Pt(II) complexes of amino acids and peptides
III. X-ray diffraction study of [Cl(Ph₃P)Pt(H-Aib-O)]

Angela Lombardi, Ornella Maglio, Vincenzo Pavone, Benedetto Di Blasio, Michele Saviano, Flavia Nastri, Carlo Pedone and Ettore Benedetti*

Biocrystallography Center of the C.N.R., Research Center of Bioactive Peptides, CEINGE, University of Naples, via Mezzocannone 4, 80134 Naples (Italy)

Abstract

The complex [Cl(Ph₃P)Pt(H-Aib-O)], where Ph₃P and H-Aib-O are triphenylphosphine and α-aminoisobutyrate, respectively, has been synthesized and characterized in the solid state by X-ray diffraction analysis. It crystallizes as a monohydrate in the triclinic system, space group $P\bar{1}$ with $a=9.020$, $b=10.011$, $c=13.748$ Å, $\alpha=91.74$, $\beta=90.29$, $\gamma=111.26°$ and $Z=2$ molecules per unit cell. The crystal structure has been solved by the Patterson technique and refined to a final R factor of 0.038 for the 3826 observed reflections with $I \geqslant 3.0\sigma(I)$. The Pt(II) atom displays the square planar coordination with the H-Aib-O⁻ amino acid acting as a bidentate ligand. The N atom of the H-Aib-O⁻ residue in *trans* position with respect to the P atom of the triphenylphosphine moiety and correspondingly the O atom of the carboxylate is *trans* to the chlorine atom. The observed distortions in the bond angles around the Pt(II) atom as well as the conformation assumed by the triphenylphosphine and the H-Aib-O⁻ residue can be all explained on the basis of the need to release the intramolecular non-bonded interactions between atoms of the various ligands. Three intermolecular hydrogen bonds, involving as donors the cocrystallized water molecule and the two hydrogen atoms of the N-H groups and as acceptors the chlorine, the oxygen of the water molecule, and one of the oxygen atoms of the carboxylic acid group, together with van der Waals interactions between hydrophobic groups held the molecules in the crystal state.

Introduction

Recently a number of reports have appeared on the synthesis and the structure of amino acids and peptide metal complexes [1–10]. These studies were aimed to investigate the use of metal ions in peptide synthesis as amino terminal protecting groups and their possible influence in the peptide bond formation [10–12]. We have already reported on the synthesis and structural characterization in solution and in the solid state of few platinum(II) complexes of α-amino acids and peptides [13–15]. In order to better evaluate the usefulness of this synthetic strategy in peptide chemistry, it would be of interest to prepare Pt(II) complexes containing only a single amino acid bound to the metal [16, 17] instead of the well characterized *cis* and *trans* bis-amino acid complexes [10–15; 18–20]. Also, metal complexes with a single amino acid residue as a monodentate ligand are of great interest in view of the possibility of carrying out reactions on this ligand with the aim

of growing only one single peptide chain which eventually would produce greater homogeneity in the final product.

The synthesis of Pt(II) complexes, having only one coordinated α-amino acid as a bidentate ligand, has been achieved by the reaction of dichlorobis-(triphenylphosphine)-μ,μ'-dichlorodiplatinum(II) with the α-amino acid. The complexes with the α-amino acid chelated to the metal either with the N-*cis* or N-*trans* configuration with respect to the phosphorous atom, depending on the synthetic procedure, were obtained.

In this paper we report the synthesis and the X-ray crystal structure analysis of the [Cl(Ph₃P)Pt(H-Aib-O)] complex. The choice of the Aib residue was based on the fact that we could test if the presence of the metal could influence the well known low reactivity toward peptide bond formation of the Aib residue which is correlated to its unusual conformational behaviour. Preparation of a series of complexes in which more than one amino acid residue has been coupled to the Aib directly linked to the platinum atom is now in progress.

*Author to whom correspondence should be addressed.

Experimental

Materials and equipment

All solvents and reagents were of analytical grade and were used without further purification. Aib was purchased from Fluka. $CDCl_3$ and TMS were Aldrich products. Precoated silica gel G-60 (Merck, F-254) was used for thin layer chromatography (tlc); for the detection of the product both the ninhydrin reaction and iodine vapor staining were used. $Cl_2Pt_2(\mu\text{-}Cl)_2(PPh_3)_2$ was synthesized according to the literature method [21].

Melting points were determined on a Mettler TC 10 Calorimeter and are uncorrected. ^1H NMR spectra were recorded on a Bruker WH 270 spectrometer in $CDCl_3$ solution with TMS as internal reference.

X-ray analyses were performed using graphite monochromated Cu $K\alpha$ radiation and a pulse-high discrimination on a CAD-4 Enraf-Nonius diffractometer equipped with a MicroVax II of the 'Centro Interdipartimentale di Metodologie Chimicofisiche' of the University of Naples.

Synthesis of [Cl(Ph₃P)Pt(H-Aib-O)]

To a solution of dimeric complex $Cl_2(\mu\text{-}Cl)_2Pt_2(PPh_3)_2$ (528 mg, 0.5 mmol) in ethyl alcohol (15 ml) H-Aib-OH (1 mmol, 103 mg), dissolved in the minimal amount of the same solvent, was added. After a few minutes 1 ml of 1 M KOH ethanolic solution was added dropwise; a yellow solid began to precipitate. The reaction mixture was allowed to stand overnight at room temperature under stirring and then it was concentrated under reduced pressure. The precipitate was filtered, washed with cold water and dried. A total of 433 mg of the title compound was obtained (yield 73%). $R_f = 0.74$ in ethyl acetate; m.p. (uncorrected) 389 K; δ_H (CDCl₃) 1.52 (6H, s, βCH₃), 3.62 (2H, m, NH₂), 7.35–7.88 (15H, m, Ph).

X-ray diffraction analysis

Unit cell determination and data collection

Suitable crystals for X-ray diffraction analysis were obtained by slow evaporation of an acetone solution. Preliminary Weissenberg photographs were used to determine the crystal system and the space group. Unit cell determination was carried out by least-squares refinement of the setting angles of 20 high angles reflections accurately centered. Crystallographic data are given in Table 1. For data collection the analysis of the peak profile suggested an ω–2Θ scan mode with a range of $(1.0 + 0.35 \tan \Theta)°$ for the peak measurements; background counts were taken at both sides of each scan. A distance crystal-counter of 368 mm was used with a counter entrance aperture of 4 mm. The tube placed between the goniometer head and the detector was evacuated by using a vacuum pump. Prescan runs

TABLE 1. Crystallographic data for [Cl(Ph₃P)Pt(H-Aib-O)]

Molecular formula	$C_{22}H_{23}NO_2PClPt \cdot H_2O$
Molecular weight (amu)	612.97
Crystal habit	needles
Crystal system	triclinic
Space group	$P\bar{1}$
Z, molecules/unit cell	2
a (Å)	9.020(1)
b (Å)	10.011(2)
c (Å)	13.748(1)
α (°)	91.74(1)
β (°)	90.29(1)
γ (°)	111.26(1)
V (Å³)	1156.3
μ_r (cm⁻¹)	134.1
D_{calc} (g/cm³)	1.760
Radiation (Å)	Cu $K\alpha$ (1.5418)
Measured reflections	4648
Observed reflections (with $I > 3\sigma(I)$)	3826
R factor	0.038
R factor, weighted	0.042
Weighting scheme used	unit weights
No. parameters refined	262
Temperature (°C)	22
Solvent of crystallization	acetone

were made at a speed of 4°/min. Reflections with a net intensity $I \leqslant \sigma(I)0.5$ were flagged as 'weak'; those with $I > \sigma(I)0.5$ were measured at lower speed in the range 1–4°/min, depending on the value $\sigma(I)/I$. The maximum time allowed for the scan was set to 60 s. Three intensity-control reflections were recorded every 60 min of X-ray exposure time; no significant change in their intensity was observed during data collection. A total of 4648 independent reflections was measured and corrected for Lorentz and polarization factors; of these 3826 were considered 'observed', having net intensity I greater than $3\sigma(I)$. The empirical method of Walker and Stuart [22] for correcting diffractometer data for absorption effects was applied.

Structure determination and refinement

The structure has been solved by Patterson techniques. The positions of the Pt, P and Cl atoms were unequivocally determined from a sharpened Patterson map. By a difference Fourier map it was possible to locate the rest of the atoms except the hydrogen atoms, which were later introduced in the calculations in their stereochemically expected positions. During the refinement a peak in the difference Fourier was detected, which was easily assigned, as proved by the successive refinement, to a cocrystallized water molecule. All Pt, P, Cl, C, N and O atoms were refined anisotropically. The parameters of the hydrogen atoms were included in the refinement, but they were kept fixed with isotropic thermal factors equal to the equivalent B of the carrier

TABLE 2. Final positional parameters and equivalent thermal factors for [Cl(Ph₃P)Pt(H-Aib-O)]

	x/a	y/b	z/c	$B_{eq}{}^a$
Pt	0.1471(0)	0.2773(0)	0.1452(0)	4.44(1)
Cl	0.0059(5)	0.0423(2)	0.1753(1)	11.49(11)
P	0.0928(1)	0.3531(1)	0.2908(1)	2.95(3)
N	0.1988(9)	0.2271(6)	0.0038(4)	6.92(17)
C$^\alpha$	0.2018(10)	0.3497(8)	−0.0570(5)	5.26(18)
C$^{\beta 1}$	0.0325(11)	0.3368(9)	−0.0761(6)	6.26(23)
C$^{\beta 2}$	0.2881(12)	0.3481(10)	−0.1519(6)	6.89(25)
C′	0.2837(11)	0.4829(9)	0.0047(5)	5.84(22)
O	0.3597(11)	0.5941(7)	−0.0325(4)	10.12(27)
O*	0.2666(6)	0.4728(5)	0.0985(3)	5.11(13)
C1	0.1576(6)	0.5470(6)	0.3020(4)	2.90(12)
C2	0.3130(8)	0.6301(7)	0.2782(4)	3.80(15)
C3	0.3641(9)	0.7785(8)	0.2805(5)	4.44(18)
C4	0.2606(10)	0.8448(7)	0.3068(5)	4.92(19)
C5	0.1052(9)	0.7639(7)	0.3317(5)	4.73(17)
C6	0.0549(7)	0.6157(6)	0.3925(4)	3.46(13)
C7	0.1760(7)	0.3015(6)	0.3984(4)	3.21(13)
C8	0.2591(8)	0.4019(7)	0.4698(4)	4.37(16)
C9	0.3139(9)	0.3565(8)	0.5537(5)	5.04(19)
C10	0.2849(9)	0.2153(8)	0.5658(5)	5.21(18)
C11	0.2008(9)	0.1150(7)	0.4959(5)	4.94(17)
C12	0.1469(8)	0.1581(7)	0.4124(4)	4.06(15)
C13	−0.1172(7)	0.2926(6)	0.3122(4)	3.44(14)
C14	−0.1808(8)	0.2627(7)	0.4049(5)	4.31(16)
C15	−0.3402(9)	0.2293(8)	0.4201(6)	5.32(20)
C16	−0.4402(10)	0.2269(9)	0.3427(7)	5.87(23)
C17	−0.3808(10)	0.2539(10)	0.2499(7)	6.53(25)
C18	−0.2197(10)	0.2852(9)	0.2348(5)	5.26(21)
Ow	0.4622(16)	0.1469(16)	0.9834(11)	21.56(60)

$^a B_{eq} = 4/3[a^2 B_{11} + b^2 B_{22} + c^2 B_{33} + ab(\cos \gamma)B_{12} + ac(\cos \beta)B_{13} + bc(\cos \alpha)B_{23}]$.

atom. The scattering factors for all atomic species were calculated from Cromer and Waber [23]. A MicroVAX computer with the SDP set of crystallographic programs was used for all calculations. The final values for the conventional and weighted R factors are 0.038 and 0.042, respectively, for the observed reflections and an estimated standard deviation for a unit weight reflection of 1.69.

Final positional parameters and equivalent thermal factors for Pt, P, Cl, O, N, and C atoms are reported in Table 2. A full list of bond lengths, bond angles and torsion angles is given in Table 3.

Results and discussion

In Fig. 1 the molecular model of the Pt(II) complex is illustrated. The platinum atom displays the square planar coordination: two corners of the square plane are occupied by the N and O atoms of the amino acid moiety, which acts as a bidentate ligand; the chlorine atom in *trans* position to the O atom, and the P atom of the triphenylphosphine moiety in *trans* position to

the N atom occupy the other two corners of the square of coordination. Within experimental error, the bond lengths Pt–N, Pt–O, Pt–P and Pt–Cl in the complex do not present appreciable differences from the literature data [14, 15, 24, 25]. The four atoms coordinated to the metal lie in a plane with very small (less than 0.003 Å) deviation from it. The metal atom lies below this plane (0.052 Å). Considerable distortion takes place in the geometry of the square planar coordination as clearly shown by the bond angles around the platinum atom: three angles are larger while one is smaller than the ideal 90° value. In fact the bond angle N–Pt–O*, which is internal to the five-membered ring system generated by the bidentate coordination, became as small as 79.6°, while the other three bond angles present small increases with respect to the ideal value of 90° (of the order of 2–5°). The increases of the O*–Pt–P and Cl–Pt–P and Cl–Pt–N angles are clearly due mostly do the need of releasing intramolecular and, to a lesser extent, intermolecular non-bonded interactions occurring between atoms of both the phenyl rings of the triphenylphosphine moiety and the methyl groups of the α-amino isobutyric acid moiety and the atoms coordinated to the platinum. Furthermore, the need to release the strains deriving from ring closure in the amino acid moiety should also be held responsible in part for the lowering of the N–Pt–O* bond angle, which is of the same order usually observed for chelated amino acid residue, as for example in the glycinato–Pt(II) compounds [25] or other Pt(II) complexes of Aib recently reported by us [15, 26].

The Cl atom is found in a staggered conformation with respect to the C1, C7 and C13 atoms of the phenyl rings: the dihedral angles Cl–Pt–P–C1, Cl–Pt–P–C7 and Cl–Pt–P–C13 are −171.9, 66.2 and −55.0°, respectively. On the contrary, the O* atom coordinated to the platinum is in an eclipsed conformation with the C1 atom, the dihedral angle O*–Pt–P–C1 is 5.2°, and in skew conformation with respect to both C7 and C13, the dihedral angles O*–Pt–P–C7 and O*–Pt–P–C13 are −116.6° and 122.1°, respectively. In this conformation the intramolecular interactions are minimized even if some short contacts still remain, as, for example, between the O* atom and the C2 atom which presents a distance of 2.83 Å. The release of intramolecular interactions is also obtained through both the opening of the angles Pt–P–C with values in the range 112–118° and the decrease of the angles C–P–C on the P atom, which on average present a value of 104°, significantly lower than the ideal tetrahedral value.

In the complex the α-amino acid moiety presents a folded conformation with values for the ϕ and ψ dihedral angles (Pt–N–C$^\alpha$–C′ and N–C$^\alpha$–C′–O*) of 40.3 and −31.1°, respectively. α-Aminoisobutyric acid residues in peptides usually show conformational constraints

TABLE 3. Bonds lengths, bond angles and torsion angles for [Cl(Ph$_3$P)Pt(H-Aib-O)] with e.s.d.s. in parentheses

Bond lengths (Å)

Pt–Cl	2.285(2)	N–C$^\alpha$	1.498(7)	C1–C6	1.387(7)	C8–C9	1.403(9)
Pt–P	2.238(1)	C$^\alpha$–C$^{\beta 1}$	1.506(13)	C2–C3	1.386(7)	C9–C10	1.357(8)
Pt–N	2.091(6)	C$^\alpha$–C$^{\beta 2}$	1.525(11)	C3–C4	1.372(9)	C10–C11	1.374(10)
Pt–O*	1.990(4)	C$^\alpha$–C'	1.502(9)	C4–C5	1.392(11)	C11–C12	1.385(9)
P–C1	1.814(4)	C'–O	1.206(10)	C5–C6	1.384(6)	C13–C14	1.396(9)
P–C7	1.826(6)	C'–O*	1.302(9)	C7–C8	1.386(8)	C13–C18	1.388(10)
P–C13	1.796(7)	C1–C2	1.393(9)	C7–C12	1.383(6)	C14–C15	1.372(11)
C15–C16	1.385(12)	C16–C17	1.382(13)	C17–C18	1.389(12)		

Bond angles (°)

Cl–Pt–P	92.8(1)	N–C$^\alpha$–C'	105.8(10)	C1–C6–C5	120.6(9)
Cl–Pt–N	92.3(3)	C$^{\beta 1}$–C$^\alpha$–C$^{\beta 2}$	111.2(11)	P–C7–C8	121.5(7)
Cl–Pt–O*	171.6(3)	C$^{\beta 1}$–C$^\alpha$–C'	108.7(10)	P–C7–C12	119.4(7)
P–Pt–N	174.0(3)	C$^{\beta 2}$–C$^\alpha$–C'	112.3(10)	C8–C7–C12	118.9(9)
P–Pt–O*	95.1(2)	C$^\alpha$–C'–O	120.5(12)	C7–C8–C9	119.6(10)
N–Pt–O*	79.6(4)	C$^\alpha$–C'–O*	117.2(11)	C8–C9–C10	120.5(11)
Pt–P–C1	112.5(3)	O–C'–O*	122.4(12)	C9–C10–C11	120.1(11)
Pt–P–C7	117.6(3)	Pt–O*–C'	115.9(8)	C10–C11–C12	120.0(11)
Pt–P–C13	112.2(3)	P–C1–C2	119.3(7)	C7–C12–C11	120.7(10)
C1–P–C7	104.8(4)	P–C1–C6	121.9(7)	P–C13–C14	122.5(8)
C1–P–C13	104.1(4)	C2–C1–C6	118.7(8)	P–C13–C18	118.8(8)
C7–P–C13	104.5(4)	C1–C2–C3	120.9(10)	C14–C13–C18	118.5(10)
Pt–N–C$^\alpha$	106.3(7)	C2–C3–C4	119.7(11)	C13–C14–C15	121.1(10)
N–C$^\alpha$–C$^{\beta 1}$	108.1(10)	C3–C4–C5	120.3(11)	C14–C15–C16	119.7(12)
N–C$^\alpha$–C$^{\beta 2}$	110.4(10)	C4–C5–C6	119.8(11)	C15–C16–C17	120.3(13)
C16–C17–C18	119.6(13)	C13–C18–C17	120.7(12)		

Torsion angles (°)

C$^\alpha$–N–Pt–Cl	145.9(8)	C4–C3–C2–C1	0.2(10)	C12–C7–P–C1	179.5(10)
C$^\alpha$–N–Pt–P	−4.0(6)	C4–C5–C6–C1	−0.4(10)	C12–C7–C8–C9	1.0(10)
C$^\alpha$–C'–O*–Pt	4.4(6)	C5–C4–C3–C2	0.5(11)	C12–C11–C10–C9	0.6(11)
C$^{\beta 1}$–C$^\alpha$–N–Pt	−76.0(9)	C5–C6–C1–P	−176.1(12)	C13–P–Pt–Cl	−55.0(4)
C$^{\beta 2}$–C$^\alpha$–N–Pt	162.1(12)	C5–C6–C1–C2	1.1(10)	C13–P–Pt–N	95.0(5)
C'–C$^\alpha$–N–Pt	40.3(7)	C6–C1–P–Pt	126.3(9)	C13–P–Pt–O*	122.1(4)
C'–O*–Pt–Cl	−1.2(7)	C6–C1–C2–C3	−0.9(10)	C13–P–C1–C2	−172.5(6)
C'–O*–Pt–P	−161.2(9)	C6–C5–C4–C3	−0.3(11)	C13–P–C1–C6	4.7(6)
C'–O*–Pt–N	16.0(8)	C7–P–Pt–Cl	66.2(4)	C13–P–C7–C8	−105.3(7)
O–C'–C$^\alpha$–N	149.9(15)	C7–P–Pt–N	−143.8(5)	C13–P–C7–C12	70.3(7)
O–C'–C$^\alpha$–C$^{\beta 1}$	−94.2(14)	C7–P–Pt–O*	−116.6(4)	C14–C13–P–Pt	148.2(10)
O–C'–C$^\alpha$–C$^{\beta 2}$	29.4(13)	C7–P–C1–C2	78.1(6)	C14–C13–P–C1	−89.9(9)
O–C'–O*–Pt	−176.6(19)	C7–P–C1–C6	−104.8(6)	C14–C13–P–C7	19.7(8)
O*–Pt–N–C$^\alpha$	−31.6(6)	C8–C7–P–Pt	129.5(9)	C15–C14–C13–P	174.0(14)
O*–C'–C$^\alpha$–N	−31.1(10)	C8–C7–P–C1	3.8(8)	C16–C15–C14–C13	−1.0(11)
O*–C'–C$^\alpha$–C$^{\beta 1}$	84.8(12)	C9–C8–C7–P	176.7(13)	C16–C17–C18–C13	−1.3(12)
O*–C'–C$^\alpha$–C$^{\beta 2}$	−151.6(14)	C10–C9–C8–C7	−0.6(11)	C17–C16–C15–C14	1.9(13)
C1–P–Pt–Cl	−171.9(4)	C10–C11–C12–C7	−0.2(10)	C17–C18–C13–P	−173.0(16)
C1–P–Pt–N	−22.0(4)	C11–C10–C9–C8	−0.2(11)	C17–C18–C13–C14	2.2(12)
C1–P–Pt–O*	5.3(4)	C11–C12–C7–P	−176.4(13)	C18–C13–P–Pt	−36.7(8)
C2–C1–P–Pt	−50.8(7)	C11–C12–C7–C8	−0.6(10)	C18–C13–P–C1	85.1(9)
C3–C2–C1–P	176.3(13)	C12–C7–P–Pt	−54.8(7)	C18–C13–P–C7	−165.2(11)
C18–C13–C14–C15	−1.1(11)	C18–C17–C16–C15	−0.8(13)		

since only helical (both of 3$_{10}$- or α-type) and, much more rarely, extended structures have been observed [27–34]. In the present work this residue is chelated to the metal and the values observed for the conformational angles are to be considered quite unique; the rather high energy spent in achieving this conformation must be evidently largely compensated by the formation of two bonds per residue with the platinum atom. The observed conformation is rather similar to that described recently by us for another Aib chelate of Pt(II) [15]. The conformation found for the Aib residue in this compound, as well as in previously described complexes [15], is not among the minimum energy conformations. Theoretical calculation and solid state experimental observations have shown that the more common conformation is characterized by ϕ and ψ values of about −60 and −30° (or the centrosymmetric 60 and 30°), which are correct for the helical region, while other
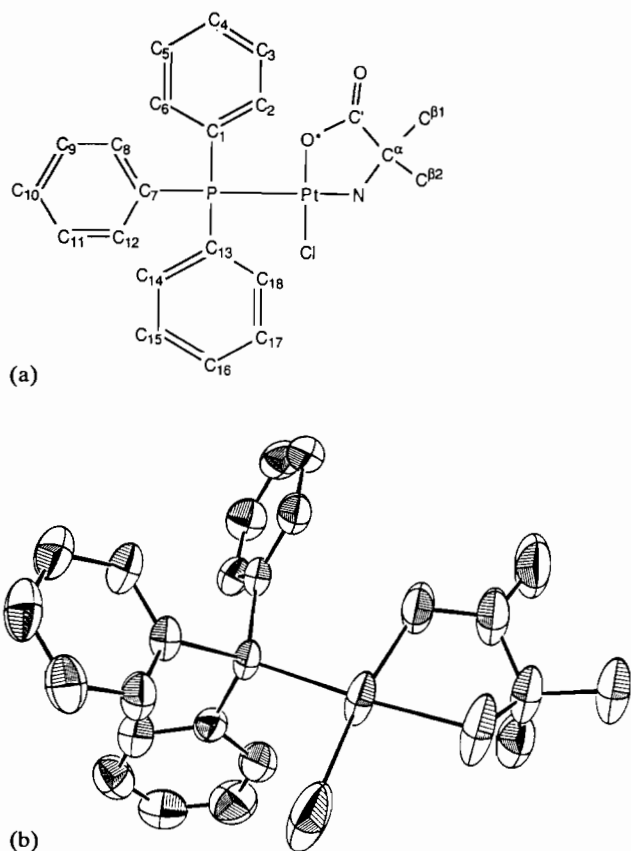
(a)

(b)

Fig. 1. (a) Schematic view of the [Cl(Ph₃P)Pt(H-Aib-O)] complex with atoms symbols and numerals. (b) ORTEP projection of the complex. The thermal ellipsoids are drawn at 50% probability level. The hydrogens are omitted for clarity.

higher energy conformations, falling in the extended region of the ϕ–ψ map are still possible. The five-membered ring system in which the Aib residue is involved when coordinated to the Pt(II) atom is therefore responsible for the unusual conformation observed. The five-membered ring system assumes an envelope conformation in which the nitrogen atom is grossly out of the mean plane of the other four atoms of the ring, similar to what we have recently observed in other Pt(II) complexes presenting α-amino acid residues acting as bidentates [15, 26].

As shown by the mode of packing represented in Fig. 2, in the solid state the molecules of the complex are held together by the three intermolecular H bonds N–H₁···Cl, N–H₂···Ow and Ow–H···O types, occurring between the cocrystallized water molecules and symmetry related complex molecules. The interactions N–H₂···Ow (2.78 Å) and Ow–H···O (2.57 Å) are considered quite strong [35, 36] while the interaction N–H₁···Cl (3.56 Å) is much weaker. Details of these interactions are given in Table 4. Van der Waals forces between hydrophobic phenyl and methyl groups further contribute to the crystal stability.
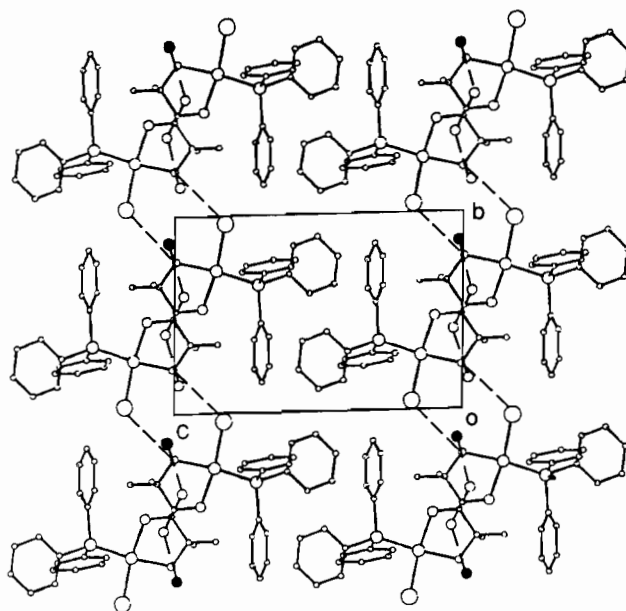

Fig. 2. Mode of packing of the [Cl(Ph₃P)Pt(H-Aib-O)] complex as view along the [100] direction. The intermolecular H bonds are indicated by dashed lines.

TABLE 4. Intermolecular hydrogen bonds for [Cl(Ph₃P)Pt(H-Aib-O)]

Donor	Acceptor	Length (Å) (D···A)	Angle (°) (D···A–X)	Symmetry operation
N–H₂	Ow	2.78	–	x, y, z
Ow	O	2.57	140	$1-x, 1-y, -z$
N–H₁	Cl	3.56	125	$-x, -y, -z$

Conclusions

The results of the present work indicate that this Pt(II) complex, being rather crowded, shows irregular geometric parameters and unusual conformational features. Furthermore, the role of geometry and conformation in determining reaction pathways can be related to the reactivity of this molecule toward peptide bond formation.

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