

Pt(II) complexes of amino acids and peptides

II. Structural analysis of *trans*-[Cl₂-Pt-(H-Aib-OH)₂] and *trans*-[Pt-(H-Aib-O⁻)₂]

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

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

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Abstract

The *trans*-[Cl₂-Pt-(H-Aib-OH)₂] and *trans*-[Pt-(H-Aib-O⁻)₂] complexes have been synthesized and characterized in solution and in the solid state. Their crystal and molecular structures have been determined by X-ray diffraction analyses. The complexes show a distorted planar coordination around the heavy atom. The organic moiety in the two complexes shows different conformations: in *trans*-[Pt-(H-Aib-O⁻)₂] the amino acid residue, acting as a bidentate, is forced to assume an unusual conformation. On the other hand, in *trans*-[Cl₂-Pt-(H-Aib-OH)₂], in which the amino acid acts as a monodentate ligand, the α -aminoisobutyric acid assumes an extended conformation, which in general for α -monosubstituted amino acid residues coordinated to the platinum should be the preferred conformation. In both crystal structures hydrogen bonds are formed between the donor and acceptor groups with further stabilization deriving from van der Waals interactions between hydrophobic moieties.

Introduction

The chemistry of amino acid complexes of Pt(II) has been the object of many investigations since 1930 [1–7]. Later, this research field obtained renewed attention due to the discovery of some pharmaceutical applications of Pt(II) complexes [8–23]. More recently, Pt(II) complexes [24–27] of amino acids and peptides have stimulated interest for the possibility of their use in peptide synthesis. We have investigated [27] 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 both to define the reactivity of these compounds toward the condensation reaction that leads to peptide bond formation and possibly to apply this method in the synthesis of peptides. We have initially focused our attention on Pt(II) complexes of sterically hindered amino acids such as valine, leucine, isoleucine and α -amino isobutyric acid (Aib), because their reduced reactivity in condensation reactions produces low reaction yields. Our studies are aimed not only at investigating the possibility of easily linking a suitable heavy metal ion to a peptide chain, in order to facilitate the solid state crystal structure determi-

nation, but also to study the effect of the metal ion on the condensation reaction of the coordinated α -amino acid residue with the formation of peptide bonds and on the conformation assumed by a peptide chain.

To achieve these goals we have prepared as starting material to be used in successive condensation reactions for dipeptide complexes preparation, *trans*-[Cl₂-Pt-(H-Aib-OH)₂], which was obtained from the white solid intermediate *trans*-[Pt-(H-Aib-O⁻)₂].

We now report the syntheses, characterization and X-ray diffraction analyses of both platinum complexes.

Experimental

Materials and equipment

All solvents and reagents were of analytical grade and were used without further purification. Aib and K₂PtCl₄ were purchased from Fluka and 'Metalli Preziosi', respectively. (CD₃)₂CO 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.

Melting points were determined on a METTLER TC 10 calorimeter and they are uncorrected.

*Author to whom correspondence should be addressed.

IR spectra were recorded on a Perkin-Elmer 684 infrared spectrophotometer; the nujol mull technique and CsI plates were used.

^1H NMR spectra were recorded on a Bruker WH 270 spectrometer in $(\text{CD}_3)_2\text{CO}$ solution with TMS as internal reference.

X-ray analyses were performed using Cu $K\alpha$ or Mo $K\alpha$ radiations and a pulse-high discrimination on a CAD-4 Enraf-Nonius diffractometer equipped with a microVax II of the 'Centro Interdipartimentale di Metodologie Chimico-fisiche' of the University of Naples.

Synthesis of the complexes

trans-[Pt-(H-Aib-O $^-$) $_2$]

The complex was prepared by refluxing in 30 ml of water 1 g (2.4 mmol) of K_2PtCl_4 and 2 g (19.4 mmol) of H-Aib-OH (molar ratio 1:8). The solution was refluxed for 5 h. A white precipitate was obtained in the form of crystals when the reaction mixture was left at room temperature for 24 h. The crystalline precipitate was filtered, washed with cold water and dried at 105 °C. 766 mg of product were obtained corresponding to a yield of 80%. The product was practically insoluble in most organic solvents. Its characterization was carried out by X-ray diffraction techniques.

trans-[Cl $_2$ Pt-(H-Aib-OH) $_2$]

trans-[Pt-(H-Aib-O $^-$) $_2$] was boiled for 5 min in 6 M HCl. The compound remained insoluble, but under reflux a new material slowly appeared as a yellow solid precipitate. The reaction mixture was left at room temperature for 2 h, then the precipitate was filtered, washed with cold water and dried at 105 °C. 816 mg of material were obtained with a 90% yield. $R_f=0.27$ in $\text{CHCl}_3:\text{CH}_3\text{OH}$ 70:30 vol.:vol.; m.p. (uncorrected) 213.3 °C. The *trans* configuration was ascertained by the IR Pt-Cl stretching at 340 cm^{-1} . ^1H NMR in $(\text{CD}_3)_2\text{CO}$: 1.72 (s, 12H, βCH_3); 4.78 (t, 4H, NH_2) ppm. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of an acetone solution containing a few drops of 1 M HCl.

X-ray diffraction analysis

Preliminary Weissenberg photographs were used to determine the crystal system and the space group. Unit cell determination was carried out for both crystals by least-squares refinement of the setting angles of 20 high angle reflections accurately centered, using Cu $K\alpha$ radiation for *trans*-[Cl $_2$ Pt-(H-Aib-OH) $_2$] and Mo $K\alpha$ radiation for *trans*-[Pt-(H-Aib-O $^-$) $_2$]. Crystallographic data for both crystals are given in Table 1. Density measurements carried out by flotation in CHCl_3 -*n*-hexane mixtures indicate that in both crystals the asymmetric unit comprised one half of the molecule, which

in turn dictates that in both structures the platinum atom must lie on a crystallographic symmetry center.

The following is the procedure used for data collection of both *trans*-[Pt-(H-Aib-O $^-$) $_2$] and *trans*-[Cl $_2$ Pt-(H-Aib-OH) $_2$]. The analysis of the peak profile suggested an ω - 2θ scan mode with a range of $(1.0 + 0.35 \tan \theta)^\circ$ 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 were made at a speed of 4°/min. Reflections with a net intensity $I \leq \sigma(I) \cdot 0.5$ were flagged as 'weak'; those with $I > \sigma(I) \cdot 0.5$ 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. The structures were solved with Patterson methods. The positions of the Pt and Cl atoms were 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. The empirical method of Walker and Stuart [28] for correcting diffractometer data for absorption effects was applied. All Pt, 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 atom. The scattering factors for all atomic species were calculated from Cromer and Waber [29]. The final values for the conventional R factors for *trans*-[Pt-(H-Aib-O $^-$) $_2$] and *trans*-[Cl $_2$ Pt-(H-Aib-OH) $_2$] are 0.051 and 0.040, respectively, for the observed reflections.

Final positional parameters and equivalent thermal factors for Pt, 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

During the crystallization of *trans*-[Cl $_2$ Pt-(H-Aib-OH) $_2$] from neat acetone the presence of two crystal forms, identified as *trans*-[Cl $_2$ Pt-(H-Aib-OH) $_2$] and *trans*-[Pt-(H-Aib-O $^-$) $_2$], was observed. We suspected that the following equilibrium exists in solution

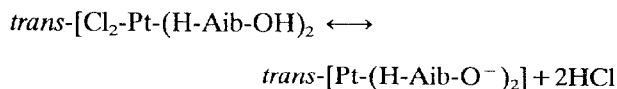


TABLE 1. Crystallographic data for *trans*-[Pt-(H-Aib-O⁻)₂] and *trans*-[Cl₂-Pt-(H-Aib-OH)₂]

Parameter	[Pt-(H-Aib-O ⁻) ₂]	[Cl ₂ -Pt-(H-Aib-OH) ₂]
Molecular formula	C ₈ H ₁₆ N ₂ O ₄ Pt	C ₈ H ₁₈ N ₂ O ₄ Cl ₂ Pt
Molecular weight (amu)	399.32	472.24
Crystal system	monoclinic	triclinic
Space group	<i>P</i> 2 ₁ / <i>a</i>	<i>P</i> 1̄
Z, molecules/unit cell	2	1
<i>a</i> (Å)	9.62(9)	5.784(6)
<i>b</i> (Å)	5.97(5)	6.097(5)
<i>c</i> (Å)	9.40(9)	10.132(2)
α (°)	90.0	94.89(9)
β (°)	98.3(2)	93.80(11)
γ (°)	90.0	94.28(8)
<i>V</i> (Å ³)	535.1	354.1
μ_r (cm ⁻¹)	132.441	405.166
<i>D</i> _{exp} (g/cm ³)	2.47	2.21
<i>D</i> _{calc} (g/cm ³)	2.478	2.214
Radiation (Å)	Mo K α (0.7092)	Cu K α (1.5418)
Measured reflections	619	1342
Observed reflections (with $I \geq 3\sigma(I)$)	562	1341
<i>R</i> factor	0.051	0.040
<i>R</i> factor, weighted	0.061	0.050
Weighting scheme used	unit weights	unit weights
No. parameters refined	66	83
Temperature (°C)	22	22
Solvent of crystallization	acetone	acetone

TABLE 2. Positional parameters with e.s.d.s in parentheses

Atom	<i>trans</i> -[Pt-(H-Aib-O ⁻) ₂]				Atom	<i>trans</i> -[Cl ₂ -Pt-(H-Aib-OH) ₂]			
	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}		<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
Pt	0.000	0.000	0.000	1.84(2)	Pt	0.0000	0.0000	0.0000	1.774(9)
C ^{α}	0.213(2)	0.00(2)	0.250(2)	2.6(4)	Cl	-0.1632(5)	0.2589(4)	0.1343(2)	3.20(5)
C ^{β^1}	0.370(2)	-0.00(3)	0.308(2)	3.2(4)	N	-0.004(1)	-0.197(1)	0.1547(7)	2.3(1)
C ^{β^2}	0.126(2)	0.032(5)	0.365(2)	2.2(5)	C ^{α}	0.203(2)	-0.207(2)	0.2490(9)	2.8(2)
N	0.170(2)	0.127(3)	0.127(2)	2.0(4)	C ^{β^1}	0.385(2)	-0.336(2)	0.178(1)	3.8(2)
C'	0.181(2)	-0.249(4)	0.197(3)	1.8(4)	C ^{β^2}	0.301(2)	0.017(2)	0.304(1)	5.2(3)
O ₁	0.100(2)	-0.286(3)	0.078(2)	3.1(4)	C'	0.116(2)	-0.330(2)	0.3646(8)	2.7(2)
O ₂	0.236(2)	-0.422(3)	0.263(2)	3.4(4)	O	-0.084(1)	-0.337(1)	0.3917(6)	3.4(1)
					O*	0.279(1)	-0.418(1)	0.4324(7)	4.4(2)

Thermal factors of the anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos \gamma)B(1,2) + ac(\cos \beta)B(1,3) + bc(\cos \alpha)B(2,3)]$.

This equilibrium was ascertained by semipreparative tlc. In fact, treatment of an acetone solution of *trans*-[Pt-(H-Aib-O⁻)₂] with HCl yields a single product (*R*_f 0.27 CHCl₃:CH₃OH 70:30). After elimination of the excess acid and keeping the product in solution for a few hours, two products were detected (*R*_f 0.27 and 0.59 CHCl₃:CH₃OH 70:30). These materials were isolated by preparative tlc and identified as *trans*-[Cl₂-Pt-(H-Aib-OH)₂] and *trans*-[Pt-(H-Aib-O⁻)₂], respectively. This unexpected behavior might be attributed to the well known propensity of the Aib residues to give a folded conformation and, therefore, the carboxylic terminal end may fold back on the metal ion, favoring

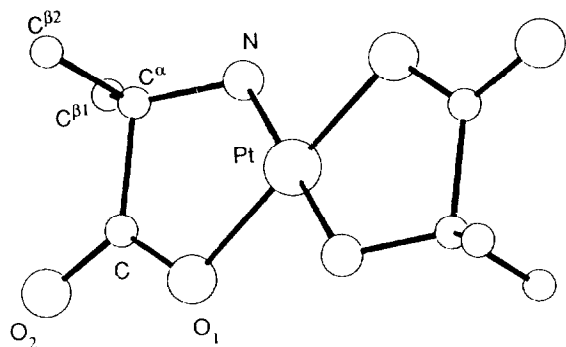
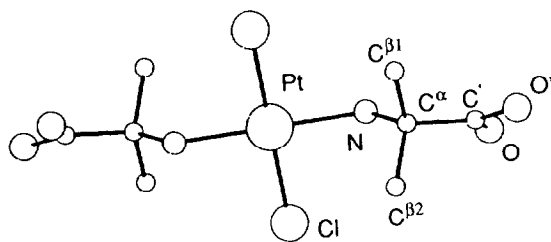
an intramolecular rearrangement with the elimination of chlorine ions.

In Figs. 1 and 2 the molecular models of the two Pt(II) complexes with α -amino isobutyric acid, as determined by X-ray diffraction analyses, are illustrated. In both complexes the platinum atom displays the square planar coordination: *trans*-[Pt-(H-Aib-O⁻)₂] shows the two nitrogen atoms and the two oxygen atoms in *trans* position to each other, while *trans*-[Cl₂-Pt-(H-Aib-OH)₂] shows both chlorine atoms as well as the nitrogen atoms in *trans* position to each other. The platinum and the four atoms directly coordinated to it are perfectly planar, since the platinum atom lies on a crystallographic center

TABLE 3. Bond distances, bond angles and dihedral angles for *trans*-[Pt-(H-Aib-O⁻)₂] and *trans*-[Cl₂-Pt-(H-Aib-OH)₂]

<i>trans</i> -[Pt-(H-Aib-O ⁻) ₂]		<i>trans</i> -[Cl ₂ -Pt-(H-Aib-OH) ₂]	
Bond distances (Å)			
Pt-N	2.03(2)	Pt-Cl	2.293(2)
C ^α -C ^{β2}	1.47(3)	Pt-N	2.054(8)
C'-O ₁	1.28(3)	C ^α -C ^{β1}	1.54(2)
Pt-O ₁	2.05(2)	N-C ^α	1.49(1)
C ^α -N	1.39(5)	C ^α -C ^{β2}	1.49(2)
C'-O ₂	1.28(3)	C'-O	1.21(1)
C ^α -C ^{β1}	1.54(3)	C ^α -C'	1.53(1)
C ^α -C'	1.59(9)	C'-O*	1.31(1)
Bond angles (°)			
N-Pt-O ₁	78.5(8)	Cl-Pt-N	87.5(2)
C ^{β2} -C ^α -C'	104.0(4)	C ^{β1} -C ^α -C ^{β2}	111.7(9)
O ₁ -C'-O ₂	116.0(2)	Pt-N-C ^α	122.5(6)
C ^{β1} -C ^α -C ^{β2}	112.0(2)	C ^{β1} -C ^α -C'	110.6(9)
N-C ^α -C'	103.0(3)	C ^α -C'-O	122.5(9)
Pt-O ₁ -C'	111.0(2)	C ^{β2} -C ^α -C'	107.7(8)
C ^{β1} -C ^α -N	117.0(6)	C ^α -C'-O*	113.9(8)
Pt-N-C ^α	114.0(3)	O-C'-O*	123.5(9)
C ^{β1} -C ^α -C'	103.0(9)	N-C ^α -C ^{β1}	109.0(7)
C ^α -C'-O ₁	120.0(2)	N-C ^α -C ^{β2}	111.5(9)
C ^{β2} -C ^α -N	115.0(4)	N-C ^α -C'	106.2(7)
C ^α -C'-O ₂	124.0(2)		
Torsional angles (°)			
O ₁ -Pt-N-C ^α	-35(3)	Cl-Pt-N-C ^α	-96.4(7)
C ^{β2} -C ^α -C'-O ₁	104(3)	N-C ^α -C'-O*	158.2(8)
N-Pt-O ₁ -C'	23(2)	Pt-N-C ^α -C ^{β1}	-72.9(10)
C ^{β2} -C ^α -C'-O ₂	-79(3)	C ^{β1} -C ^α -C'-O	-141.8(10)
C ^{β1} -C ^α -N-Pt	148(8)	Pt-N-C ^α -C ^{β2}	50.9(10)
N-C ^α -C'-O ₁	-17(3)	C ^{β1} -C ^α -C'-O*	40.1(11)
C ^{β2} -C ^α -N-Pt	-77(5)	Pt-N-C ^α -C'	168.0(6)
N-C ^α -C'-O ₂	161(2)	C ^{β2} -C ^α -C'-O	95.9(11)
C'-C ^α -N-Pt	35(2)	N-C ^α -C'-O	-23.7(13)
C ^α -C'-O ₁ -Pt	-10(2)	C ^{β2} -C ^α -C'-O*	-82.3(11)
C ^{β1} -C ^α -C'-O ₁	-139(3)		
O ₂ -C'-O ₁ -Pt	172(2)		
C ^{β1} -C ^α -C'-O ₂	39(4)		

Numbers in parentheses are e.s.d.s in units of the least significant digit.

Fig. 1. Molecular model of the *trans*-[Pt-(H-Aib-O⁻)₂] complex with the numbering of the atoms.Fig. 2. Molecular model of the *trans*-[Cl₂-Pt-(H-Aib-OH)₂] complex with the numbering of the atoms.

of symmetry. However, the geometry of the coordination plane shows some distortion: while Pt-N, Pt-O and Pt-Cl in both complexes do not present appreciable differences with literature data [21, 30, 31] within the experimental errors, significant differences are observed in the bond angles around the platinum atom. These deviations are due in the case of *trans*-[Cl₂-Pt-(H-Aib-OH)₂] to the need to release mostly intramolecular and to a lesser extent intermolecular interactions. Instead in the case of *trans*-[Pt-(H-Aib-O⁻)₂] most of the observed distortion of the bond angles around the platinum atom is due to the need to release the strains deriving from ring closure, since the amino acid residue acts as a bidentate ligand. In the first case the distortion is limited to 2.5°, while in the second case it is as large as 11.5°, as usually observed for chelated amino acid residues, as for example in the glycinate-Pt(II) compounds [31].

In the two complexes the organic moiety obviously presents quite different conformations, which are defined by the φ and ψ angles, i.e. the Pt-N-C^α-C' and N-C^α-C'-O dihedral angles, respectively. In *trans*-[Pt-(H-Aib-O⁻)₂], where the two α -amino isobutyric acid residues act as bidentate, the observed conformation is folded with values for the φ and ψ dihedral angles of 35 and -16°, respectively, for one of the two residues, while the opposite values (-35, 16°) are observed for the second residue related by the symmetry center. The values observed for the conformational angles are absolutely new for this amino acid residue; the rather high energy spent to achieve this conformation is however largely compensated by the formation of two bonds per each residue with the platinum atom. Instead, in *trans*-[Cl₂-Pt-(H-Aib-OH)₂], where the two α -amino acid residues act as monodentate, the organic moiety assumes an extended conformation with φ and ψ values of 168.1 and 158.2° or their centrosymmetric values (-168.1, -158.2°). The extended conformation observed for the organic moiety is very similar to that found by us recently for *trans*-[Cl₂-Pt-(H-Ala-OH)₂] [30]. It is worth noting that in both *trans*-[Pt-(H-Aib-O⁻)₂] and *trans*-[Cl₂-Pt-(H-Aib-OH)₂] the conformation assumed by the organic moiety is rather different from the minimum energy conformation, as calculated theoretically, which

is also that commonly observed for α -amino isobutyric acid residues in peptide crystal structures [32–37]. This conformation, characterized by φ and ψ values of about -60° , -30° (or the centrosymmetric 60° , 30°) falls in the helical region of the φ – ψ map [38]. An all *trans* conformation, characterized by values of about 180° for both conformational angles is still possible even if of higher energy [39]. Evidently in this structure the steric hindrance represented by the non-bonded interactions that the two C^β substituents on the α -carbon atom experience with the platinum atom and the atoms coordinated to it, coupled with the need of forming strong intermolecular H-bonds, forces the residue to assume an unusual conformation. But, as in the other structure, the energy spent in assuming this conformation is largely regained by the formation of a bond between the N and the platinum atoms and by the establishment of a strong O–H...O H bond between symmetry related facing carboxylic groups in the crystal.

The hydrogen bonding parameters are reported for both structures in Table 4; the mode of packing of the two complexes *trans*-[Pt-(H-Aib-O[−])₂] and *trans*-[Cl₂-Pt-(H-Aib-OH)₂], as viewed along the *b* and the *a* axes, respectively, is represented in Figs. 3 and 4. In the crystal the complexes are held together by the formation of intermolecular hydrogen bonds. In *trans*-[Pt-(H-Aib-O[−])₂] two H bonds of the N–H...O type, involving both hydrogen atoms of the amino group are found: one quite strong (N–H...O₂, 3.01 Å) by translation along the *b* axis, and the other rather weak (N–H...O₁, 3.17 Å), between symmetry related neighboring molecules. van der Waals interactions between facing methyl groups parallel to the *ab* plane contribute to the stabilization of the crystal. In the case of *trans*-[Cl₂-Pt-(H-Aib-OH)₂], also, the molecules are held together in the solid state by two H bonds. The first H bond involves one hydrogen of the amino group with the chlorine atom of a molecule translated along the *b* axis (N–H...Cl, 3.36 Å); the second H bond involves the hydrogen atom and the carbonyl oxygen of facing, symmetry related carboxylic acid groups (O*–H...O,

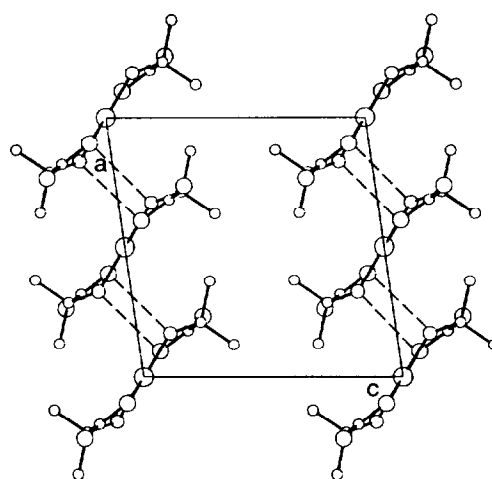


Fig. 3. Mode of packing of *trans*-[Pt-(H-Aib-O[−])₂] as viewed along the *b* axis. The intermolecular H bonds are indicated by dashed lines.

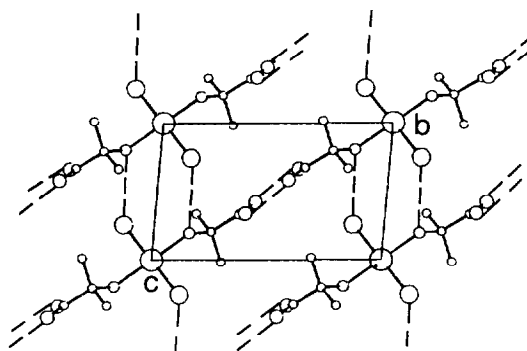


Fig. 4. Mode of packing of *trans*-[Cl₂-Pt-(H-Aib-OH)₂] as viewed along the [100] direction. The intermolecular H bonds are indicated by dashed lines.

2.67 Å). Both interactions should be considered rather strong.

From our results, as well as literature data [21, 30], we can confidently conclude that in platinum(II) amino acid complexes of the type *trans*-[Cl₂-Pt-(H-AA-OH)₂]: (i) the organic moiety prefers an extended conformation, in order to release intramolecular repulsions with the inorganic portion of the molecule; (ii) the extended conformation should be even more easily achieved by metal-coordinated α -monosubstituted amino acid residues. Therefore, in preparing peptide–platinum complexes for an easier determination of the solid state structure, it should be taken into account that the N-terminal end of the peptide may assume a conformation somehow affected by the presence of the metal ion.

As far as the usefulness of the investigated compounds in peptide synthesis, preliminary results seem to indicate that the metal ion affects the condensation reaction between the coordinated and another amino acid or

TABLE 4. Intermolecular D–H...A–X for (a) *trans*-[Pt-(H-Aib-O[−])₂] and (b) *trans*-[Cl₂-Pt-(H-Aib-OH)₂]

Donor	Acceptor	Length (Å) (D...A)	Angle (°) (D...A–X)	Symmetry operation
(a)				
N	Cl	3.36	124	$x, 1+y, z$
O*	O	2.67	127	$-x, -1-y, 1-z$
(b)				
N	O1	3.17	145	$-\frac{1}{2}-x, \frac{1}{2}+y, -z$
N	O2	3.01	118	$x, 1+y, z$

peptide fragment. In fact, the electron-withdrawing properties of the metal ion could increase the reactivity of the coordinated amino acid toward peptide bond formation.

Further studies are presently in progress in order to better understand this behavior.

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