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Pt(II) Complexes of Amino Acids and Peptides.
I. Structural Analysis of *trans*-[Cl_2Pt(L-HAlaOH)$_2$]

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Abstract

We have recently undertaken the synthesis and physicochemical characterization in solution and in the solid state of a series of amino acid and peptide complexes of Pt(II), in order to investigate the reactivity of these compounds toward the condensation reaction for the amide bond formation and to evaluate their usefulness in peptide synthesis. This is the first of a series of papers in preparation concerning the synthesis and characterization of *trans*-[Cl_2-Pt(L-HAlaOH)$_2$]. The solution results by IR and ^{1}H NMR spectroscopy and the detailed X-ray analysis of the structure in the solid state are reported.

Introduction

In recent years a number of researchers have been devoted to the use in peptide synthesis of metal ions as protecting groups of both the N- and C-terminal ends of a peptide chain. In particular, complexes of Cu(II) [1, 2], Co(III) [3, 4] and Pt(II) [5] have been used.

We have undertaken a study on the reactivity of the Pt(II) N-coordinated α-amino acids in the formation of the peptide bond, and therefore we have prepared a series of Pt(II) complexes, some of which have also been characterized by spectroscopic methods in solution and diffraction analysis in the solid state.

We report here the synthesis and crystal structure of the *trans*-bis(L-alanine)dichloroplatinum(II) complex as determined by X-ray diffraction, together with preliminary investigations in solution by IR and ^{1}H NMR spectroscopies.

Experimental

Equipment

^{1}H NMR spectra were recorder on a Brucker WH 270 spectrometer in $(CD_3)_2CO$ solution with Me_4Si as internal reference. Infrared spectra were recorded on a Perkin-Elmer 684 infrared spectrophotometer. The nujol mull technique with CsI plates was used. Optical activities were measured on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Mettler TC10 calorimeter. X-ray studies were performed using a Ni-filtered Cu Kα radiation and a pulse-height discrimination on a CAD-4 Enraf-Nonius diffractometer equipped with a PDP8/E and a PDP11/34 Digital computer of the 'Centro Interdipartimentale di Metodologie Chimico-Fisiche' at the University of Napoli.

Synthesis

According to Lifschitz and Froentjes [6], an aqueous solution of L-alanine and K_2PtCl_4 (molar ratio 8:1) was heated for 1 h in a water bath. White crystals (corresponding to the inner complex *trans*-[Pt(L-HAlaO$^-$)$_2$]) began to precipitate. The mixture was allowed to stand overnight and then *trans*-[Pt(L-HAlaO$^-$)$_2$] was filtered off, washed with cold water and dried at 110 °C; the yield was 75%. *trans*-[Pt(L-HAlaO$^-$)$_2$] in 5 N HCl was boiled for 4–5 min, cooled and filtered. The yellow *trans*-[Cl_2Pt(L-HAlaOH)$_2$] crystals were washed with water and dried (yield 80%; melting point (m.p.) 194 °C followed by decomposition). In order to verify the absence of racemization in the reactions, the amino acid was suspended in a small amount of concentrated HCl and treated with 1,2-bis(diphenylphosphino)ethanc (diphos); after slow but complete dissolution, the [Pt(diphos)$_2$]$^{2+}\cdot 2Cl^-$ complex began to precipitate. After 1 day the precipitate was filtered and the solution of HCl·L-HAlaOH was evaporated to dryness. The optical activity of the amino acid hydrochloride indicated the absence of racemization. The *trans* configuration of the desired compound was ascertained by IR because of the presence of a single Pt–Cl stretching band at 345 cm^{-1}. ^{1}H NMR characteristic data are: 1.65 (doublet, 6H, βCH_3); 3.82 (multiplet, 2H, αCH); 4.11 and 4.72 (multiplets, 4H, NH_2) ppm.

Unit Cell Determination and Data Collection

Suitable crystals for X-ray diffraction studies were obtained by slow evaporation of a water solution as

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TABLE I. Crystal Data

Molecular formula	$C_6H_{14}N_2O_4Cl_2Pt$
Molecular weight	442 a.m.u.
Space group	$P2_122_1$
Z (molecules/unit cell)	2
a (Å)	7.460(1)
b (Å)	8.544(1)
c (Å)	9.754(1)
Reflections ($I > 3.0\sigma(I)$)	681
Total reflections $1° \leqslant \theta \leqslant 70°$	720
R (unweighted)	0.038
R (weighted)	0.050
μ_R	2.1
D_{exp}	2.36
D_{calc}	2.373
Temperature	ambient
Radiation	Cu Kα 1.5418 Å

yellow regular prisms of $0.18 \times 0.15 \times 0.60$ mm. Preliminary oscillation and Weissenberg photographs taken with Cu Kα radiation indicated an orthorhombic symmetry with $P2_122_1$ space group. The refined unit cell dimensions and orientation matrix for data collection were determined using a least-squares procedure on the angular settings of 20 well centered high-angle reflections. In Table I the relevant crystallographic data are reported.

Density measurements carried out by flotation techniques enabled us to determine that the asymmetric unit is composed of a half molecule, imposing that the complex retains in the solid state a binary axis passing through the platinum atom.

Details of the data collection are given in the following. An ω–2θ scan mode with a scan angle $\Delta\omega = (1.0 + 0.35 \tan \theta)°$ was chosen for the peak measurements; background counts were taken on an additional area of $\Delta\omega/4°$ on both sides of the main scan with the same scan speed for each reflection. A distance crystal-counter of 368 mm was used with a horizontal and vertical counter entrance aperture of 4 mm and $(3.0 + 1.0 \tan \theta)$ mm, respectively. The tube placed between the goniometer head and the detector was evacuated using a vacuum pump. Prescan runs were made at a speed of 5°/min. Reflections with a net intensity $I \leqslant 0.5\sigma(I)$ were flagged as 'weak'; those having $I > 0.5\sigma(I)$ were measured at lower speed (in the range 1–5°/min) depending on the value of $\sigma(I)/I$. Two control reflections were measured every 60 min of X-ray exposure to monitor the crystal decay and the electronic stability of the apparatus; no significant change in their intensities was observed during the entire data collection.

A total of 720 reflections in the range 1–70° of θ was collected; of these 681 reflections had a net intensity greater than $3.0\sigma(I)$. These reflections were considered as 'oberved' and they were used in the subsequent calculations after correction for Lorentz and polarization effects. Anomalous dispersion correction for atomic scattering parameters were applied to the Pt, Cl, C, N, and O atom scattering curves. No absorption correction was applied since the μR calculated for the crystal used in the data collection, in the cylindrical approximation, presented a value of 2.1.

Structure Determination and Refinement

The structure of *trans*-[$Cl_2Pt(L\text{-}HAlaOH)_2$] was determined by direct application of the heavy-atom method. The positions of the Pt and the Cl atoms were calculated from the Patterson map and by successive Fourier synthesis the positions of the O, N, and C atoms of the independent unit were determined.

Refinement was carried out by full-matrix least-squares procedure with weights $w = 1/\sigma(F_o^2)$. Anisotropic temperature factors for Pt, Cl, O, N and C atoms were used. The hydrogen atoms in the stereochemical expected positions with isotropic temperature factors were included in the calculations and not refined. The final R factor values for the 681 observed reflections are $R = 0.038$ and $R_w = 0.050$. All calculations were carried out on the PDP 11 computer with the SDP set of crystallographic programs. The final atomic parameters are given in Table II.

TABLE II. Final Atomic Parameters[a]

Atom	x/a	y/b	z/c	B_{eq} [b]
Pt	0.0000(0)	0.8442(1)	0.5000(0)	1.02(3)
Cl	0.7454(7)	0.8410(62)	0.6326(4)	2.3(2)
N	0.8315(20)	0.8515(19)	0.3328(13)	1.8(6)
C^α	0.8671(26)	0.7541(20)	0.2087(17)	1.8(7)
C^β	0.8974(34)	0.5837(24)	0.2488(26)	3.8(10)
C'	0.7081(23)	0.7615(20)	0.1158(17)	1.7(6)
O(1)	0.7503(18)	0.7512(16)	−0.0150(13)	2.4(8)
O(2)	0.5580(17)	0.7696(18)	0.1585(11)	2.1(8)

[a] e.s.d.s (in unit of last significant digits) given in parentheses.
[b] B_{eq} defined as $4(B_{11}B_{22}B_{33}/a^{*2}b^{*2}c^{*2})^{1/3}$.

Results and Discussion

trans-[$Cl_2Pt(L\text{-}HAlaOH)_2$] was synthesized and purified in high yields using the procedure described earlier [6]. The amino acid was cleaved from the metal using diphos in HCl and measurements of optical rotation of the hydrolyzed amino acid revealed the absence of racemization. The compound was also characterized by IR and ^1H NMR spectroscopy, by which the *trans* configuration and the presence of a binary axes relating the two halves of the molecule were determined. Using suitable single crystals the structure was solved and accurately refined by X-ray diffraction techniques.

The platinum atom displays the square planar coordination with both the two chlorine and the two nitrogen atoms of the alanine molecules in the *trans* position.

The *trans*-[$Cl_2Pt(L\text{-}HAlaOH)_2$] complex retains in the solid state a crystallographic binary axis perpendicular to the square plane of coordination and passing through the platinum atom. This imposes that the platinum atom is in a special position and only half of the coordinated ligands represents the asymmetric unit (the presence of a binary axis imposes the same chirality for the two optically active C^{α} atoms). The square planar coordination around the heavy atom shows deviations from planarity mainly due to the release of intramolecular interactions generated by the organic moiety of the complex. In Fig. 1 a view of the molecular complex with the observed geometry is represented. It can be noted that, while bond lengths do not present deviations from the values observed for similar complexes [7, 8], the bond angles around the platinum atom are somehow different from the ideal values (90°, 180°), with deviations of about 3.3°. These deviations partially contribute to the release of the steric interactions between the methyl groups of the coordinated L-alanines and the chlorine atoms: the N–Pt–Cl angle on the side where these interactions occur is 93.4° (the distance between the methyl group and the platinum atom is 3.4 Å).

The organic molecule of L-alanine can be roughly described as planar with the exception of the methyl group (and the hydrogen atoms of the N and C^{α} atoms); the mean square deviations of each atom from the best plane passing through them are less than 0.3 Å. The dihedral angles around the C^{α}–C' bond, N–C^{α}–C'–O(1) and N–C^{α}–C'–O(2), are 148° and −33°, respectively: the resulting conformation is such that the N–C^{α} bond is nearly synplanar with the C'=O carbonyl bond. The angle between the mean plane of the square of coordination and the mean plane of the organic moiety is 13°. The dihedral angles Pt–N–C^{α}–C' and Pt–N–C^{α}–C^{β} are 170° and 51°, respectively so that the methyl group and the C' atom are in the g^{+} and t conformations with respect to the platinum atom.

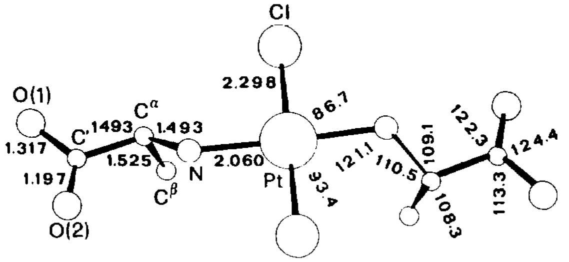

Fig. 1. Molecular structure of *trans*-[$Cl_2Pt(L\text{-}HAlaOH)_2$] with bond geometries. Estimated deviation of bond lengths and bond angles are less than 0.03 Å and 3° respectively.

In the solid state the crystal presents an extensive network of hydrogen bonds, in which are involved the carboxylic and the secondary amine groups of the alanine and the chlorine atoms. The structure is mainly characterized by double layers, held together by hydrogen bonds, while the double layers interact with each other by van der Waals interactions. Within a layer, the hydroxyl group of the carboxylic acid moiety of the coordinated alanine is involved in an intermolecular hydrogen bond of the type O–H··· O=C with a carbonyl oxygen of a symmetry related molecule (the resulting O···O distance is 2.68 Å) This interaction occurs in a plane nearly parallel to the (*ac*) plane, as shown in Fig. 2. The second strong H-bond interaction of the N–H···Cl type, within a layer, occurs between one of the two hydrogen atoms of the amino group and a chlorine atom of a symmetry related molecule (the N···Cl distance is 2.30 Å), as shown in Fig. 3 where the packing mode of the molecules as seen along the *b* direction is given. A third weaker H bond corresponds to an intramolecular interaction of the N–H···O=C type occurring in each coordinated alanine molecule with the formation of a cyclic structure of the C_5 type [9], similar to those recently observed in homopeptides of α,α-dialkylated glycines [10]. This interaction even if rather weak is also observed by infrared absorption of the complex in the solid state as demonstrated by the presence in the stretching region of the N–H groups of two distinct bands at 3260 and 3220 cm^{-1}, respectively (in addition, a third band

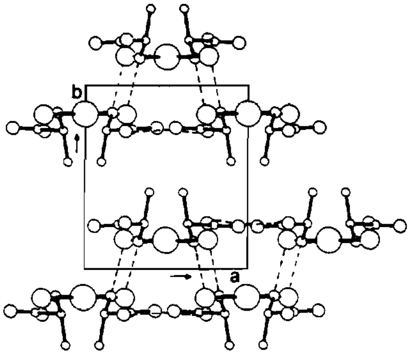

Fig. 2. Molecular packing of the molecule as seen along the *c* axis.

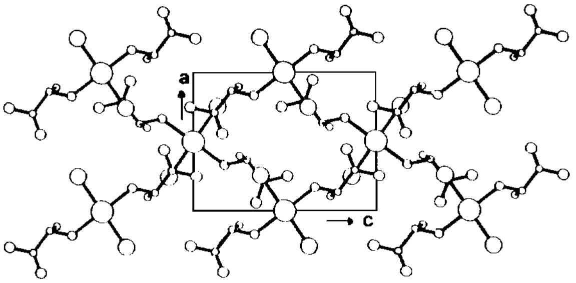

Fig. 3. Molecular packing of the molecule as seen along the *b* axis.

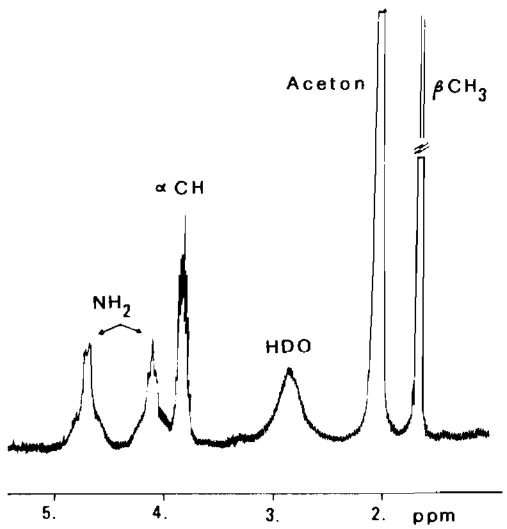

Fig. 4. ^{1}H NMR spectrum in $(CD_3)_2CO$ solution at 270 MHz; peak assignments are reported.

positioned at 3150 cm^{-1} can be attributed to the O–H stretching).

The ^{1}H NMR spectrum (Fig. 4) also shows two distinct resonances of the NH_2 protons at 4.11 and 4.72 ppm respectively. Each resonance could be tentatively attributed to a chemical equivalent pair of protons linked, however, to symmetry related N atoms. This follows from the observation that in $(CD_3)_2CO$ solution the molecule shows, also, one doublet resonance for the C^β protons and one multiplet for the C^α protons of both alanine moieties, thus indicating that the two organic halves of the complex are symmetry related.

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