TERNARY COMPLEXES OF *cis*-$(NH_3)_2PtCl_2$ (*cis*-DDP) WITH GUANOSINE (guo), CYTIDINE (cyd) AND THE AMINOACIDS GLYCINE (gly), L-ALANINE (ala), L-2-AMINOBUTYRIC ACID (2-aba), L-NORVALINE (nval) AND L-NORLEUCINE (nleu)

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Abstract

The ternary complexes of formulae *cis*-[$(NH_3)_2$Pt(nucl)(amac)]NO_3, where nucl=guo and cyd (guanosine and cytidine) and amac=the deprotonated aminoacids glycine (gly), L-alanine (ala), L-2-aminobutyric acid (2-aba), L-norvaline (nval) and L-norleucine (nleu), were prepared from the reactions of the binary chelated ones *cis*-[$(NH_3)_2$Pt(amac)]NO_3 with the nucleosides.

They were characterized by ^{1}H, ^{13}C and ^{195}Pt NMR and IR spectra, together with elemental analysis and conductivity measurements. The aminoacids coordinate with Pt(II) in the ternary complexes with their terminal -NH_2 groups, guo through N_7 and cyd through N_3. Ligand-ligand hydrophobic interactions were also observed in the ternary complexes and were stronger with longer aliphatic chains of the aminoacids. The ^3E sugar conformation increased by 5-7% in the ternary systems, as compared to the free nucleosides, while the percentage of the *gg* conformation remained almost constant and the one of the *anti* conformation of the sugar increased also slightly. Finally, the *h* conformer around the C_α-C_β bonds of the aminoacids reached a maximum in the binary systems and decreased again considerably in the ternary ones.

Introduction

In recent years, we have been studying ternary systems of Pt(II) and Pd(II) with nucleobases-nucleosides and aminoacids-peptides as the simpler models of DNA-Pt-protein crosslinks, known to take place with the anticancer drug *cis*-DDP and its inactive congener *trans*-DDP [1-11].

A large variety of complexes of general formulae, *cis*-[$(ino)_2$Pt(amac)]Cl_2, *cis*-[(ino_2)Pt(amacH)Cl]Cl, *trans*-[$(guo)_2$Pt(amacH)$_2$]Cl_2, *cis*-[$(NH_3)_2$Pt(Nb)(amac)]NO_3, *trans*-, *cis*-[$(NH_3)_2$Pt(9-MeG)(dipeptide)]$(NO_3)_2$, *cis*-[$(guo)_2$Pd(amac)]Cl, *cis*-[$(guo)_2$Pd(amacH)Cl]Cl, *trans*-[$(nucl)_2$Pd(dipeptide)$_2$]Cl_2 and *cis*-[$(nucl)_2$Pt(dipeptide esters)$_2$]Cl_2 (ino=inosine, guo=guanosine, Nb=9-methylguanine, 1-methylcytosine, 9-MeG=9-methylguanine, nucl=guo, ino, cyd (cytidine), amacH=zwitterionic form of aminoacids).

Sugar conformations and ligand-ligand interactions of the bases and aminoacids-peptides, simultaneously coordinated with Pt(II) were examined in these studies. For example, the hydrophobic ligand-ligand interactions are usually stronger with the increase of the aliphatic side chain of the aminoacids-peptides, but are usually weaker with increasing distance from the bonding sites. They are stronger in the *cis*- rather than the *trans*-series of complexes [3,7,8,10]. Also, the *anti* conformation of the sugar was increasing in the ternary complexes, compared to the free ligands and it was larger in the *trans*- than the *cis*-ternary complexes.

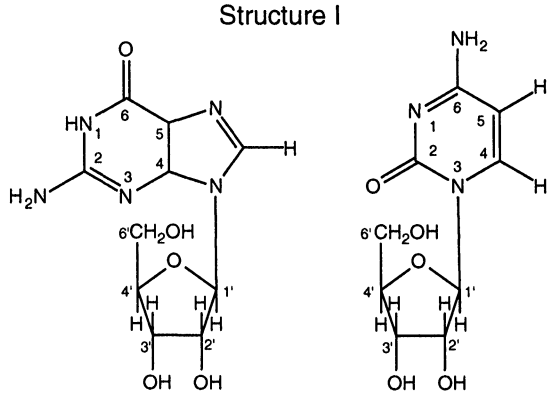
The present paper concludes our studies on such simple ternary systems. It reports on complexes of the general formulae *cis*-[$(NH_3)_2$Pt(nucl)(amac)]NO_3, where nucl is guo or cyd (Structure I) and amac the conjugated bases of the aminoacids glycine, L-alanine, L-2-aminobutyric acid, L-norvaline and L-norleucine. Similar ligand-ligand interactions and variations in sugar conformation were also found here and are compared with the previous results.

Experimental

Materials

All the L-aminoacids together with guanosine and cytidine were purchased from Sigma Chemical Company and were used without further purification. *Cis*-DDP was prepared from K_2PtCl_4 according to published methods [12,13].

Structure I



guanosine (guo) cytidine (cyd)

Methods

The elemental analysis (C,H,N) of the compounds was carried out on an EA-1108 Carlo Erba analyser at the Department of Chemistry of the University of Ioannina. The conductivity measurements were performed in an E365B Conductoscope, Metrohm Ltd., Herisau, Switzerland. The IR spectra were recorded in KBr pellets or nujol mulls on a Perkin-Elmer model 783 spectrophotometer, covering the region 4000-200 cm^{-1}. The ^{1}H-NMR spectra were recorded at room or higher temperatures on a Brucker AMX-400 MHz or a DRX-600 MHz spectrometer in D_2O, with TSP as internal reference. The usual ^{1}H spectrometer conditions consisted of 6024 Hz and 6009 Hz sweep widths in the 400 MHz and 600 MHz instruments respectively. 16 scans and 16K data points were used. A line broadening factor of 0.3 Hz was used in processing the data. ^{13}C NMR spectra were recorded on the same spectrometer (Brucker AMX-400 MHz) at 100.62 MHz. A sweep width of 22727 Hz , 2500-3000 scans (sample concentration 20 mM) and 16K data points were used, as well as a line broadening factor of 2.5 Hz in processing the data.

^{195}Pt NMR spectra were recorded on the Brucker AMX-400 MHz spectrometer at 86.02 MHz. Shifts are reported relative to K_2PtCl_6 (external standard 1630 ppm for K_2PtCl_6). Spectra were run typically with 40000 transients (sample concentration 20 mM) and a spectral width of 125 KHz. A pulse duration of 35.6 ms, followed by aquisition time of 65 ms and a delay time of 0.1 s was used. A line broadening factor of 25 Hz was used in the processing the data.

Preparation of the Complexes

The binary complexes cis-[$(NH_3)_2$Pt(amac)]NO_3 where amac=glycine, L-alanine, L-2-aminobutyric acid, L-norvaline and L-norleucine.

These were prepared according to previously described methods [14,15].

The complexes cis-[$(NH_3)_2$Pt(guo)(amac)]NO_3, where amac are the anions of the above aminoacids and nucl are guanosine or cytidine.

1.5 mmoles of guo or cyd were dissolved in about 100 ml of water under stirring at 60°C. 1 mmole of the complex *cis*-[$(NH_3)_2$Pt(amac)]NO_3 was added to the solution and this was stirred for 48 h at 60°C, in the dark. The pH of the solution was kept at 5 during the reaction, by addition of a 10^{-1} M solution of HNO_3. After cooling to 0°C and filtration of the unreacted guo, the solution was concentrated to 1 ml and passed through a Sephadex column (G-10, Pharmacia, 60 × 1.5 cm) using water as eluent. Fractions of 2 ml were collected. The ternary complexes of guo were eluted after unreacted binary ones (*cis*-[$(NH_3)_2$Pt(amac)]NO_3). Ocassionally, a second elution was required, in order to get pure complexes in larger amounts. The yields were varying 15-40 %.

Deuterated Complexes

These were prepared by dissolving the complexes in D_2O, followed by lyophilization.

Results and Discussion

The complexes were prepared according to the general reactions:

cis-[$(NH_3)_2Pt(H_2O)_2$]$(NO_3)_2$+amacH→cis-[$(NH_3)_2$Pt(amac)]NO_3+HNO_3+$2H_2O$ (1)

cis-[$(NH_3)_2$Pt(amac)]NO_3 + nucl → cis-[$(NH_3)_2$Pt(amac)(nucl)]NO_3 (2)

(amacH=glycine, L-alanine, L-2-aminobutyric acid, L-norvaline, L-norleucine and nucl=guanosine, cytidine).

The elemental analyses are in agreement with the general formulae of the complexes. The molar conductance values confirm the 1:1 electrolytic nature of the complexes.

Binding Sites

^{1}H-NMR

The chemical shifts of all compounds are included in Table I. The H_8 proton of guo in the ternary complexes shifts downfield by about 0.6 ppm compared to the free ligand, while the H_6 and H_5 aromatic protons of cyd by only 0.07-0.10 ppm, indicating N_7 and N_3 coordination with the metal, of guo and cyd respectively [11,16-19]. These shifts are smaller than the ones caused by *cis*- and *trans*-DDP bound to the same nucleosides of about 1 ppm [17,19]. It was explained by the hydrophobic ligand-ligand interactions, taking place between the aminoacids and the nucleosides, bound simultaneously to the same metal [7,8,11].

^{13}C-NMR

The results obtained from the ^{1}H-NMR spectra on the binding sites are confirmed by the ^{13}C-NMR spectra of the compounds [20,21]. All ^{13}C-NMR chemical shifts of the free aminoacids, the binary and the ternary complexes are given in Table II.

In the ternary complexes with guo all nucleoside carbon atoms are shifted downfield compared to the free ligand, with the most downfield shifted the C_8 atom (~7 ppm), near the N_7 binding site with Pt(II) of guo [20-22]. (See Table 2). In the cyd ternary complexes on the other hand, the C_2 atom near the binding site is shifted upfield by ~3 ppm, thus confirming the N_3 coordination with Pt(II) in solution [23,24]. The other base carbon atoms are not considerably shifted on passing from free cyd to its ternary complexes. It is worthwhile mentioning that most of cyd carbon atoms including the sugar are observed as doublets in the ternary complexes (Table II), thus confirming the hindered rotation around the Pt-N_3 bond, observed also in the ^{1}H-NMR spectra [24].

The aminoacid carbon atoms on the other hand, are also not considerably shifted in the complexes, except the C_α atoms near the -NH_2 coordination site with Pt(II) (2-3 ppm on passing from the free aminoacids to the binary complexes and ~6 ppm to the ternary ones) [11].

Finally, the terminal carboxylate carbons of the aminoacids shift by about 15 ppm on passing from the free aminoacids to their chelates with Pt(II), but only by about 3 ppm in the ternary complexes, thus confirming the non existence of the Pt-O bonds in the latter case.

^{195}Pt-NMR

The ^{195}Pt-NMR spectra of the compounds *cis*-$[(NH_3)_2Pt(gly)]NO_3$, *cis*-$[(NH_3)_2Pt(guo)(gly)]NO_3$ and *cis*-$[(NH_3)_2Pt(cyd)(gly)]NO_3$ were recorded in D_2O solutions. They all consist of a single band at -2128, -2560 and -2625 ppm respectively. The first corresponds to a PtN_3O coordination [25]. The two others to a PtN_4 coordination as expected [26].

IR Spectra

IR assignments, whenever possible, were based on deuteration experiments and literature data [3,4,8,9]. Characteristic bands are included in Table III.

The region of 2800-3500 cm^{-1} is covered by a very strong and broad band containing all the νNH_2, the νOH and aliphatic and aromatic νCH motions. This broad band shifts to about 2400 cm^{-1} upon deuteration.

In the region however 1500-1700 cm^{-1} the series of complexes *cis*-$[(NH_3)_2Pt(guo)(amac)]NO_3$ show a strong band near 1700 cm^{-1}, which is due to the overlapping of the νC=O of guo and of the $\nu^{as}(COO^-)$ of amac. This indicates N_7 coordination of guo and -NH_2 coordination of the aminoacids with the metal, as in other similar cases [3,4,27]. The other two maxima at 1635 and 1590 cm^{-1} have been assigned to δNH_2 and purine skeletal vibrations.

In the series *cis*-$[(NH_3)_2Pt(cyd)(amac)]NO_3$ on the other hand, the strong band near 1650 cm^{-1} has been attributed to the νC=O motion of cyd overlapped with the $\nu^{as}(COO^-)$ of the aminoacids. These indicate N_3 coordination of cyd and -NH_2 of the aminoacids [8,27].

Further in the guo ternary systems a decrease in the intensity of the band at 825 cm^{-1} is observed, together with an increase of the one at 802 cm^{-1}, compared to the free guo. This indicates an increase of the percentage of the $C_{3'}$-*endo* (^3E) sugar conformation in the complexes, as it is also suggested from the ^{1}H-NMR spectra (See *Sugar Conformation*).

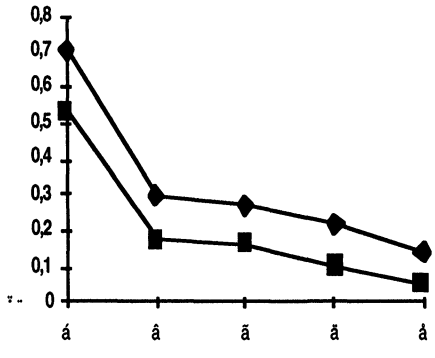
Ligand-Ligand Interactions

^{1}H-NMR spectra reveal the existence of hydrophobic ligand-ligand interactions in solution. Thus, the chemical shifts of the α -aliphatic protons of the aminoacids near the bonding sites with Pt(II), are observed upfield by about 0.7 ppm, on passing from the binary to the ternary complexes [8,18,19,28]. The shifts of the other aminoacid protons are also upfield in the ternary complexes, compared to the binary ones, but decreased with distance from the bonding sites (See Table I).

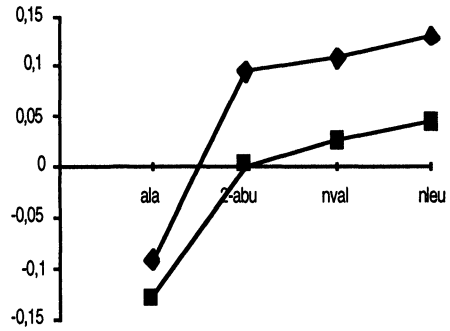
More particularly, the difference in chemical shifts, Δδ=δ amacH(free)-δ amac(tern.complex) between the zwitterionic forms of the aminoacids and their ternary complexes, given in Table IV, shows quantitatively the strength of ligand-ligand interactions [3,8,9]. They are larger in the case of guo complexes than cyd (See Figure 1).

Table V contains the difference in the chemical shifts of the terminal methyl groups of the anionic forms of the aminoacids and their ternary Pt(II) complexes, Δδ(ppm)=δamac-δtern.complex. The more positive Δδ values, the stronger the hydrophobic ligand-ligand interactions [8,28,29]. Thus,they increase with longer aliphatic side chain and they are stronger in the ternary guo complexes than in the cyd ones, as expected.

Figure I. (a) Difference in chemical shifts Δδ(ppm) of the protons of the zwitterionic form of nleu and the coordinated nleu in *cis*-$[(NH_3)_2Pt(guo)(nleu)]NO_3$ (◆) and *cis*-$[(NH_3)_2Pt(cyd)(nleu)]NO_3$ (■) ternary complexes (Positive Δδ values correspond to upfield shift upon coordination). (b) Variation of the Δδ(ppm) of the terminal methyl groups, of the anionic forms and the -NH_2 coordinated aminoacid anions in *cis*-$[(NH_3)_2Pt(guo)(amac)]NO_3$ (◆) and *cis*-$[(NH_3)_2Pt(cyd)(amac)]NO_3$ (■) ternary complexes.



(a)



(b)

Like in other similar cases [8,11], a hindered rotation around the Pt-N_3 bonding of the ternary complexes with cyd is also observed in the present system, except the complex containing also gly (See Figure II). Both H_6 and H_5 of cyd are shown up as two doublets in all the other cases containing chiral aminoacids [30-32] and it persists even at 90°C. Two sets of signals are also observed for the $H_{1'}$ sugar protons of cyd and two triplets for the á protons of the aminoacids (except glycine). This hindered rotation around the Pt-N_3 bonding was assigned to two diastereoisomers of head to tail oriented nucleobases and due to ortho substituents of cytidine [30,33].

Sugar Conformation

Estimation of the $^3J_{HH}$ coupling constants from the ^{1}H-NMR spectra and application of the Karplus equations [34-37] allows the calculation of the percentages of the various sugar conformations, i.e, ^3E=$C_{3'}$-*endo,anti* and ^2E=$C_{2'}$-*endo,anti* conformations of the furanose ring, the conformations around the $C_{4'}$-$C_{5'}$ bond of the sugar moiety, described also as *gg, gt* and *tg* conformations (See Figure III) and the *syn* and *anti* conformations of the sugar in the nucleosides.

The ^2E, ^3E and *gg* % conformations can be calculated from the equations:

$$X_{2E} = \frac{J_{1'2'}}{J_{1'2'}+J_{3'4'}} \quad (3) \qquad , \quad X_{3E} = \frac{J_{3'4'}}{J_{1'2'}+J_{3'4'}} \quad (4)$$

and

$$X_{3E} = \frac{J_{3'4'}}{J_{1'2'}+J_{3'4'}} \quad (5) \quad , \quad \text{with} \quad \Sigma = J_{4'5'}+J_{4'5''} \quad (6)$$

Figure II. Splitting of H_6, H_5 and $H_{1'}$ protons of Cyd in the *cis*-[$(NH_3)_2$Pt(cyd)(nval)]NO_3 ternary complex in the ^{1}H-NMR spectrum (D_2O, pD=5.5)

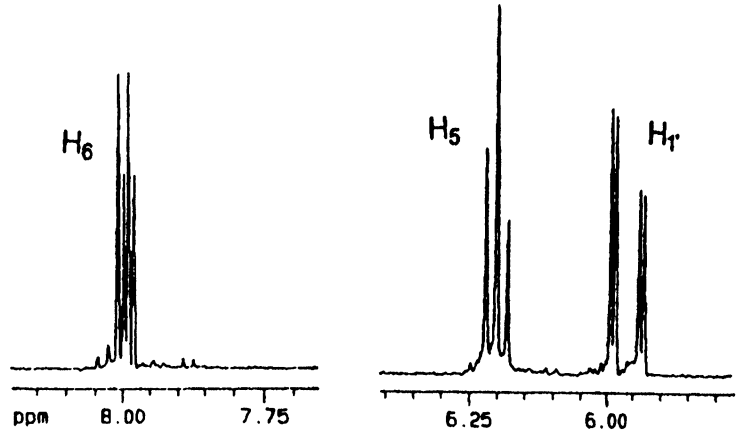
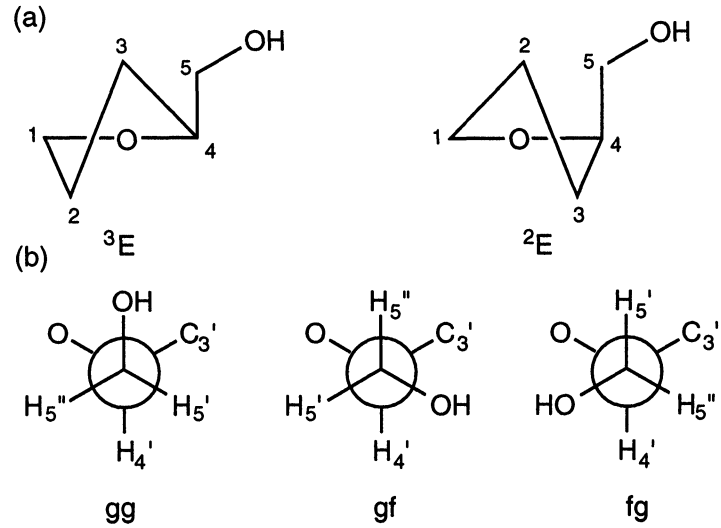


Figure III. (a) The ^3E=$C_{3'}$-*endo,anti* and the ^2E=$C_{2'}$-*endo,anti* conformations of the furanose ring. (b) The sugar *gg, gt* and *tg* conformations around the $C_{4'}$-$C_{5'}$ bond of the sugar moiety.



The ^{1}H-NMR chemical shifts of the sugar protons, the coupling constants and the percentages of the various conformers are included in Table VI.

The percentage of the ^3E conformation increases by about 5-7% from the value of 38% for free guo [35], in the ternary complexes with guo and it does not depend on the aminoacid. An increase of about 8-11% was found also in the case of the complexes *cis*-[$(guo)_2$Pt(dipeptide ester)$_2$]Cl_2 [11] and 9-10% in *trans*-[$(guo)_2$Pt(amacH)$_2$]Cl_2 [7]. The increase was a little higher in the Pd(II) series of complexes, *cis*-[$(guo)_2$Pd(amac)]Cl [4] and *trans*-[$(guo)_2$Pd(dipeptide)$_2$]Cl_2 [10], 11-16%, but in no case it was depending on the aminoacid or the peptide.

The ^3E percentage in the ternary complexes with cyd however, does not appear to change from the value of the free ligand, ~60% [35].

The percentage of the *gg* conformation around the $C_{4'}$-$C_{5'}$ bond on the other hand, remains almost constant in the ternary complexes, compared to free guo, as it is also true when the ligand was coordinated to *cis*-DDP [38,39]. However, it was found to decrease slightly in other similar systems [2,7,11]. In the case of the ternary complexes with cyd on the other hand, it decreases by 4-9% (See Table 6).

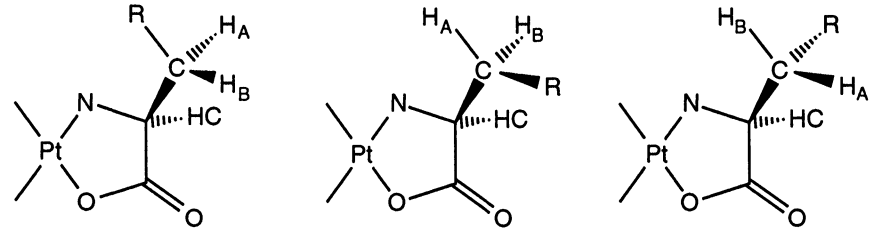
The percentage of the *syn-anti* conformations can be calculated from the relationship $\delta_{obs} = P_{syn}\delta_{syn} + P_{anti}\delta_{anti}$ (7), with ä the chemical shift of the $H_{2'}$ proton, assuming 100% *syn* conformation for

t-Buguo [39] with ä = 5.073 ppm and 100% *anti* conformation for the "closed" form of the compound *trans*-$[(guo)_2Pd(dipeptide)_2]Cl_2$ [3] with ä = 4.37 ppm. The results show a very slight increase of the *anti* conformation on passing from the free ligand to the ternary complexes. The increase of the *anti* conformation was much larger however in the *cis*-$[(guo)_2Pt(dipeptide\ ester)_2]Cl_2$ system [11].

Conformation Around the $C_á$-$C_â$ Bond of the Aminoacids

The percentage of the three possible conformations around the $C_á$-$C_â$ bond, *g, h, t,* designed in Figure 4 for aminoacids chelates, could be calculated in the case of the ternary complexes with cyd, where the sum of the coupling constants $J_{ÁÂ}+J_{BC}$ (Hz) [8,9,11,40] could also be calculated. In the case of the ternary complexes with guo, this sum could not be calculated, due to overlapping with sugar protons.

Figure IV. The three possible conformations *h, g, t* of the aminoacid chelates.



h *g* *t*

The results are included in Table VII.

Table VII: Vicinal coupling constants and rotamerdistribution in the ternary complexes with Cyd

Compound	J_{AB+BC} (Hz)	*h*(%)	*t+g*(%)	K
2-abaH	11.74	36.4	63.6	1.14
cis-$[(NH_3)_2Pt(2\text{-}aba)]NO_3$	10.11	51.3	48.7	2.11
cis-$[(NH_3)_2Pt(cyd)(2\text{-}aba)]NO_3$	12.29	31.3	68.7	0.91
nvalH	12.24	31.8	68.2	0.93
cis-$[(NH_3)_2Pt(nval)]NO_3$	10.02	52.1	47.9	2.18
cis-$[(NH_3)_2Pt(cyd)(nval)]NO_3$	12.59	28.5	71.5	0.80
nleuH	11.64	37.2	62.8	1.18
cis-$[(NH_3)_2Pt(nleu)]NO_3$	10.50	47.4	52.6	1.80
cis-$[(NH_3)_2Pt(cyd)(nleu)]NO_3$	12.64	28.1	71.9	0.78

Taken from Ref. 14, "Calculated from K=h/(1-h)/2

As expected [8,9,11], the percentage of the *h* conformer which directs the aliphatic side chain towards the metal ion (Fig. IV), increases first on passing from the free aminoacids to their chelates with Pt(II), by about 10-20%. However, on passing to the ternary complexes, a decrease of about 19-24% of the *h* conformer is again observed, with values lower than the ones of the free ligands. This is possibly due to the monocoordination of the aminoacids with Pt(II) through the terminal $-NH_2$ group alone and to the ligand-ligand interactions taking place in the ternary complexes.

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