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Platinum(II) and Palladium(II) Complexes with Amino Acid Derivatives. Synthesis, Interpretation of IR and ^{1}H NMR Spectra and Conformational Implications

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The Pt(II) and Pd(II) complexes of D,L-phenylglycine, D,L-phenylglycine-o-methyl ester and D,L-phenylglycine-o-benzyl ester have been prepared. The data of the elemental analysis, infrared and ^{1}H NMR spectra of the complexes and the free ligands have been analysed to determine the coordination sites. It was concluded that the amino acid derivatives behave as unidentate ligands, being bound to the metal atom via *the amino group only. The metal complexes are being tested for antitumour activity.*

Introduction

The cells of living organisms are surrounded by a semi-permeable membrane which is composed of hydrophobic proteins and in most cases is highly charged. Antitumour agents must have the structure which permits them to diffuse through the membrane and form strong linkages to biological molecules in the interior of the cell as a tool for their biological activity. Also, when designing antitumour chemical compounds we have to bear in mind their ionic or non-ionic character and any change of their lipophilicity that might occur inside the cell.

In the present investigation we synthesized complexes of Pt(II) and Pd(II) with D,L-phenylglycine and its o-methyl and o-benzyl esters and we studied their chemical structure by IR and ^{1}H NMR spectra, because these complexes have similarities to the *cis*-dichlorodiammineplatinum(II) prepared by Rosenberg *et al.* [1] and analogues containing other nitrogen compounds [2] which proved to be strong antitumour agents.

The *cis*-dichlorodiammineplatinum(II) has been proved as a strong anticancer drug destroying established tumours that fail to respond to other forms of treatment. The *trans* configuration showed to be inactive. The activity of the *cis*-isomers has been correlated to their mode of action, namely, that upon entering the cell they lose their two chlorine atoms leaving two positions empty for nucleophilic substitution, thus enabling the reaction with the DNA-protein particle in the interior of cell.

Furthermore, the amino acids are very important compounds for the transfer inside the cell of biologically active alkylating agents and especially the first of them, glycine [3]. Also, glycine was used by other researchers in the synthesis of complexes with Pt(II) and Pd(II) and their structure were studied [4].

Also, in collaboration with the U.S. National Cancer Institute, we have commenced a survey of the antitumour activity of the complexes of D,L-phenylglycine and its esters in the Leukaemia L1210 test system.

Results and Discussion

The D,L-phenylglycine and its esters and their complexes with Pt(II) and Pd(II) have been prepared as described in the experimental section. These compounds and their elemental analysis are listed in Table I.

The IR and ^{1}H NMR spectra of the free ligand and their complexes are listed in Table II and Table III respectively.

Of the various vibrational modes of the IR spectra the amino group stretching vibrations and the carboxyl group stretching vibrations are mainly identified because they are the most sensitive to changes of the metal–nitrogen and the metal–oxygen interactions which are also the most probable coordination sites. Also, we identified the M–nitrogen (where M is Pt or Pd) stretching vibrations and the M–chlorine stretching vibrations.

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TABLE I. Elemental Analysis of the Pt(II) and Pd(II) Complexes.

Compound	Molecular formula	M.p. (°C)	Analyses %	Calcd.	Found
			C	H	N
$(D,L\text{-PGly})_2PtCl_2$	$[C_6H_5CH(NH_2)COO]_2PtCl_2$	120	33.8	3.1	4.9
			33.7	3.0	4.7
$(D,L\text{-PGly})_2PdCl_2$	$[C_6H_5CH(NH_2)COO]_2PdCl_2$	189–92	40.0	3.7	5.8
			39.8	3.8	5.6
$(D,L\text{-PGly-oMe})_2PtCl_2$	$[C_6H_5CH(NH_2)COOCH_3]_2PtCl_2$	113–5	36.2	3.6	4.6
			36.5	3.8	4.3
$(D,L\text{-PGly-oMe})_2PdCl_2$	$[C_6H_5CH(NH_2)COOCH_3]_2PdCl_2$	165–7	42.4	4.3	5.5
			39.8	4.1	5.4
$(D,L\text{-PGly-oBz})_2PtCl_2$	$[C_6H_5CH(NH_2)COOCH_2C_6H_5]_2PtCl_2$	62	48.1	4.0	3.74
			47.8	4.2	3.5
$(D,L\text{-PGly-oBz})_2PdCl_2$	$[C_6H_5CH(NH_2)COOCH_2C_6H_5]_2PdCl_2$	60	54.6	4.5	4.2
			53.9	5.0	4.0

TABLE II. Assignment of Infrared Frequencies in cm^{-1} of Amino Acid Derivatives and their Pt(II) and Pd(II) Complexes.

Compound	IR frequencies (cm^{-1})[a]
D,L-PGly	210w, 228w, 280w, 315w, 350w, 388m, 472 m, 508s, 595s, 615w, 670s, 695s, 730s, 775vw, 855m, 900m, 920m, 968vw, 1025m, 1045m, 1075m, 1105vw, 1145m, 1165w, 1200m, 1298w, 1325w, 1340w, 1360s, 1405m, 1455s, 1520s, 1590vs, 1610w, 1622w, 1660w, 1952w, 2100w, 2300w, 2660w, $2900s_b$, 2980 s.
$(D,L\text{-PGly})_2PtCl_2$	210w, 225w, 250w, 280w, 340s, 400w, 550w, 585w, 605w, 665m, 700m, 735w, 805w, 940w, 1060w, 1000m, 1180w, 1260m, 1360w, 1395m, 1415w, 1440w, 1500w, 1660vs, 2440w, 2500w, 3030m, 3060w, 3110w, 3200w, 3250w, $3500m_b$.
$(D,L\text{-PGly})_2PdCl_2$	210w, 235w, 340w, 390m, 440w, 485m, 505s, 520m, 618vs, 690vs, 730s, 775s, 820m, 855w, 910w, 935m, 1000vw, 1020w, 1075m, 1145vs, 1192s, 1208s, 1260w, 1290w, 1315vs, 1335s, 1350s, 1450vs, 1495m, 1582vs, 1595s, 1630vs, 1660s, 3100s, 3250s.
D,L-PGly-oMe ester	210w, 225sh, 240w, 280w, 340m, 365sh, 445m, 460vw, 505s, 575s, 615m, 665m, 694s, 738s, 778m, 835m, 850w, 885m, 922m, 955s, 1000w, 1030m, 1054s, 1073w, 1135m, 1190m, 1250s, 1280w, 1295w, 1315w, 1335vw, 1350w, 1385w, 1435s, 1464w, 1500w, 1520w, 1580w, 1590w, 1700sh, 1744vs, 1895vw, 2830m, 2580w, $2820s_b$, $3080s_b$.
$(D,L\text{-PGly-oMe})_2PtCl_2$	210s, $225sh_w$, 240w, 265vw, 325m, 360w, 440vw, 495m, 525sh, 620vw, 645vs, 725w, 755w, 788w, 815vw, 860w, 925w, 970m, 1005w, 1030m, 1050s, 1080w, 1175vs, 1250vs, 1348w, 1375w, 1440s, 1455s, 1500m, 1565s, 1640w, 1660w, 1740vs, 2850sh, 2960m, 3100sh, 3190s.
$(D,L\text{-PGly-oMe})_2PdCl_2$	210w, 222w, 325sh, 332w, 390vw, 440vw, 485vw, 505m, 620m, 690s, 720m, 750w, 790w, 821w, 858w, 925w, 970w, 1005w, 1030w, 1055m, 1078w, 1150w, 1178m, 1195m, 1235s, 1255w, 1315m, 1335w, 1360w, 1435w, 1450s, 1490m, 1585s, 1590s, 1628vs, 1740vs, 2950w, 3110w, 3240s, 3270w.
D,L-PGly-oBz ester	210s, 240w, 278vw, 342m, 395w, 450m, 518vs, 580vw, 600w, 690vs, 720s, 730sh, 772m, 830m, 875m, 950s, 1030m, 1085s, 1145m, 1182s, 1230s, 1280w, 1310w, 1350m, 1392s, 1455m, 1500m, 1530m, 1600s, 1748vs, 2620w, $2960–2840s_b$.
$(D,L\text{-PGly-oBz})_2PtCl_2$	212w, 228w, 240w, 250w, 275w, 328m, 310sh, 378w, 450m, 484m, 505w, 575w, 600w, 615vw, 693vs, 745vs, 845w, 915m, 950m, 1004m, 1030s, 1050s, 1080m, 1170vs, 1215m, 1267vs, 1335w, 1350w, 1380w, 1400w, 1455s, 1498vs, 1565s, 1587s, 1740vs, 1810w, 1892w, 1960w, 3040vs, 3065vs, 3240sh.
$(D,L\text{-PGly-oBz})_2PdCl_2$	210s, 223sh, 240w, 278w, 335m, 450w, 478w, 505w, 575w, 695s, 745m, 780w, 850w, 910w, 950w, 1005w, 1030m, 1050m, 1080w, 1170s, 1225s, 1270m, 1342w, 1390w, 1450s, 1498m, 1565m, 1588m, 1740vs, 3040w, 3070w, 3230s, 3260w.

[a]Abbreviations: s = strong, m = medium, w = weak, sh = shoulder, v = very, b = broad.

TABLE III. Proton Chemical Shifts of Amino Acid Derivatives and their Complexes with Pt(II) and Pd(II) in ppm.

Compound	δC–H	δNH_2	δNH_3^+	δCH–φ and δCH_2–φ	δO–CH_3	δCH_2
D,L-PGly[b]	5.1		6.0	7.4		
$(D,L\text{-PGly})_2PtCl_2$[c]	–		–	–		
$(D,L\text{-Pgly})_2PdCl_2$[c]	–		–	–		
D,L-PGly-oMe[a]	5.2	3.3	9.25	7.5	3.7	
$(D,L\text{-PGly-oMe})_2PtCl_2$[a]	4.8	3.3[d]		7.3	3.6	
$(D,L\text{-PGly-oMe})_2PdCl_2$[a]	4.6	3.3[d]		7.4	3.6	
D,L-PGly-oBz[a]	5.1		6.5	7.3		5.2
				7.4		
$(D,L\text{-PGly-oBz})_2PtCl_2$[a]	4.7	3.2		7.3		4.9
				7.35		
$(D,L\text{-PGly-oBz})_2PdCl_2$[a]	4.5	3.4		7.0		5.1
				7.1		

[a]Compound was dissolved in DMSO. [b]Compound was dissolved in D_2O. [c]Compound was insoluble in the solvents used. [d]The band is broad.

In the ^1H NMR spectra we are mainly concerned for the proton chemical shifts for the C–H group of the coordination site M–N–C–H.

The interpretation of the IR and NMR spectra and the elemental analysis were used to clarify the chemical structure of the complexes. Our final aim is to correlate structural features of the complexes with their biological activity.

The results of the elemental analysis for C, H and N strongly support the ratio 2:1 between amino acid derivative and metal, when compared to the theoretical calculations.

The bands of IR spectra in the region 3000–3300 (cm^{-1}) for the complexes of D,L-PGly with Pt(II) and Pd(II) reveal that the N–H stretching vibration [in the free ligand the N–H band appears at 2980–2900 (cm^{-1})] is considerably changed upon the formation of the metal–nitrogen bond [5].

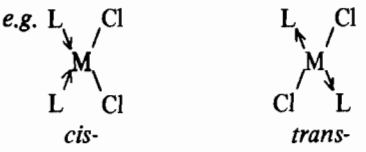
The same changes appear in the IR spectra of the complexes of D,L-PGly-oMe and D,L-PGly-oBz esters with Pt(II) and Pd(II) compared to the spectra of the free ligands.

The ^1H NMR spectra of the complexes indicate that the metal atoms are linked at the amino group. Comparison for the C–H bond in the free ligands and their complexes shows a considerable upfield shift due to complexation (Table III).

The IR spectra for the absorption bands of the carboxylic group shows no difference between the free ligands and their complexes, an indication that there is no coordination between the metals and the oxygen.

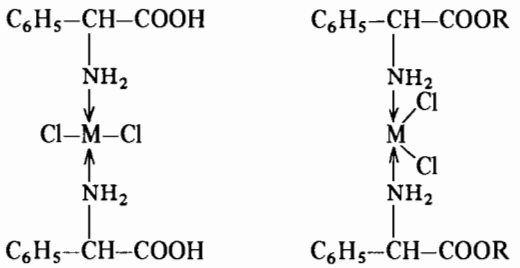
According to Nakamoto and Kieft [6], Lane *et al.* [7] and Watt and Klett [8] the absorption bands for the metal–nitrogen stretching vibration in complexes of amino acid derivatives with Pt(II) and Pd(II) have been assigned as weak bands at 550, near 440 and in the region 585–510 (cm^{-1}). For the complexes of D,L-PGly we observe a new band near 440 (cm^{-1}) which corresponds to the stretching vibration of the metal–nitrogen bond. In the case of D,L-PGly-oMe ester an absorption band appears at 445 (medium to weak) (cm^{-1}) whereas in their complexes with Pt(II) and Pd(II) the band becomes very weak, at 440 (cm^{-1}). As for the D,L-PGly-oBz ester, the metal–nitrogen stretching vibration appears at 450 w (cm^{-1}), and in its complexes the band at 450 is very weak. In the case of the Pt(II) complex a new band appears at 505 vw (cm^{-1}).

The absorption bands in the region near 340 (cm^{-1}) can be used as indicators for the *cis*- and *trans*-configurations for the metal–chlorine bonds. The *cis*-configuration shows two absorption bands because the stretching vibrations are additive (sometimes is a doublet and sometimes the one is the shoulder of the other), where the *trans*-configuration shows only one [9].



In the far infrared, the complexes of D,L-PGly-oMe and D,L-PGly-oBz esters with Pt(II) and Pd(II) show a doublet absorption band (in some a faint doublet and in others the one band appears as a shoulder of the other) at *ca.* 340 (cm^{-1}) for the metal–chlorine group, which can be an indication of *cis*-configuration. In the case of D,L-PGly complexes the IR spectra shows one sharp band at *ca.* 340 (cm^{-1}) which can be taken as an indication of *trans*-configuration.

From the above discussion we conclude that the most probable structures for the complexes are:



trans- *cis-*

(where M = Pt or Pd and R = $-CH_3$ or $-CH_2H_5C_6$).

Experimental

Preparation of Amino Acid Derivatives

Melting points were taken on a Büchi Mel-temp apparatus and are uncorrected.

D,L-phenylglycine (D,L-PGly)

Purum (Fluka AG, Switzerland). It was used without any further purification, m.p. 290–291 °C.

D,L-phenylglycine-o-methyl Ester Hydrochloride Salt (D,L-PGly-oMe)

This was prepared by the method of thionyl-chloride [10], m.p. 209–211 °C.

D,L-phenylglycine-o-benzyl Ester Hydrochloride Salt (D,L-PGly-oBz)

This was synthesised in three stages. First, we prepared the N-carbobenzoxy-D,L-phenylglycine according to the general method [11], second we prepared the anhydride of N-carbobenzoxy-D,L-phenylglycine and finally we esterified it with benzyl alcohol in ether solution saturated with HCl gas, m.p. 140–141 °C.

Preparation of Pt(II) Complexes

Preparation of Pt(II) complexes was achieved with the following general method in ratio 2:1 amino acid:metal. In a solution of $PtCl_2$ in 2 *N* HCl, which contained 0.001 mol of $PtCl_2$, we added 0.002 mol of the amino acid derivative and the solution was stirred with a magnetic stirrer at room temperature. The solution was then titrated with 1 *N* NaOH solution and stirring continued with parallel monitoring of the pH of the solution. The pH was kept in the range 5.0–6.5.

After one hour of continuous stirring the reaction mixture was evaporated at 40 °C under reduced pressure and the precipitate was filtered and washed with ether and acetone. Complexes were recrystallised and finally dried carefully in a vacuum desiccator.

Preparation of Pd(II) Complexes

The same method was used for the preparation of Pd(II) complexes in ratio 2:1 amino acid:metal. The pH was kept in the range 2.5–3.5. The metal used was in the form of a solution of $PdCl_2$ in 2 *N* HCl. Precipitates were filtered, washed with ether or acetone, recrystallised and dried in a vacuum desiccator.

Yields for the Pt(II) and Pd(II) complexes were in the range 70–80%. Purity of the complexes was tested by thin layer chromatography.

Infrared Absorption Spectra

Spectra were obtained by means of a Perkin-Elmer Infrared Spectrophotometer Model 283 B (4000–200 cm^{-1}) from samples prepared in accordance with the KBr disk technique.

^1H NMR Spectra

^1H NMR spectra were obtained by dissolving the amino acid derivatives and their complexes in DMSO or D_2O for less soluble compounds. Spectra were recorded with a Varian EM 360 proton NMR spectrophotometer (60 MHz) at room temperature. Chemical shifts were measured with respect to internal TMS in DMSO or deuterated DSS in D_2O.

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