ($-NH_2$) complexes were obtained, which were very hygroscopic, however, and not easily analyzable. Elemental analysis only for the complex *cis*-$[Pt(NH_3)_2(valH)Cl](NO_3)\cdot 0.5HNO_3$ is included in Table 1. Others were also detected with $^1H$ NMR (see below).

### *IR Spectra*

The ($-NH_2$, $COO^-$) bidentate chelation or the ($-NH_2$) monodentate coordination of the amino acids with Pt(II) is easily seen from the IR spectra of the compounds.

The assignments for the various bands were based on literature data [21–28] by analogy of the corresponding bands, with comparisons with the zwitterionic and anionic forms of the amino acids and by deuteriation experiments.

In the high frequency region, the spectra of the compounds show a broad band consisting of at least three components from 3000–3350 $cm^{-1}$, which shifts upon deuteriation to 2290–2470 $cm^{-1}$. These include all the NH stretching modes of the ammonias and the amino group of the amino acid, which cannot be distinguished.

The deformation motions of the NH on the other hand, coincide with the $\nu^a_{COO}$-coordinated carboxylate group of the amino acids, in one broad band at 1560–1680 $cm^{-1}$. The shoulder that this band shows at the lower frequency region, however, can be assigned to the $-NH_2$ group of the amino acids, coordinated with Pt(II) [22]. Upon deuteriation, these broad bands disappear, leaving only one band, assigned to the $\nu^a_{COO}$ of the coordinated (chelate) amino acid, near 1650 $cm^{-1}$ [22]. New bands appear then in the region of 1160–1170 $cm^{-1}$, assigned to $ND_2$ motions (NH/ND = 1.40–1.43).

In the monodentate species *cis*-$[Pt(NH_3)_2(am$-$acH)Cl]^+$ on the other hand, only one single strong

TABLE 1. Elemental analysis and molar conductance values of the compounds

| Compound | C (%) | | H (%) | | N (%) | | Pt (%) | | ΛM (s $cm^2$ $mol^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|
| | Calc. | Found | Calc. | Found | Calc. | Found | Calc. | Found | |
| *cis*-$[Pt(NH_3)_2(gly)](NO_3)$ | 6.57 | 6.79 | 2.75 | 2.79 | 15.34 | 15.56 | 53.40 | 53.20 | 106 |
| *cis*-$[Pt(NH_3)_2(ala)](NO_3)$ | 9.50 | 9.77 | 3.18 | 3.19 | 14.77 | 14.78 | 51.40 | 50.80 | 108 |
| *cis*-$[Pt(NH_3)_2(2\text{-}aba)](NO_3)$ | 12.21 | 12.00 | 3.60 | 3.70 | 14.25 | 14.30 | 49.60 | 49.80 | 122 |
| *cis*-$[Pt(NH_3)_2(nval)](NO_3)$ | 14.74 | 14.70 | 3.97 | 3.90 | 13.76 | 13.70 | 47.90 | 48.00 | 100 |
| *cis*-$[Pt(NH_3)_2(val)](NO_3)$ | 14.74 | 14.46 | 3.97 | 3.98 | 13.76 | 13.44 | 47.90 | 47.93 | 110 |
| *cis*-$[Pt(NH_3)_2(valH)Cl](NO_3)\cdot 0.5HNO_3$ | 12.63 | 12.20 | 3.78 | 3.45 | 13.26 | 13.01 | | | |

band appears at about 1730 $cm^{-1}$, showing the protonation of the free carboxylate group (COOH), as well as one broad band at 1575 $cm^{-1}$ for the coordinated NH groups.

The difference between the $\nu^{a}_{COO}$ and the $\nu^{s}_{COO}$ frequencies of the coordinated carboxylate groups are known to reflect the degree of the asymmetry of the group, e.g. the degree of covalency of the metal–oxygen bonds [21]. Based on such measurements, the degree of covalency has been shown to decrease in the order $Pt^{+4} < Pt^{+2} < Pd^{+2} < Cu^{+2} < Zn^{+2} < Ni^{+2} < Co^{+2}$ in their corresponding complexes with gly [21]. In our case, the situation varies with the amino acid, platinum being always the same. The order of decreasing covalency of the Pt–O bond is consequently as follows: val < n-val < 2-aba < ala < gly, i.e. it decreases with the aliphatic side chain.

### *$^1$H NMR Spectra*

The $^1$H NMR spectra of the synthesized compounds were recorded in aqueous solutions at different pD values and the chemical shifts are given in Table 2. The different pD values of the aqueous solutions of the chelates recorded, may be due to the presence of small impurities of $HNO_3$ in the solid compounds, produced during the reaction.

Chelation of the amino acids produces invariably a downfield shift of their proton resonances, relative to the corresponding amino acid anions [12, 13]. Platinum deshields the $\alpha$ and the aliphatic chain protons, attracting electron density. The $\alpha$ protons are affected more (shield of ~0.4 ppm), while the side chain protons, away from the coordination site, are less affected.

Appleton and Hall [9] noticed the formation of a glycine chelate in solution with $^1$H NMR, among other species formed. Their reported chemical shift of 3.61 ppm of the $-CH_2$ group of the amino acid, is close to the one cited in Table 2 (3.63 ppm).

In the case of 2-aba and n-val complexes, the triplet of the $\alpha$ protons observed in the free amino acid, was split into two doublets, because of hindered rotation around the $C_\alpha$–$C_\beta$ bond (see Table 2). Such a splitting was not observed in the valine chelate, which shows a doublet at 3.578 ppm, although it possesses a bulky side chain. Valine shows only one doublet for the $\alpha$ protons in similar chelates with Pt(II) [29].

The vicinal proton coupling constant $^3J_{\alpha\beta}$ of alanine does not change on coordination, being always around 7.2 Hz. This indicates equally populated rotamer distribution, due to free rotation

TABLE 2. $^1$H NMR chemical shifts (in ppm) and observed coupling constants (in Hz) for the Pt/amino acid complexes

| Compound | pD | –CH– | $-CH_2-$ | $-CH_3-$ | $^3J_{\alpha\beta}$ (Hz) | $^3J_{\beta\gamma}$ (Hz) | Other |
|---|---|---|---|---|---|---|---|
| Glycinate ion | 9.0<br>12.5[a] | | 3.406s<br>3.22[a] | | | | |
| *cis*-$[(NH_3)_2Pt(gly)]NO_3$ | 3.3<br>10.0 | | 3.630t<br>3.605s | | | | $^3J_{\alpha,\ NH_3^+}$ = 6.31 Hz |
| L-Alaninate ion | 12.5[a]<br>13.0 | 3.32[a]<br>3.308q | | 1.22[a]<br>1.222d | 7.3[a]<br>7.1 | | |
| *cis*-$[(NH_3)_2Pt(ala)]NO_3$ | 4.4<br>1.3 | 3.774q<br>3.775q | | 1.462d<br>1.460d | 7.17<br>7.21 | | |
| L-Valinate ion | 12.5[a] | $\alpha$: 3.05[a]<br>$\beta$: 1.92[a] | | 0.86[a]<br>0.92[a] | 5.0[a]<br>5.0[a] | 7.0[a]<br>7.0[a] | |
| *cis*-$[(NH_3)_2Pt(val)](NO_3)$ | 4.6 | $\alpha$: 3.578d<br>$\beta$: 2.257m | | 1.130d<br>1.045d | 3.37<br>3.37 | 7.02<br>7.02 | |
| 2-Aminobutyric acid | 6.4<br>10.5 | 3.710t<br>3.352 | 1.899qn<br>1.692 | 0.978t<br>0.912t | 5.87 | 7.54 | |
| *cis*-$[(NH_3)_2Pt(2\text{-}aba)]NO_3$ | 6.0 | 3.629dd | 1.884m | 1.077dd | 5.09<br>5.02 | 7.43<br>6.99 | |
| L-Norvaline | 5.0 | 3.734t | $\alpha$: 1.833m<br>$\beta$: 1.395m | 0.949t | 6.12 | | $^3J_{\gamma\delta}$ = 7.30 Hz |
| L-Norvalinate | 13.5 | 3.233t | $\alpha$: 1.539m<br>$\beta$: 1.315m | 0.903t | 6.36 | | $^3J_{\gamma\delta}$ = 7.30 Hz |
| *cis*-$(NH_3)_2Pt(nval)NO_3$ | 4.8 | 3.677dd | $\alpha$: 1.824m<br>$\beta$: 1.527m | 0.961t | 5.04<br>4.98 | | $^3J_{\gamma\delta}$ = 7.29 Hz |

s: singlet; d: doublet; t: triplet; q: quartet; qn: quintet; m: multiplet; dd: double doublet. [a]Data taken from ref. 45.

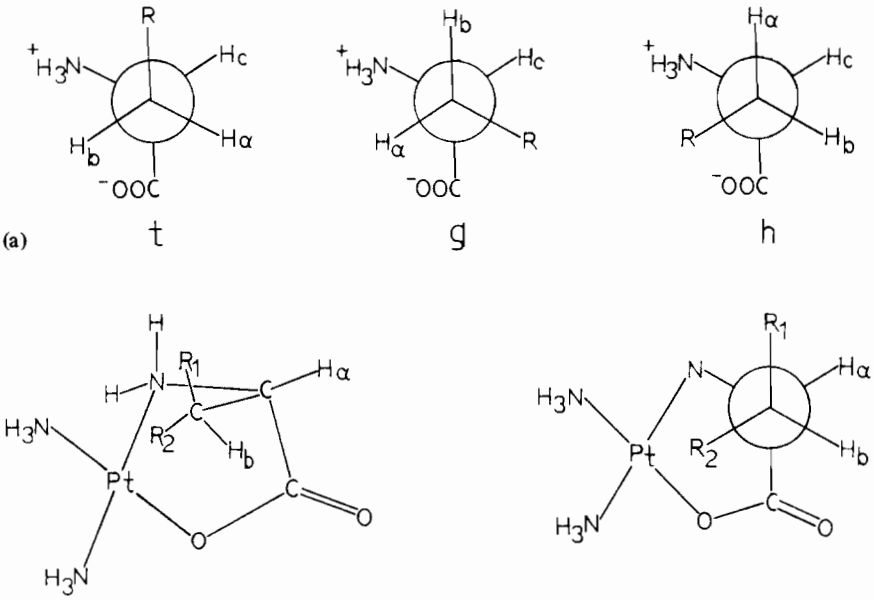



Fig. 1. (a) The t, g and h rotamers of the amino acids around the C–C bond. (b) The most stable rotamer of the *cis*-$[Pt(NH_3)_2$-(am-ac)$]^+$ anions. $R_1 = -CH_3$, $R_2$ = H for 2-aba, $R_1 = -CH_2CH_3$, $R_2$ = H for n-val and $R_1 = -CH_3$, $R_2 = -CH_3$ for val.

of the methyl group [30]. The same is observed for $^3J_{\beta\gamma}$ of the n-val complex, while a small decrease in $^3J_{\beta\gamma}$ is observed in the complex of 2-aba (see Table 2).

Using the data of Table 2, we calculated the relative populations of the different conformers in solution (Fig. 1) as described [31–33] and the equilibrium constant $K$ between the (h) or (t) conformer and the remaining two forms [34] from the relation

$$K = (\text{t or h}) \Big/ \frac{1 - (\text{t or h})}{2} \qquad (3)$$

The results (Table 3) show a predominance of the hindered *gauche* conformer (h) for the 2-aba and n-val chelates, which possibly indicates that the aliphatic side chain is directed towards the metal (Fig. 1(b)).

A large decrease in the population of the *trans* (t) rotamer, relative to the free amino acid, was found for the valine chelate, in agreement with analogous Pd(II) complexes of dipeptides [31, 35]. It is assumed that a strong metal side chain interaction takes place, since the *trans* (t) rotamer is the only one in which both methyl groups of the $\beta$ position are headed away from the metal. Although similar aliphatic chain–metal interactions have been reported earlier for Pd(II) and diamagnetic Ni(II) [32, 34], it is observed for the first time also with Pt(II) here.

TABLE 3. Vicinal proton coupling constants and rotamer distribution in binary Pt(II)–amino acid complexes with 2-aba, n-val, val and its Pt(II) chelate

| Compound | $J_{AB} + J_{BC}$ (Hz) | h (%) | (t + g) (%) | $K$ |
|---|---|---|---|---|
| 2-abaH | 11.736 | 36.4 | 63.6 | 1.14 |
| *cis*-$[(NH_3)_2Pt$(2-aba)$]NO_3$ | 10.109 | 51.3 | 48.7 | 2.11 |
| n-valH | 12.239 | 31.8 | 68.2 | 0.93 |
| *cis*-$[(NH_3)_2Pt$(n-val)$]NO_3$ | 10.023 | 52.1 | 47.9 | 2.18 |
| | $J_{BC}$ (Hz) | t (%) | (h + g) (%) | |
| valH | 4.4[a] | 18.3 | 81.7 | 0.45 |
| val | 5.0[a] | 23.8 | 76.2 | 0.62 |
| *cis*-$[(NH_3)_2Pt$(val)$]NO_3$ | 3.37 | 8.9 | 91.1 | 0.20 |

[a]Data taken from ref. 45.

Upon dissolution of the complex *cis*-$[Pt(NH_3)_2$-(ala)$](NO_3)$ in 0.1 N DCl and recording its $^1$H NMR spectrum after 6 h at room temperature, a new product was detected in about 60% yield. This showed a quartet at 3.840 ppm and a doublet at 1.572 ppm, 0.065 and 0.110 ppm downfield from the starting complex, respectively. The product should correspond to the formula *cis*-$[Pt(NH_3)_2$(alaH)Cl$]$-$(NO_3)$ reaction (2), rather than being the diprotonated free amino acid $alaH_2^+$, which shows peaks at 4.30 and 1.65 ppm, respectively.

*Crystal Structures*

The crystal structure of the chelate *cis*-$[Pt(NH_3)_2(ala)](NO_3)$ is given in Fig. 2, as an example. Figure 3 includes the unit cell of the same chelate.

The crystallographic data for the three structures solved are given in Table 4. Table 5 gives the atomic coordinates and Table 6 gives the distances (Å) and angles (°).

The Pt–N, Pt–O distances and the distances among the amino acid atoms (Table 6) are normal [36–39]. The N (amino acid)–Pt–O (amino acid) angle is smaller than 90° (84.5°, 83.2° and 81°, 82°, for the three chelates respectively), due to the formation of the five membered chelate rings. The ala anion in the *cis*-$[Pt(NH_3)_2(ala)](NO_3)$ adopts an envelope conformation, with the amino group lying above the platinum plane and the oxygen atom of the carboxylate group below the plane. The deviations of the atoms $N_{10}$, $N_{11}$, $N_1$ and $O_4$ surrounding platinum, from the average plane of the square, are −0.067, 0.062, 0.065 and −0.073 for *cis*-$[Pt(NH_3)_2(ala)](NO_3)$. The plane defined by the atoms $N_{11}$, $Pt_1$ and $N_{10}$ was also calculated and $O_4$ was found at 0.1607 (0.0181 Å) below the plane, while $N_1$ was 0.0970 (0.0191 Å) above it. These values, which show significant tetrahedral distortion from planarity, are not observed for the glycine [37, 38] or the valine chelate.

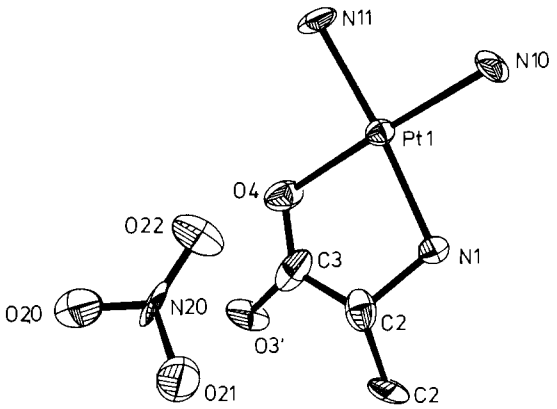



Fig. 2. Molecular structure of *cis*-$[(NH_3)_2Pt(ala)](NO_3)$ (**2**). (XP - Plot of the anisotropically refined structure.)

Torsional and dihedral angles, as well as hydrogen atom coordinates and possible interatomic contacts were also calculated for the alanine chelate. The dihedral angle between the planes defined by $Pt_1$–$N_1$–$C_2$ and $C_2$–$C_2$–$N_1$ is 159.64° (2.15°), which implies an equatorial position of the methyl group, preferred by the more voluminous substituents. The presence of $NO_3^-$ as a counter ion, was found to stabilize the crystal, through the formation of two hydrogen bonds. Namely, the amino acid amine group ($N_1$) hydrogen bonds to a nitrate oxygen atom ($O_{22}$), so that $N_1$–$O_{22}$ is 2.860(29) Å. The amino group *trans* to the amino acid amino group ($N_{11}$) also hydrogen bonds to a nitrate oxygen atom ($O_{21}$), so that $N_{11}$–$O_{21}$ is 2.912(35). A hydrogen bond chain is thus formed.

Since the Pt–C2′ distance is over 4 Å, there is no interaction between the metal and the methyl group. The $Pt_1$–$O_{20}$ distance of 3.6 Å on the other hand, should not indicate interaction either.

In the structures of the other two chelates, glycine adopts a puckered conformation in the molecule, with the coordinated groups lying almost on the platinum coordination plane and the rest of the amino acid above it. Valine favors an envelope conformation, similar to the one described above for alanine. The dihedral angles between $C_{31}$–$C_{21}$–$C_{41}$ and $C_{21}$–$C_{41}$–$C_{61}$ (Fig. 4) were calculated and found to be 67° and 69°, for the two crystallographically independent molecules, respectively. The values show that the *gauche* (h) rotamer of the amino acid is favored in the solid state, as also happens in solution (see $^1H$ NMR 'Discussion'). The distances of $Pt_1$–$C_{61}$ or $Pt_1$–$C_{51}$ exceed 4 Å.

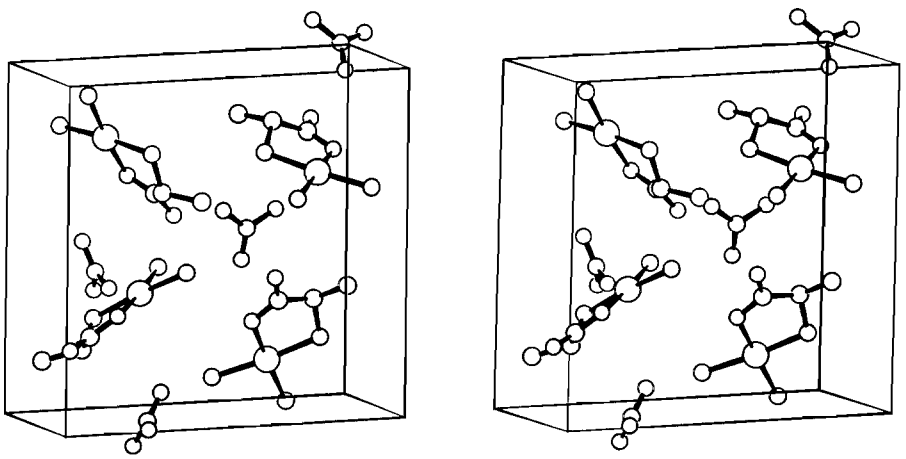


Fig. 3. Stereo drawing of the unit cell of *cis*-$[(NH_3)_2Pt(ala)](NO_3)$.

TABLE 4. Crystallographic data for *cis*-[Pt($NH_3$)$_2$(gly)]($NO_3$) (1), *cis*-[Pt($NH_3$)$_2$(ala)]($NO_3$) (2) and *cis*-[Pt($NH_3$)$_2$(val)]($NO_3$) (3)

| | 1 | 2 | 3 |
|---|---|---|---|
| Formula weight | 365.1 | 379.1 | 407.1 |
| Space group | $P2_1/n$ | $P2_12_12_1$ | $C2$ |
| $a$ (Å) | 7.930(2) | 13.097(2) | 23.065(2) |
| $b$ (Å) | 17.583(3) | 5.616(2) | 5.926(2) |
| $c$ (Å) | 5.825(2) | 12.704(2) | 18.062(2) |
| $\beta$ (°) | 93.62(2) | | 100.12(2) |
| $V$ (Å$^3$) | 810.6 | 934.4 | 2430.01 |
| $Z$ | 4 | 4 | 4 |
| Crystal size (mm) | 0.1, 0.1, 0.2 | 0.1, 0.1, 0.2 | 0.1, 0.1, 0.2 |
| $\mu$ (cm$^{-1}$) | 166.4 | 144.3 | 111.12 |
| $\theta$ range (°) | 2–25 | 2–25 | 2–25 |
| Scan mode | $\theta/2\theta$ | $\theta/2\theta$ | $\theta/2\theta$ |
| No. unique reflections | 1425 | 1653 | 2366 |
| No. reflections in calculations | 1330 ($F_o > 2\sigma F_o$) | 1586 ($F_o > 2\sigma F_o$) | 2266 ($F_o > 2\sigma F_o$) |
| No. parameters | 109 | 118 | 130 |
| $R$ | 0.058 | 0.063 | 0.069 |

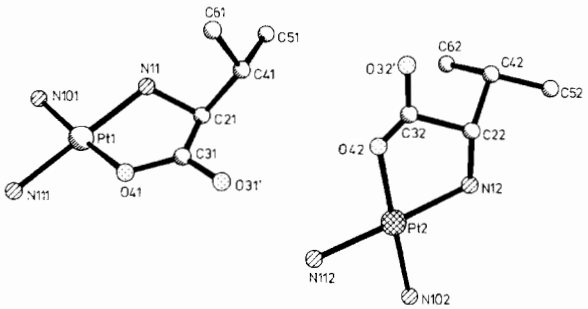



Fig. 4. Molecular structure of *cis*-[($NH_3$)$_2$Pt(val)]($NO_3$).

TABLE 5. Atomic coordinates for compounds 1, 2 and 3

| Atom | x | y | z |
|---|---|---|---|
| Compound **1** | | | |
| Pt1 | 0.0975(1) | 0.1239(1) | 1.0011(1) |
| N10 | 0.0810(15) | 0.0706(7) | 1.3098(21) |
| N11 | 0.3311(13) | 0.0760(6) | 0.9656(21) |
| N1 | −0.1289(16) | 0.1790(8) | 1.0156(22) |
| C2 | −0.1464(19) | 0.2370(8) | 0.8289(28) |
| C3 | −0.0158(17) | 0.2239(9) | 0.6522(29) |
| O3′ | −0.0262(15) | 0.2585(7) | 0.4619(18) |
| O4 | 0.1075(11) | 0.1752(6) | 0.7007(17) |
| Compound **2** | | | |
| Pt1 | 0.3570(1) | 0.3010(1) | 0.1647(1) |
| N10 | 0.3548(19) | −0.0022(39) | 0.0676(17) |
| N11 | 0.5056(14) | 0.3714(51) | 0.1181(15) |
| N1 | 0.2110(14) | 0.2434(43) | 0.2243(16) |
| C2 | 0.2059(19) | 0.3904(51) | 0.3241(21) |
| C2′ | 0.0970(23) | 0.4349(66) | 0.3527(18) |
| C3 | 0.2691(19) | 0.6153(63) | 0.3069(22) |

*(continued)*

TABLE 5. *(continued)*

| Atom | x | y | z |
|---|---|---|---|
| O3′ | 0.2453(16) | 0.8001(33) | 0.3579(15) |
| O4 | 0.3478(13) | 0.6078(34) | 0.2516(14) |
| N20 | 0.4023(14) | 0.4049(50) | 0.5386(21) |
| O20 | 0.3398(16) | 0.2846(51) | 0.5989(14) |
| O21 | 0.4290(17) | 0.3396(39) | 0.4536(14) |
| O22 | 0.4389(15) | 0.5892(47) | 0.5783(17) |
| Compound **3a**[a] | | | |
| Pt1 | 0.4030(0) | 0.5000(0) | 0.8713(1) |
| N101 | 0.3144(11) | 0.507(6) | 0.8451(15) |
| N111 | 0.3971(15) | 0.555(7) | 0.9819(19) |
| N11 | 0.4155(10) | 0.465(4) | 0.7657(12) |
| C21 | 0.4764(10) | 0.382(8) | 0.7640(13) |
| C31 | 0.5152(11) | 0.440(4) | 0.8368(14) |
| O31′ | 0.5704(9) | 0.440(4) | 0.8407(12) |
| O41 | 0.4927(12) | 0.518(6) | 0.8914(15) |
| C41 | 0.5021(14) | 0.465(6) | 0.6931(17) |
| C51 | 0.4656(16) | 0.369(11) | 0.6222(21) |
| C61 | 0.5029(13) | 0.731(6) | 0.6886(17) |
| Compound **3b**[a] | | | |
| Pt2 | 0.6606(0) | −0.1218(4) | 0.7504(0) |
| N102 | 0.6811(10) | −0.426(5) | 0.7967(13) |
| N112 | 0.6289(11) | −0.037(5) | 0.8436(13) |
| C22 | 0.6826(10) | 0.013(5) | 0.6052(13) |
| C32 | 0.6502(11) | 0.205(5) | 0.6380(13) |
| O32′ | 0.6386(8) | 0.387(6) | 0.6000(10) |
| O42 | 0.6378(8) | 0.176(4) | 0.7003(10) |
| C42 | 0.6526(14) | −0.023(7) | 0.5187(18) |
| C52 | 0.6894(19) | −0.207(9) | 0.4856(23) |
| C62 | 0.5898(14) | −0.122(10) | 0.5144(18) |

[a]The crystal structure of this compound showed the presence of two crystallographically independent molecules.

TABLE 6. Distances (Å) and angles (°) of **1**, **2**, **3a** and **3b** (two independent molecules)

| | **1** | **2** | | **3a** | | **3b** |
|---|---|---|---|---|---|---|
| Pt1–N10 | 2.04(1) | 2.10(2) | Pt1–N101 | 2.01(3) | Pt2–N102 | 2.04(3) |
| Pt1–N11 | 2.06(1) | 2.07(2) | Pt1–N111 | 2.08(4) | Pt2–N112 | 2.04(3) |
| Pt1–N1 | 2.05(1) | 2.08(2) | Pt1–N11 | 2.00(3) | Pt2–N12 | 2.01(2) |
| Pt1–O4 | 1.98(1) | 2.05(2) | Pt1–O41 | 2.01(3) | Pt2–O42 | 2.01(2) |
| N1–C2 | 1.49(2) | 1.52(3) | N11–C21 | 1.53(4) | N12–C22 | 1.45(4) |
| C2–C3 | 1.52(2) | 1.53(4) | C21–C31 | 1.50(4) | C22–C32 | 1.60(4) |
| C3–O3′ | 1.26(2) | 1.26(4) | C31–O31′ | 1.26(4) | C32–O32′ | 1.26(5) |
| C3–O4 | 1.32(2) | 1.25(3) | C31–O41 | 1.30(4) | C32–O42 | 1.11(3) |
| C2–C2′ | | 1.49(4) | C21–C41 | 1.57(5) | C22–C42 | 1.63(4) |
| | | | C41–C51 | 1.59(6) | C42–C52 | 1.58(6) |
| | | | C41–C61 | 1.52(6) | C42–C62 | 1.58(6) |
| N10–Pt1–N11 | 90.5(5) | 90(1) | N101–Pt1–N111 | 91(2) | N102–Pt2–N112 | 86(1) |
| N10–Pt1–N1 | 94.4(5) | 94.3(9) | N101–Pt1–N11 | 95(1) | N102–Pt2–N12 | 98(1) |
| N10–Pt1–O4 | 178.6(4) | 174.7(9) | N101–Pt1–O41 | 175(2) | N102–Pt2–O42 | 179(1) |
| N11–Pt1–O4 | 90.6(5) | 92.8(9) | N111–Pt1–O41 | 92(2) | N112–Pt2–O42 | 95(1) |
| N11–Pt1–N1 | 174.8(5) | 174.9(8) | N111–Pt1–N11 | 166(2) | N112–Pt2–N12 | 176(1) |
| N1–Pt1–O4 | 84.5(5) | 83.2(8) | N11–Pt1–O41 | 82(1) | N12–Pt2–O42 | 81(1) |
| Pt1–N1–C2 | 110(1) | 105(2) | Pt1–N11–C21 | 110(2) | Pt2–N12–C22 | 110(2) |
| N1–C2–C3 | 111(1) | 108(2) | N11–C21–C31 | 106(3) | N12–C22–C32 | 111(2) |
| C2–C3–O3′ | 121(1) | 118(2) | C21–C31–O31′ | 121(3) | C22–C32–O32′ | 116(3) |
| O3′–C3–O4 | 121(2) | 121(3) | O31′–C31–O41 | 119(3) | O32′–C32–C42 | 129(3) |
| C2–C3–O4 | 119(1) | 120(3) | C21–C31–O41 | 121(3) | C22–C32–O42 | 115(3) |
| C3–O4–Pt1 | 115(1) | 112(2) | C31–O41–Pt1 | 113(2) | C32–O42–Pt2 | 122(2) |
| N1–C2–C2′ | | 110(2) | C31–C21–C41 | 108(3) | C32–C22–C42 | 108(3) |
| C2′–C2–C3 | | 115(3) | C41–C21–N11 | 111(3) | C42–C22–C62 | 117(3) |
| | | | C21–C41–C61 | 116(4) | C22–C42–C62 | 111(3) |
| | | | C21–C41–C51 | 107(3) | C22–C42–C52 | 106(3) |
| | | | C61–C41–C51 | 112(4) | C62–C42–C52 | 107(4) |

## Experimental

### *Materials and Methods*

The amino acids used were purchased from Fluka AG and Sigma Chemical Company. *cis*-DDP was prepared from $K_2PtCl_4$ (Degussa AG, F.R.C.), according to published methods [40, 41].

### *The Elemental Analysis of Pt*

The elemental analysis of Pt was carried out by burning a known amount of the complex at 900 °C in a furnace for 30 min, and weighing the remaining residue, consisting of pure Pt.

### *The Analysis for C, H, N*

The analysis for C, H and N was carried out at the Institut für Anorganische und Analytische Chemie, Universität Freiburg, 7800 Freiburg, F.R.G.

### *Measurements*

The conductivity measurements were performed in an E 365 B Conductoscope, Metrohm Ltd., Herisau, Switzerland.

### *IR Spectra*

The IR spectra were recorded on a Perkin-Elmer model 580 spectrophotometer, covering the region 4000–200 $cm^{-1}$, in KBr pellets of Nujol mulls, between KBr windows.

### *$^1H$ NMR Spectra*

$^1H$ NMR spectra were recorded on an AM-300 Bruker spectrophotometer (0.2M $D_2O$, $(CH_3)_4NBF_4$ as internal standard). Chemical shifts are given in ppm, relative to sodium 3-(trimethyl-silyl)propane sulfonate (3.118 ppm) upfield from the internal standard. pD values were measured with a glass electrode and obtained by adding 0.4 to the reading value.

### *Crystallography*

The X-ray data were collected at room temperature on a Philips PW-1100 single-crystal diffractometer by using graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). Crystal and structure determination data for **1**, **2** and **3** are listed in Table 4. Lp correction and at a larger stage an empirical absorption [42] correction were applied. The coordinates for the heavy metal atoms were determined from a three-dimensional Patterson map.

Subsequent $F$ syntheses lead to the positions of the non-hydrogen atoms. Hydrogens were ignored. All atoms were refined with anisotropic thermal parameters. Final atomic coordinates for **1**, **2** and **3** are given in Table 5. Complex scattering factors for neutral atoms were taken from ref. 43. For the calculations the SHELX program package was used [44].

*Preparation of the Compounds*

*cis*-$[Pt(NH_3)_2(gly)](NO_3)$ was prepared as described previously [8], from *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ which was prepared as described below. The corresponding chelates of the other amino acids could not be obtained by the same method and a slight modification was followed.

The *cis*-$[Pt(NH_3)_2(am\text{-}ac)](NO_3)$ chelates were prepared for the amino acids alaH, 2-abaH, n-valH and valH as follows. *cis*-DDP (2.5 mmol) was heated with 10 ml $H_2O$ at 40 °C under stirring. To the suspension, an aqueous solution of 4.9 mmol of $AgNO_3$ was added and the mixture was heated at 90 °C for 1–2 h. After cooling for some hours, the precipitated AgCl was filtered off (washed with warm $H_2O$). The filtrate was concentrated in a rotary evaporator to 7–8 ml and 7.5 mmol of the corresponding amino acid were added. The pH of the mixture, which was acidic, was adjusted to 4 with NaOH. Heating in a water bath (60 °C) followed for about 20 h keeping the pH constant at 4. After cooling the solution to room temperature and concentrating to 3 ml (the resulting precipitate was filtered off), it was passed through a Sephadex column (G-10, Pharmacia) using $H_2O$ as eluent. The unreacted amino acids were eluted first, followed by the complex. The latter was obtained as a crude material by evaporation of the water. Recrystallization from $H_2O$ gave white transparent crystals in all cases. The yield ranged between 60–70% but was only 29% for n-val.

*Preparation of the Deuteriated Derivatives*

These were prepared by dissolving the complexes in $D_2O$ and reprecipitating them with acetone. They were filtered off in a filter paper and washed with ether.

## Supplementary Material

The following items are available from the authors on request: a Table with the assignment of the various bands of the free and coordinated amino acids, as well as the counter anion, $NO_3^-$. They include among others, wagging and twisting modes of NH, rocking and wagging motions of $-COO^-$ and $CH_2$, $CH_3$ and skeletal vibrations; a Table with possible H-bonding interactions in the crystal structures of the three chelates; a Table for the observed and calculated structure factor amplitudes; a Table with the deviations of the atoms from the square plane of the central Pt(II) atom and the plane equations; the isotropic temperature factors $U_{ij}$.

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