Ternary complexes of cisplatin with amino acids and nucleobases. The crystal structure of *cis*-$[(NH_3)_2Pt(1\text{-MeC-}N^3)(Gly\text{-}N)](NO_3)\cdot 2H_2O$

Akis Iakovidis, Nick Hadjiliadis*

University of Ioannina, Department of Chemistry, Laboratory of Inorganic and General Chemistry, Ioannina 45-110 (Greece)

James F. Britten, Ian S. Butler

McGill University, Department of Chemistry, 801 Sherbrooke Street West, Montreal, Que., H3A 2K6 (Canada)

Frank Schwarz and **Bernhard Lippert**

Fachbereich Chemie, Universitat Dortmund, W-4600 Dortmund (F.R.G.)

(Received January 17, 1991)

Abstract

Ternary complexes of Pt(II) with the amino acids = amacH, glycine = GlyH, L-alanine = AlaH, L-2-aminobutyric acid = 2-AbaH, L-valine = ValH and L-norvaline = nValH and the nucleobases, 1-methylcytosine = 1-MeC and 9-methylguanine = 9-MeG were prepared in aqueous solutions via two synthetic routes: by reacting the binary complexes, either *cis*-$[(NH_3)_2Pt(amac)](NO_3)$ with 1-MeC or 9-MeG (route 1)), or the *cis*-$[(NH_3)_2Pt(nucleobase)Cl](NO_3)$ with the amino acids. Complexes of the following formulae were isolated as solid adducts: *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Gly)](NO_3)$, *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Ala)](NO_3)$, *cis*-$[(NH_3)_2Pt(1\text{-MeC})(2\text{-Aba})](NO_3)$, *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Val)](NO_3)$, *cis*-$[(NH_3)_2Pt(1\text{-MeC})(nVal)](NO_3)$ (not obtained analytically pure), *cis*-$[(NH_3)_2Pt(9\text{-MeG})(Gly)](NO_3)$, *cis*-$[(NH_3)_2Pt(9\text{-MeG})(Ala)](NO_3)$, *cis*-$[(NH_3)_2Pt(9\text{-MeG})(2\text{-Aba})](NO_3)$, *cis*-$[(NH_3)_2Pt(9\text{-MeG})(Val)](NO_3)$ and *cis*-$[(NH_3)_2Pt(9\text{-MeG})(n\text{-Val})](NO_3)$. These were characterized by elemental analysis, conductivity measurements and IR, Raman and ^1H NMR spectra. The results show that the amino acids are monodentate (coordination through NH_2) and their carboxylate groups are deprotonated. The nucleobases coordinate through N(3) (1-MeC) and N(7) (9-MeG). Hindered rotation was also observed in the case of the ternary complexes with 1-MeC, in D_2O solutions persisting up to 90 °C. A *cis–trans* isomerization was also taking place in solution, increasing with temperature. A hydrophobic ligand–ligand interaction was detected to take place between the amino acid with aliphatic side chains (starting with 2-Aba), and the nucleobase ring systems, by ^1H NMR spectroscopy in aqueous solution, increasing with increasing length of the aliphatic side chain. Finally the crystal structure of the complex *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Gly)](NO_3)$ was solved by X-ray diffraction: space group $P\bar{1}$ (No. 2), triclinic, $a = 7.495(3)$, $b = 16.388(4)$, $c = 6.846(3)$ Å, $\alpha = 97.58(3)$, $\beta = 104.86$, $\gg \gamma = 102.05(3)°$, $V = 779.5(6)$ Å^3, $Z = 2$. A weak Pt interaction with the O(2) of 1-MeC was observed as in other similar cases. No hydrophobic ligand–ligand interactions were found, however, in this complex, as expected.

Introduction

Metal ions in biological systems are known to promote specific protein–nucleic acid interactions in certain cases, through the formation of ternary complexes [1]. For example, nucleic acid–enzyme ternary complexes are formed with bivalent metals, during DNA replication or RNA synthesis [1d, e], while Cu^{2+} and Zn^{2+} ions mediate polypeptide–polynucleotide interactions [1c]. Such interactions can be one or more of the following: hydrogen bondings, electrostatic interactions, aromatic ring stacking and hydrophobic aromatic–aliphatic, or aliphatic–aliphatic interactions [2]. Hydrophobic interactions are the weakest of such interactions and their precise nature is not perfectly understood [3]. Various solution and other studies, however, have revealed their existence [2–7] and the role they may play in creating distinct chemical structures has been emphasized [2c, 3]. The larger of these interactions contributes to an increase of the stability in solution of the ATP–metal–amino acid system [2c], the orotic acid–Cu–amino acid system [7d], and the dipeptide–Pd–aromatic or aliphatic amine system [7b], etc.

*Author to whom correspondence should be addressed.

0020-1693/91/$3.50

The antitumor drug *cis*-DDP (*cis*-$Pt(NH_3)_2Cl_2$) on the other hand, is today believed to interfere directly in DNA replication and transcription in exhibiting its antitumor properties [8]. However, interactions of the drug with other biological molecules in the body are also possible, and are not clear at present [9]. It was suggested that *cis*-DDP toxicity is related to its ability to inactivate proteins [10]. It is also known that both *cis*-DDP and its inactive *trans* isomer form DNA–Pt–protein crosslinks, both with histone and non-histone proteins [11]. Such a crosslink model had also been proposed as the cause of the antitumor action of *cis*-DDP [12], or the cause of the toxicological side effects of the drug, constituting 0.15% of its total action [10, 13]. However, the importance of such crosslinks, as well as the role that they may play, are not exactly known at present.

In an attempt to better understand the hydrophobic aromatic aliphatic ligand–ligand interactions on the one hand and to create the simplest models of the DNA–Pt–protein crosslinks that are known to take place, we have recently undertaken a systematic study of the ternary systems formed between Pt(II) or Pd(II), nucleosides–nucleotides and amino acids–peptides [2a, 14] both of the *cis* and *trans* structures. Intramolecular aromatic–aliphatic hydrophobic interactions were detected in solution in these studies [2a, 14]. The characteristic properties and the implications of the formation of such *cis* and *trans* ternary systems were also reported [2a, 14].

The present paper is a continuation of similar studies and deals with the ternary system formed between *cis*-DDP, the nucleobases 1-methylcytosine (1-MeC) and 9-methylguanine (9-MeG), and the amino acids glycine (GlyH), L-alanine (AlaH), L-2-aminobutyric acid (2-AbaH), L-norvaline (nValH) and L-valine (ValH), with increasing aliphatic side chain length. The results are compared with those for similar systems already reported [14]. The crystal structure of the complex *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Gly)](NO_3)$ is also reported here. This, however, does not show any intramolecular ligand–ligand interaction, as expected for gly [15] or gly–gly [7b] containing systems.

Experimental

Starting materials

1-Methylcytosine (1-MeC) [16] and *cis*-$(NH_3)_2PtCl_2$ [17] were prepared as previously described. 9-Methylguanine (9-MeG) was purchased from Chemogen, Konstanz, F.R.G. The amino acids were purchased from Fluka A.G. and Sigma Chemical Company.

Preparation of the compounds

cis-$[(NH_3)_2Pt(1\text{-MeC})(amac)](NO_3)$

Route (1). 1.7 mmol of the corresponding amino acid chelate complex *cis*-$[(NH_3)_2Pt(amac)](NO_3)$, prepared as previously described [18], were dissolved in 10 ml of H_2O, and 2.5 mmol of 1-MeC were added. The resulting solution was heated at 50 °C for 2 days. On evaporating the solution to a small volume and cooling, an amount of the nucleobase is crystallized out. It was removed by filtration and the filtrate was passed through a Sephadex column (40 cm × 1.5 cm) (G-10, Pharmacia) using H_2O as eluent. Fractions of 2 ml were collected and the corresponding ternary complexes were obtained as white solids by evaporation of the solvent. (Normally the obtained complexes were satisfactorily pure, but occasionally a second chromatographic purification through Sephadex was needed.) The yields were 30–40%.

Route (2). 1.0 mmol of *cis*-$[(NH_3)_2Pt(1\text{-MeC})Cl](NO_3)$, prepared as previously described [19a, b], was dissolved in 7 ml H_2O and the equivalent quantity of $AgNO_3$ (1.0 mmol in 3 ml H_2O) was added. After stirring the mixture at room temperature for 24 h, the resulting AgCl was removed by filtration (or centrifugation). 5.0 mmol of the appropriate amino acid (amacH) were then added to the filtrate and the solution obtained was heated at 35 °C for 2–3 days, keeping a constant pH of 5.2, by addition of small amounts of dilute NaOH. The resulting solution was concentrated to a small volume. The corresponding complexes were obtained as white solids, by means of gel chromatography, as described above. Yields 10–15%.

cis-$[(NH_3)_2Pt(9\text{-MeG})(amac)](NO_3)$

Route (1). 0.7 mmol of 9-MeG was suspended in 60 ml of H_2O and the pH was adjusted to about 5.0 with dilute HNO_3. The mixture was heated at 60 °C until a clear solution was obtained. 0.5 mmol of each of the respective complexes *cis*-$[(NH_3)_2Pt(amac)](NO_3)$ [18] was then added to this solution, in the solid form. The heating at 60 °C was continued for 2 days with stirring and keeping a constant pH of about 5, by adding small amounts of dilute HNO_3 at certain intervals. After this time, the mixture was cooled in an ice bath and the precipitated 9-MeG was filtered off. The filtrate was evaporated to a small volume. The complexes were thus obtained pure by means of gel chromatography, as described above. Yields 12–40%.

Route (2). 1.0 mmol of *cis*-[$(NH_2)_2$Pt(9-MeG)Cl](NO_3), prepared as previously described [19b, c] and 5.0 mmol of the appropriate amino acid were mixed with 10 ml H_2O. An equivalent amount of $AgNO_3$ (1.0 mmol) was added to the resulting suspension. After stirring for 24 h at room temperature, the precipitated AgCl was filtered off and the filtrate was heated at 30 °C and constant pH = 5 (addition of dilute NaOH), for 2–3 days. The resulting solution was filtered to remove any insoluble impurities and concentrated to a small volume. The complexes were obtained as pure white powders by means of gel chromatography after solvent evaporation, as described above. Yields 30–40%.

Preparation of the deuterated derivatives

10–20 mg of each of the solid complexes were dissolved in 0.3–1 ml of D_2O and heated gently for a few minutes. The resulting solution was lyophilized (if necessary the procedure was repeated once more) to obtain the corresponding deuterated derivative.

Methods and spectra

The elemental microanalyses and the conductivity measurements were made as previously described [18a]. The same was true for the IR and ^{1}H NMR spectra. The Raman spectra were recorded on an Instruments S.A. spectrometer with a Jobin-Yvon U-1000 1.0-m double monochromator that was interfaced to a IBM PS/2 model 60 microcomputer. The 647.1 nm line of a Spectra Physics model 164, 3-W krypton ion laser, was used to excite the Raman spectra. The laser power was 30 mW at the samples. The samples were in powder forms. The resolution for both the IR and Raman measurements was about 2 cm^{-1}.

The elemental analyses of all the isolated complexes were satisfactory. The molar conductance (Λ_M) values measured in 10^{-3} M concentrations, in aqueous solutions at room temperature, corresponded to 1:1 electrolytes (Table A, see 'Supplementary material').

Crystallography

Crystals of the compound *cis*-[$(NH_3)_2$Pt(1-MeC)(Gly)](NO_3)·$2H_2O$, suitable for X-ray analysis, were obtained by slow evaporation of an aqueous solution of it in a refrigerator (4 °C) after 2–3 days.

X-ray data were collected on a Rigaku AFC6S diffractometer with graphite monochromated Mo Kα (0.71069 Å) radiation at 1.75 kW. The data were collected using the ω–2θ scan technique to a maximum 2θ of 59.9, at a temperature of 21 °C. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.34° with a take-off angle of 6.0°. Scans of (1.44 + 0.30 tan θ)° were made at a speed of 32.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary backround counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 280.0 mm.

Of the 4913 reflections collected, 4519 were unique ($R_{int} = 0.055$). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection, indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for Mo Kα is 91.4 cm^{-1}. An empirical absorption correction, using the program DIFABS [20], was applied which resulted in transmission factors ranging from 0.67–1.30. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods [21]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions (fixed). The final cycle of full-matrix least-squares refinement* was based on 3510 observed reflections ($I > 300\sigma(I)$) and 208 variable parameters and converged (largest parameter shift was 0.02 times its e.s.d.) with unweighted and weighted agreement factors of: $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.047$, $R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2]^{1/2} = 0.046$.

The standard deviation of an observation of unit weight** was 1.77. The weighting scheme was based on counting statistics and included a factor ($p = 0.00$) to downweight the intense reflections. Plots of $\Sigma w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 3.65 and −3.94 ē/Å, respectively.

Neutral atom scattering factors were taken from Cromer and Waber [22]. Anomalous dispersion effects were included in F_{calc} [23]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer [24]. All calculations were performed using the TEXSAN [25] crystal-

*Least-squares: function minimized $\Sigma w(|F_o| - |F_c|)^2$, where $w = 4F_o^2/\sigma^2(F_o)^2$, $\sigma^2(F_o)^2) = [S^2(C + R^2B) + (pF_o^2)^2]/Lp^2$, S = scan rate, C = total integrated peak count, R = ratio of scan time to background counting time, B = total background count, Lp = Lorentz–polarization factor, p = p-factor.

**Standard deviation of an observation of unit weight: $[\Sigma w(|F_o| - |F_c|)^2/(N_o - N_v)]^{1/2}$, where: N_o = number of observations, N_v = number of variables.

TABLE 1. Crystallographic data for *cis*-$[(NH_3)_2Pt(Gly)(1\text{-MeC})](NO_3)\cdot 2H_2O$

Empirical formula	$C_7H_{21}N_7O_8Pt$
Formula weight	526.38
Crystal color, habit	colorless, chunk
Crystal dimensions (mm)	$0.400\times0.400\times0.060$
No. reflections for unit cell determinations (2θ range)	18 (7.0–15.6°)
Crystal system	triclinic
Space group	$P\bar{1}$ (No. 2)
a (Å)	7.495(3)
b (Å)	16.388(4)
c (Å)	6.846(3)
α (°)	97.58(3)
β (°)	104.86(4)
γ (°)	102.05(3)
V (Å^3)	779.5(6)
Z	2
D_{calc} (g cm^{-3})	2.243
$F(000)$	508
μ(Mo Kα) (cm^{-1})	91.44
No. unique reflections	4519 ($R_{int}=0.055$)
No. total reflections	4913
R	0.047
$R_w(F)$	0.046
Corrections	Lorentz–polarization absorption (transmission factors 0.71–1.15)

lographic software package of the Molecular Structure Corporation.

Details of the crystal data collection are listed in Table 1.

Results and discussion

Preparation

The reactions for the preparation of the ternary complexes (via route (1) and route (2)) can be represented as follows.

$$cis\text{-}[(NH_3)_2Pt(amac)](NO_3) + Nbase \xrightarrow[2\text{–}3\ days]{50\ °C} cis\text{-}[(NH_3)_2Pt(amac)(Nbase)](NO_3) \quad (1)$$

$$cis\text{-}[(NH_3)_2Pt(Nbase)Cl](NO_3) \xrightarrow[-AgCl]{+AgNO_3} cis\text{-}[(NH_3)_2Pt(Nbase)(H_2O)](NO_3) \xrightarrow[pH=5.2,\ 35\ °C,\ 2\text{–}3\ days]{amac(excees)} cis\text{-}[(NH_3)_2Pt(Nbase)(amac)](NO_3) + NaNO_3 + H_2O \quad (2)$$

with amac the deprotonated amino acids, Gly, L-Ala, L-2-aba, L-nVal and L-Val and Nbase the nucleobases 1-MeC and 9-MeG.

In these complexes, the amino acids coordinate to Pt(II) through their amino ($-NH_2$) groups with their free carboxylate ($-COO^-$) groups deprotonated and the nucleobases coordinate through N(3) for 1-MeC and through N(7) for 9-MeG, as the ^{1}H NMR and IR–Raman spectra reveal. This is confirmed in the case of the X-ray structure of *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Gly)](NO_3)$.

Vibrational spectra

The IR spectra of the complexes consist mostly of broad bands, due to the overlapping of several ligand absorption modes. The nucleobase vibrational modes in general produce stronger signals, thus obscuring the amino acid ones in both the IR and Raman spectra. Band assignments in the IR were based on deuteration experiments and on comparison with previous studies [2a, 14, 18a, 19a]. The Raman assignments were also made with comparison to previous reports [19a, 26]. Characteristic bands are given in Table 2.

In the 3000–3500 cm^{-1} IR region of both series of complexes *cis*-$[(NH_3)_2Pt(nucleobase)(amac)](NO_3)$, the overlap of the various νNH vibrations (NH_3, NH_2 of amino acid, NH_2 of the bases) gives rise to very strong absorptions at 3200–3300 cm^{-1}. These bands shift upon deuteration to near 2250–2500 cm^{-1}. However, the various νNH modes could not be distinguished, as had been possible in the case of the two forms of *cis*-$[(NH_3)_2Pt(1\text{-MeC})Cl](NO_3)$ [19a].

In the 1600–1700 cm^{-1} region, on the other hand, δNH_2 of the various amino groups, are coupled with the ν^aCOO^- of the free $-COO^-$ group of the amino acids and the $\nu C{=}O$ of 1-MeC, to a very strong

TABLE 2. Characteristic IR and Raman frequencies[a] of the 1-MeC complexes

1-MeC		*cis*-[$(NH_3)_2$-Pt(1-MeC)Cl]Cl		*cis*-[$(NH_3)_2$-Pt(1-MeC)(amac)](NO_3)		*cis*-[$(NH_3)_2$-Pt(1-MeC)(Gly)](NO_3)		Assignments
IR	Raman	IR	Raman	IR	Raman	IR	Raman	
	1524		1533		1532–1535		1534	ring stretching
1262	1261	1259	1259	1250–1260	1254	1260	1260	ring stretching
784	771[b]	794	796[b]	792	793	792	793	ring breathing
622	627	646	647	645	645–655	645	655	ring motion
482		457	485	450	478–480	450	480	ring deformation
422		420	424	420–424	420–424	422	420	ring deformation
						998, 970(720)[c]		ωNH_2(Gly)
						811, 792(612)[c]		rNH_2(Gly)
						695(900)[c]		rNH_2(Gly)
						920	923	ρCOO^-
			513–540[b]		524–530		524–530	νPt–NH_3
							540	νPt–NH_2(Gly)

[a]Frequencies in cm^{-1}. [b]Taken from ref. 20a. [c]Frequencies for the deuterated compounds.

and broad band near 1650 cm^{-1} in the *cis*-[$(NH_3)_2$Pt(1-MeC)(amac)](NO_3) series of complexes, so that no recognition of the individual bands could be made, even after partial deuteration. In the case of the *cis*-[$(NH_3)_2$Pt(9-MeG)(amac)](NO_3) series of complexes however, the maxima at 1695, 1635 and 1590 cm^{-1}, with two shoulders at 1560 and 1610 cm^{-1}, due to above mentioned vibrations and skeletal vibrations, are reduced to two maxima only at 1670 and 1590 cm^{-1}, with a shoulder near 1610 cm^{-1}. The former is assigned to the $\nu C{=}O$ of 9-MeG and the latter to the $\nu^a COO^-$ of the amino acids and skeletal purine vibrations. The δND_2 are found near 1160 (νNH/νND = 1.4). This is supported by the fact that the deuterated *cis*-[$(NH_3)_2$Pt(9-MeG)Cl](NO_3) complex shows only one sharp band near 1590 cm^{-1} without a shoulder. This gives a good indication for the existence of a free $-COO^-$ group in the ternary complexes, the free $\nu^a COO^-$ of the amino acids being expected in this region [27].

The coordination sites of 1-MeC and 9-MeG are the N(3) and N(7) nitrogen atoms, respectively, for the ternary complexes prepared by either of the two routes already described [19a, 26] (see 'Experimental'). This is mainly seen from the variation of certain ring vibrations in the complexes. Thus, the pyrimidine breathing motion, found at 771 cm^{-1} in free 1-MeC, shifts to the strong band at 793 cm^{-1} in the Raman spectra of the ternary complexes, while the 1261 ring stretching shifts to 1254 cm^{-1}. This also indicates monodentate coordination of 1-MeC [19a, 26a]. Other shifts in characteristic 1-MeC bands, include the 645–655 and 1532–1535 cm^{-1} shifts in the ternary complexes, of the 627 and 1524 cm^{-1} bands of free 1-MeC [19a, 26]. In the IR, these bands are observed at 646 and 1540 cm^{-1}, respectively.

The Raman bands at 1550 and 1470 cm^{-1} of free 9-MeG on the other hand, shifted to 1590 and 1502 cm^{-1} in *cis*-[$(NH_3)_2$Pt(9-MeG)Cl](NO_3) and near 1580 and 1500 cm^{-1} in the ternary complexes which are assigned to ring stretching motions, are indicative of N(7) coordination of the base [26a, b, 28]. The same is true also for the strong band at 636 cm^{-1} in the Raman spectra of the binary and ternary complexes and near 630 cm^{-1} in the IR, assigned to the breathing motion of 9-MeG and observed near 650 cm^{-1} in the guanine derivatives [26].

In *cis*-[$(NH_3)_2$Pt(1-MeC)(Gly)](NO_3), the IR bands at 792 and 811 cm^{-1} are due to the rNH_2 (rocking) motion of coordinated Gly, shifted to 612 cm^{-1} (NH/ND = 1.33) in the deuterated derivative and not observed in the binary compound [27, 29]. This is a good indication for the existence of a Pt–NH_2 (Gly) bonding [27]. The coordinated Gly also shows a band at 695 cm^{-1} shifted to 500 cm^{-1} (NH/ND = 1.39) upon deuteration and absent from the spectrum of the binary compound, that can also be assigned to an NH_2 deformation motion [29]. For the same reasons, the band at 998 and 990 cm^{-1} are assigned to the ωNH_2 (wagging) motion of the amino acid [29], shifted to 720 cm^{-1} upon deuteration. The band near 920 cm^{-1} can be assigned to the scissoring motion of the free $-COO^-$ group of the amino acid; it is absent from the spectra of the binary compound with 1-MeC and is not shifted upon deuteration [30]. It is observed at 923 cm^{-1} in the Raman spectrum and is also absent from the spectrum of the binary compound with 1-MeC.

The Pt–NH_3 and Pt–NH_2 stretchings are found at 524–530 cm^{-1} as medium intensity broad bands in the Raman spectra of the ternary complexes with 1-MeC. In the complex with Gly, a distinct band was observed at 480 cm^{-1} assignable to the νPt–NH_2 of the coordinated amino acid, having lower donor strength [19a, 28, 31]. The band at 513 cm^{-1} assigned to the νPt–NH_3 *trans* to Cl in the complex *cis*-$[(Pt(NH_3)_2(1\text{-MeC})Cl]^+$ [19a], is now observed at 524 cm^{-1} reflecting the lower *trans* effect of the –NH_2 group of Gly compared to Cl. Also, the bands near 420–424 and 478–480 cm^{-1} in the Raman, with corresponding bands at the same position and about 450 cm^{-1} in the IR, are assigned to ring deformation motions of coordinated 1-MeC, in its ternary complexes [32].

Finally, the NO_3^- bands are observed near 708–725(w), 831–845(w), 1044–1047(vs) cm^{-1} in the Raman and near 820–828(s) and 1385–1388(vs) cm^{-1}, in the IR spectra [19a].

^1H NMR spectroscopy

Coordination of the amino acids has a very small effect on the base protons of 1-MeC in the ternary complexes. The H(5) and H(6) protons of the base shift by less than 0.03 ppm downfield, compared to the starting material *cis*-$[(NH_3)_2Pt(1\text{-MeC})Cl](NO_3)$. This is consistent with the retention of the N(3) coordination of the ligand in the ternary complexes [19a, 33].

An important point to be noticed here is the splitting of the H(5) signal of 1-MeC, which shows up as two doublets at around 6 ppm in the ^1H NMR spectra. This was observed with all the amino acids in the ternary complexes, except Gly and can be explained by a hindered rotation of the nucleobase around the Pt–N(3) bond, similar to what was observed earlier in a number of cases with cytidine [34] and purine nucleosides [35]. In fact, when one of the two ligands in a *cis* geometry of a platinum(II) complex is chiral (the amino acids, expect Gly in the present case), two sets of signals are expected for a slow rotation around the Pt–ligand bond [34] (Pt–N(3) of 1-MeC in the present case).

Hindered rotation of the bases was also observed in the *cis* and *trans* ternary complexes of Pd(II) nucleosides–peptides, amino acids at room temperature, contrary to the complexes of Pt(II) and it was explained by the smaller size of the former [14a, b, c]. The H(6) doublet naturally does not split, since this proton lies on the rotational axis. The hindered rotation was also evidenced from the splitting of the terminal amino acid methyl group signal [14f], observed occasionally. The hindered rotation of 1-MeC persists up to 90 °C in aqueous solutions but it disappears at low pH values (see Fig. 1), where the carboxylate terminus of the amino acid is protonated. This result is similar to that found for the *cis*-$[Pt(Cyd)(Me_2SO)_2Cl]^+$ species [34] where the hindered rotation persists up to 80 °C.

The ^1H NMR spectra also reveal the presence of an amount of the corresponding *trans* isomer in the *cis* ternary complexes, except the one with Gly, prepared according to both reactions (1) and (2). It was readily identified with the original *trans* ternary complexes, prepared by a reaction analogous to reaction (2) [36]. The amount of the *trans* isomer could be estimated from the ^1H NMR spectra and it varied from 2.8–13.5%, increasing with increasing temperature. *cis* to *trans* isomerization although rare in platinum chemistry, has been observed occasionally [34, 37]. *cis*-DDP has also been reported to isomerize to the *trans* analog spontaneously in aqueous solutions [38].

In the ternary complexes with 9-MeG, the aromatic H(8) proton is slightly shifted upfield in the presence of amino acids, compared to the complex [19] *cis*-$[(NH_3)_2Pt(9\text{-MeG})(H_2O)]^+$. The H(8) proton signal of 9-MeG does not show any splitting due to hindered

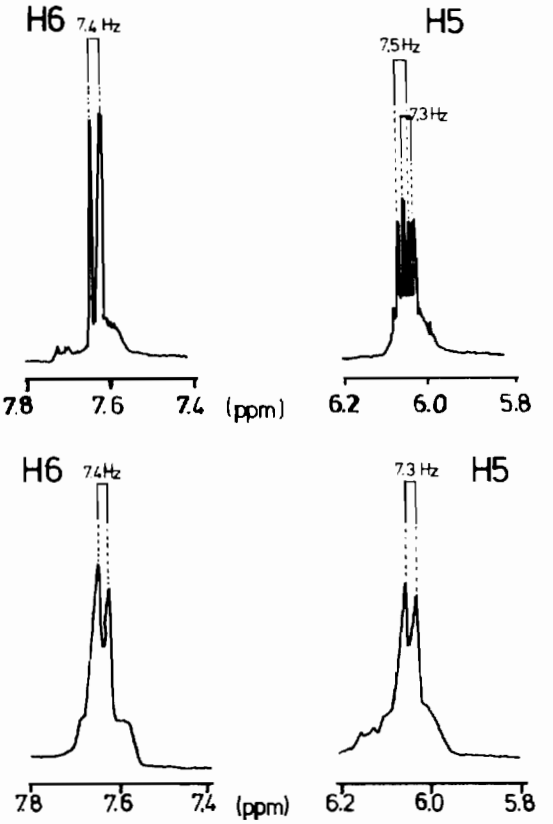

Fig. 1. 300 MHz ^1H NMR spectra of *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Ala)](NO_3)$ in the H(5) and H(6) protons region, in D_2O solutions pD = 5.4 (top) and 2.6 (bottom).

rotation, as one would expect. A similar situation was also observed in the *trans*-$[(Guo)_2Pt(amacH)_2]Cl_2$ system [14f], with a doubling of the amino acid protons in the ^1H NMR spectra, but not of the H(8) of guanosine. This difference in hindered rotation around the Pt–N(3) bonding in 1-MeC compared to the fast rotation around the Pt–N(7) bond in 9-MeG was observed previously in similar complexes [34]. It was explained by the fact that in the former case the 1-MeC substituents, NH_2 and C=O groups are *ortho* to the metal position, resulting in a greater hindrance than in the latter case, with the substituents being further away [34].

The intramolecular hydrophobic aromatic–aliphatic ligand–ligand interactions in the present case, although weaker than in other similar cases [2a, 14a, b, c], still exist and can be detected with ^1H NMR spectroscopy. The plot of Fig. 2(a) shows that the terminal methyl group of the amino acids is shifted upfield in the ^1H NMR spectra of the ternary complexes, as the amino acid aliphatic side chain length increases. The shifts are larger in the 9-MeG complexes than they are in the 1-MeC ones, since in the former the aromatic–aliphatic interactions are expected to be larger. The Gly complexes were not included in the plot, since no interactions were expected and indeed not found (see 'Crystal structure') with this amino acid [7b, 15]. Also, in the case of Ala, a downfield shift of its methyl group was observed as in other similar cases [2c, 3], indicating also the absence of such an interaction in the present case. Interactions are observed, however, with the other amino acids and the size of Pt(II) does not seem to prevent them [2a, 3], though the shifts of this methyl group are smaller than for the corresponding *cis*-$[(guo)_2Pd(amac)]Cl$ system [14c]. It should be noted that they were hardly observed (only with Ileu) also in the case of the *cis*-$[(Ino)_2Pt(amac)]Cl$ system [2a]. It is also worthwhile mentioning that Val with a branch side chain and the same number of carbon atoms as nVal, shows the same upfield shift of its terminal methyl group, with the one of 2-Aba. nVal on the other hand, shows the largest such shift.

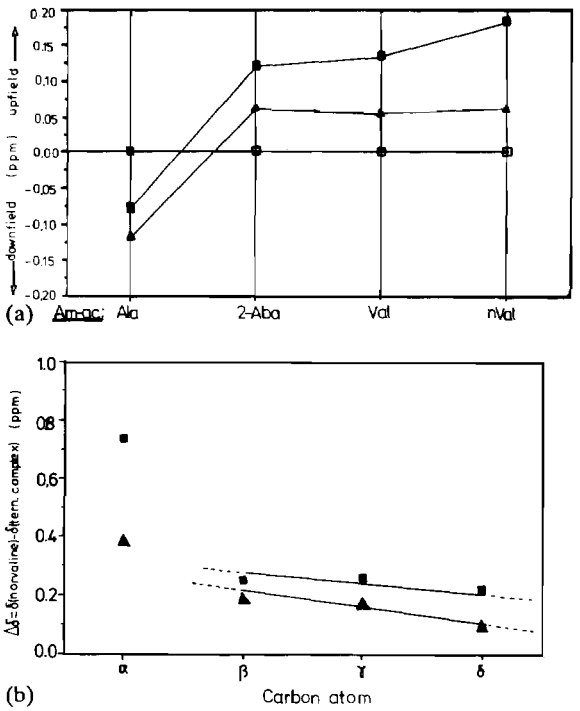

Fig. 2. (a) Variation of the $\Delta\delta$ (ppm) of the terminal methyl groups, of the anionic forms and the $-NH_2$ coordinated amino acids, as a function of the amino acids. Amino acid anions, □; *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(amac)](NO_3)$ complexes, ▲; *cis*-$[(NH_3)_2Pt(9\text{-}MeG)(amac)](NO_3)$ complexes, ■. (b) Difference in chemical shifts $\Delta\delta$ (ppm) of the protons of the zwitterionic form of nVal and the coordinated nVal in *cis*-$[(NH_3)_2Pt(nVal)(1\text{-}MeC)](NO_3)$ (▲) and *cis*-$[(NH_3)_2Pt(nVal)(9\text{-}MeG)](NO_3)$ (■) ternary complexes. (Positive $\Delta\delta$ values correspond to upfield shift upon coordination.)

The upfield shifts of the various aliphatic protons of nVal, being larger for the α proton near the coordination site are also shown in Fig. 2. This behavior is similar to the *trans* analogous systems, where the amino acids or peptides are also monocoordinated (through NH_2) with the metals [14b, f].

The percentage of the three possible conformers around the Cα–Cβ bond (Fig. 3) of the amino acids were calculated for the ternary complexes of 1-MeC with 2-Aba, Val and nVal, as described [7b, 39]. The vicinal proton coupling constant values and the rotamer distribution, as well as the equilibrium constant values between the *h* or *t* conformers and the remaining two forms are included in Table 3. The values of the corresponding 1:1 chelate complexes of the type *cis*-$[(NH_3)_2Pt(amac)](NO_3)$ used as starting materials [18a], are also included in Table 3. It is seen from this Table that as a result of the incoming new aromatic ligand (1-MeC), the percentage of the *h* conformer decreases in the complexes with 2-Aba and nVal, while the one of *t* increases in the complex

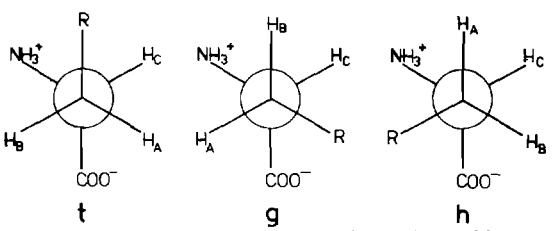

Fig. 3. The *t*, *g* and *h* rotamer of the amino acids around the C(α)–C(β) bond.

TABLE 3. Vicinal proton coupling constants and rotamer distribution in the ternary complexes with 1-MeC

Compound	$J_{AB}+J_{BC}$ (Hz)	J_{BC} (Hz)	h (%)	$t+g$ (%)	t (%)	$h+g$ (%)	k
cis-[$(NH_3)_2$Pt(2-Aba)](NO_3)[a]	10.109		51.3	48.7			2.11
cis-[$(NH_3)_2$Pt(2-Aba)(1-MeC)](NO_3)	12.200		32.1	67.9			0.97
cis-[$(NH_3)_2$Pt(nVal)](NO_3)[a]	10.023		52.1	47.9			2.18
cis-[$(NH_3)_2$Pt(nVal)(1-MeC)](NO_3)	12.400		30.3	69.7			0.87
cis-[$(NH_3)_2$Pt(Val)](NO_3)[a]		3.37			8.9	91.1	0.20
cis-[$(NH_3)_2$Pt(Val)(1-MeC)](NO_3)		4.60			20.2	79.8	0.51

[a]Taken from ref. 18a.

with Val. These values are close to those of the free amino acids (zwitterionic or ionic forms) [18a]. The percentage of the $g+h$ conformers in similar Pt(II) or Pd(II) systems with nucleosides and amino acids–peptides was higher however, reflecting the stronger ligand–ligand interactions in these systems [2a, 14b, c, f], than in the present case.

Crystal structure

A drawing of the complex with the labelling scheme is given in Fig. 4. The unit cell contains two cations, two anions and four water molecules. Confirming the other experimental data, this structure shows clearly that the base (1-MeC) coordinates through N(3) and the amino acid (Gly) through its amino ($-NH_2$) group, while the carboxylate group of Gly is free and deprotonated.

Selected bond distances and angles are included in Tables 4 and 5. The various distances and angles are within the expected ranges [19a, 28a, 41, 42]. The Pt–N distance of Gly also compares well with

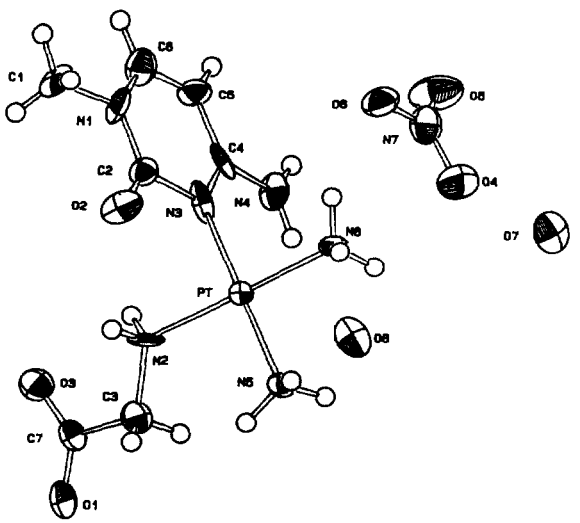

Fig. 4. A drawing of the complex with the label scheme ORTEP [40]. 50% thermal ellipsoids shown, Hs have arbitrary size.

TABLE 4. Intramolecular distances (Å) involving the non-hydrogen atoms[a]

Atoms	Distance	Atoms	Distance
Pt–N(2)	2.054(8)	N(1)–C(1)	1.48(1)
Pt–N(3)	2.015(8)	N(1)–C(2)	1.37(1)
Pt–N(5)	2.025(8)	N(1)–C(6)	1.34(1)
Pt–N(6)	2.031(8)	N(2)–C(3)	1.47(1)
O(1)–C(7)	1.27(1)	N(3)–C(2)	1.40(1)
O(2)–C(2)	1.23(1)	N(3)–C(4)	1.34(1)
O(3)–C(7)	1.23(1)	N(4)–C(4)	1.33(1)
O(4)–N(7)	1.24(1)	C(3)–C(7)	1.53(1)
O(5)–N(7)	1.23(1)	C(4)–C(5)	1.42(1)
O(6)–N(7)	1.26(1)	C(5)–C(6)	1.36(1)

[a]e.s.d.s in the least significant figure are given in parentheses.

TABLE 5. Intramolecular bond angles (°) involving the non-hydrogen atoms[a]

Atoms	Angle	Atoms	Angle
N(2)–Pt–N(3)	88.1(3)	O(4)–N(7)–O(6)	119(1)
N(2)–Pt–N(5)	93.4(3)	O(5)–N(7)–O(6)	120(1)
N(2)–Pt–N(6)	178.1(4)	O(2)–C(2)–N(1)	120.3(9)
N(3)–Pt–N(5)	176.9(4)	O(2)–C(2)–N(3)	120.5(9)
N(3)–Pt–N(6)	90.3(3)	N(1)–C(2)–N(3)	119.1(9)
N(5)–Pt–N(6)	88.2(3)	N(2)–C(3)–C(7)	111.9(8)
C(1)–N(1)–C(2)	117.2(8)	N(3)–C(4)–N(4)	118.8(9)
C(1)–N(1)–C(6)	121.3(8)	N(3)–C(4)–C(5)	122.2(9)
C(2)–N(1)–C(6)	121.4(8)	N(4)–C(4)–C(5)	119.1(9)
Pt–N(2)–C(3)	122.0(6)	C(4)–C(5)–C(6)	116.9(9)
Pt–N(3)–C(2)	115.2(6)	N(1)–C(6)–C(5)	121.6(9)
Pt–N(3)–C(4)	126.0(7)	O(1)–C(7)–O(3)	125.4(9)
C(2)–N(3)–C(4)	118.8(8)	O(1)–C(7)–C(3)	115.8(8)
O(4)–N(7)–O(5)	121(1)	O(3)–C(7)–C(3)	118.7(9)

[a]e.s.d.s in the least significant figure are given in parentheses.

the corresponding one in *trans*-[(CH_3NH_2)Pt(1-MeC)(Gly)](NO_3) [14e] and with those of the binary chelates [18a], being a little longer than the Pt–N distance of 1-MeC.

It is noticeable that the Pt–O(2) distance of the exocyclic carbonyl group of 1-MeC is 2.987 Å, the O(2) atom occupying an axial position. This C(2)

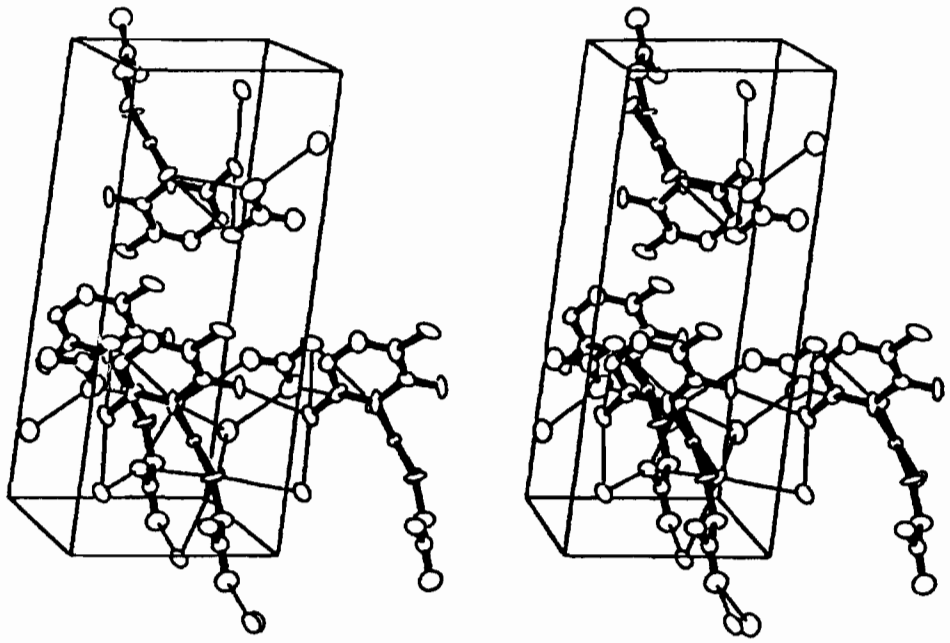

Fig. 5. A crystal packing diagram showing the important hydrogen bonds (thin lines). View down a^*, with c parallel to the bottom of the page.

TABLE 6. Possible hydrogen bondings and contacts in *cis*-$[(NH_3)_2Pt(1\text{-MeC})(Gly)](NO_3)\cdot 2H_2O$

Atoms	Distance (Å)
Hydrogen bonds	
O(1)–O(8)^{i}	2.69(1)
O(1)–O(7)^{ii}	2.75(1)
O(2)–N(4)^{iii}	2.95(1)
O(3)–O(8)^{iv}	2.74(1)
O(3)–N(6)^{iv}	3.02(1)
O(3)–N(5)^{iv}	3.18(1)
O(4)–O(7)	2.85(1)
O(4)–N(6)	3.13(1)
O(5)–N(6)^{v}	2.95(1)
O(6)–N(6)	3.09(1)
O(6)–N(4)	3.19(1)
O(7)–N(5)^{v}	2.98(1)
O(7)–N(6)^{v}	3.06(1)
O(8)–N(5)^{v}	2.93(1)
O(8)–N(4)	3.18(1)
O(8)–N(5)	3.19(1)
Other relevant distances	
Pt–O(2)	2.987(7)
C(5)–C(5)^{iv}	3.72(2)

(i) $2-x, -y, 1-z$; (ii) $1-x, -y, 1-z$; (iii) $x, y, z-1$; (iv) $1+x, y, z$; (v) $x, y, 1+z$; (vi) $2-x, 1-y, 2-z$.

atom was occupying a similar position in the structure of Pd(Gly-1-Tyr)(Cyd) [1g], though the corresponding distance was a little longer (3.113 Å). In both cases, however, the distances are too long for any significant bonding interactions. They contribute however to

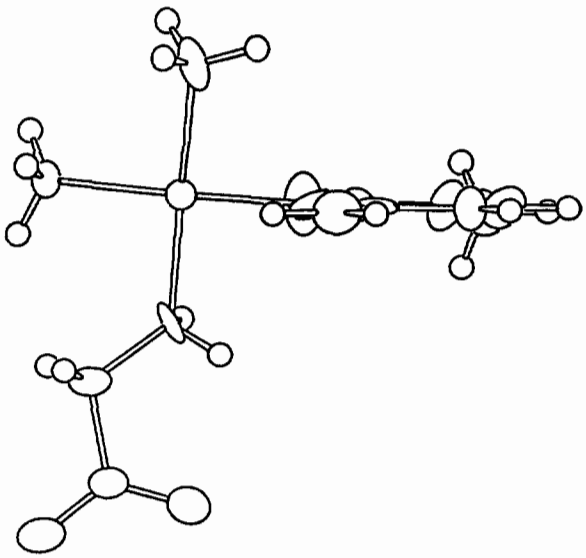

Fig. 6. A diagram showing the dihedral angles of the various planes. The 1-MeC ring is perpendicular to the paper plane, while the Pt(II) coordination plane makes an angle of 19.01° with the paper plane.

the stabilization of the molecule and they are manifested by the smaller PtN(3)C(2) angle of 115.2°, compared to the PtN(3)C(4) angle of 126°. Slightly stronger interactions (2.7–2.8 Å) were found in the case of Cu(II) complexes with the same ligands [43], the metal having a greater tendency to coordinate with oxygen ligands and being smaller.

TABLE 7. Least-squares planes and the deviations of the individual atoms from them

Plane number 1 (platinum coordination plane)
$1.4967x + 9.5087y - 6.0133z - 0.78160 = 0$

Atoms defining plane	Distance	e.s.d.
Pt	−0.0004	0.0004
N(2)	0.0202	0.0094
N(3)	0.0435	0.0078
N(5)	0.0500	0.0084
N(6)	0.0178	0.0088
Additional Atoms		
C(3)	−0.3719	

Mean deviation from plane is 0.0264 angstroms chi-squared: 66.4

Plane number 2 (1-MeC Plane)
$6.1838x - 11.384y + 0.43561z - 2.3903 = 0$

Atoms defining plane	Distance	e.s.d.
N(1)	0.0040	0.0083
C(2)	0.0126	0.0103
N(3)	−0.0167	0.0081
C(4)	0.0187	0.0094
C(5)	−0.0031	0.0114
C(6)	−0.0103	0.0101
Additional atoms		
C(1)	0.0964	
O(2)	0.0583	
N(4)	0.0529	
Pt	−0.0935	

Mean deviation from plane is 0.0109 angstroms chi-squared: 10.4

Dihedral angles between least-squares planes

Plane	Plane	Angle
2	1	108.16

Plane number 3 (glycine plane)
$3.0518x + 5.2491y - 6.5341z - 1.4274 = 0$

Atoms defining plane	Distance
N(2)	0.0000
C(3)	0.0000
C(7)	0.0000
Additional atoms	
Pt	−0.5897
O(1)	−0.0267
O(3)	−0.0354

Mean deviation from plane is 0.0000 angstroms chi-squared: 0.0

Dihedral angles between least-squares planes

Plane	Plane	Angle
3	1	17.88
3	2	91.99

(*continued*)

TABLE 7. (*continued*)

Plane number 4 (NO_3^- plane)
$6.2717x - 11.628y - 0.67623z - 1.6312 = 0$

Atoms defining plane	Distance	e.s.d.
N(7)	0.0140	0.0091
O(4)	−0.0062	0.0100
O(5)	−0.0076	0.0109
O(6)	−0.0045	0.0083

Mean deviation from plane is 0.0081 angstroms chi-squared: 3.1

Dihedral angles between least-squares planes

Plane	Plane	Angle
4	1	100.96
4	2	9.84
4	3	84.04

The molecules of the complex are held together in the crystal by hydrogen bonds and electrostatic interactions, with the intervention of the two water molecules per complex molecule and the nitrate anion. No stacking of hydrophobic intra- or intermolecular interactions are observed. The closest contact of the pyrimidines is 3.72(2) Å between the C(5) atoms of two different molecules of adjacent unit cells. The reason for this distance between the two 1-MeC rings, however, seems to be the stronger hydrogen bonding interactions of the O(2) of one molecule with the N(4) of another molecule, the distance being 2.95(4) Å, and not a base–base stacking interaction.

In Fig. 5, the crystal packing with the hydrogen bonding network is shown. The water (1), O(7) atom, is hydrogen bonded to O(4) of the nitrate ion and O(1) of the deprotonated carboxylate group of Gly. Also the N(5) and N(6) ammonia groups donate to O(7). The water (2), O(8) atom bridges from O(1) to O(3) of two different Gly carboxylates. Also it hydrogen bonds with the N(4) of cytosine, the N(5) of ammonia of a second molecule and the N(5) of ammonia of a third molecule. The oxygens of the planar NO_3^- anion also form hydrogen bonds with the ammonia (N(6)···O(5)) and the N(4) amino group (N(4)···O(6)) of the base of a second molecule. A third complex molecule has its N(6) of ammonia showing interaction with both O(4) and O(6). The carboxylate oxygens are also bonded to the N(5), N(6) ammonia molecules, in addition to the water molecules. Details of the hydrogen bondings and contact interactions are included in Table 6.

Both the Pt(II) coordination and the pyrimidine ring planes deviate only slightly from planarity, by a mean deviation of 0.0264 Å for the former and 0.0109 Å for the latter. Their least-square planes are given in Table 7.

The 1-MeC ring makes an angle of 108.11° with the Pt(II) coordination plane. This angle is the largest ever found in similar compounds: 97° in *cis*-$[(NH_3)_2Pt(1\text{-}MeC)Cl]_2[Pt(CN)_4]$ [41], 84 and 88° in the two forms of *cis*-$[(NH_3)_2Pt(1\text{-}MeC)Cl](NO_3)$ [19a], 80.35° in *trans*-$[(CH_3NH_2)_2Pt(1\text{-}MeC)(Gly)](NO_3)\cdot 2H_2O$ [14e] and 64° in *trans*-$[Cl_2Pt(NH_3)(1\text{-}MeC)]\cdot \frac{1}{2}H_2O$ [42].

In the analogous cytosine [42] or cytidine [42d] Cu(II)–glycylglycine complexes, they had the values of 68.1(3) and 104(1)°, without any consequence in the Cu···O(2) interaction, which remained constant [42].

The Gly, N(2)C(3)C(7) plane on the other hand, makes an angle of 17.88° with the Pt(II) coordination plane. As a result, the 1-MeC and Gly planes are practically perpendicular (91.99°). Consequently, the free $-COO^-$ group of Gly points out the pyrimidine plane (Fig. 6), as is the case for *trans*-$[(CH_3NH_2)_2Pt(1\text{-}MeC)(Gly)](NO_3)$ [14e]. No hydrophobic intramolecular interactions can take place under these conditions, even with an amino acid with an aliphatic side chain, because this would also be directed away from the 1-MeC ring. However, the whole conformation could be completely different in such a case and crystal structures with other amino acids of the same system remain to be solved, in order to verify such interactions, shown to exist in solution.

Supplementary material

Table A with the elemental analysis, the molar conductance values and the yields of the complexes, according to their route of preparation; Table B with the positional parameters of the complex *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(Gly)](NO_3)$, including the calculated hydrogen atoms; Table C with the final temperature factors; and Table D with the structure factors are available from the authors on request.

Acknowledgements

This work was supported in part by a grant of a bilateral agreement between Greece and the F.R.G. awarded to N.H. and B.L. and in part by a NATO grant awarded to N.H. and I.S.B.

References

1 (a) G. L. Eichhorn, in H. Sigel (ed.), *Metal Ions in Biological Systems*, Vol. 10, Marcel Dekker, New York, 1980, pp. 1–21; (b) C. Helene and J. C. Maurizot, *Crit. Rev. Biochem., 11* (1981) 213; (c) A. Bere and C. Helene, *Biopolymers, 18* (1979) 2659; (d) R. Koren and A. S. Mildvan, *Biochemistry, 16* (1977) 241; (e) B. L. Bean, R. Koren and A. S. Mildvan, *Biochemistry, 16* (1979) 3322; (f) C. Helene, *Nucl. Acid Res., 2* (1975) 961; (g) M. Sabat, K. A. Satyshur and M. Sundaralingam, *J. Am. Chem. Soc., 105* (1983) 976.

2 (a) A. Garoufis, R. Haran, M. Pasdeloup, J. P. Laussac and N. Hadjiliadis, *J. Inorg. Biochem., 31* (1987) 65; (b) O. Yamauchi, *J. Mol. Catal., 23* (1984) 255; (c) H. Sigel, B. E. Fischer and E. Farkas, *Inorg. Chem., 22* (1983) 925; (d) L. D. Pettit and R. J. W. Hefford, in H. Sigel (ed.), *Metal Ions in Biological Systems*, Vol. 9, Marcel Dekker, New York, 1980, pp. 173–212.

3 B. E. Fischer and H. Sigel, *J. Am. Chem. Soc., 102* (1980) 2998, and refs. therein.

4 (a) H. Sigel and C. F. Naumann, *J. Am. Chem. Soc., 98* (1976) 730; (b) G. Liang, R. Tribolet and H. Sigel, *Inorg. Chem., 27* (1988) 2877; (c) H. Sigel, R. Tribolet and K. H. Scheler, *Inorg. Chim. Acta, 100* (1985) 151.

5 (a) P. Amico, P. R. Bonomo, R. Cali, V. Cucinotta, P. Q. Daniele, G. Ostacoli and E. Rizzarelli, *Inorg. Chem., 28* (1989) 3555; (b) G. Arena, R. Cali, V. Cucinotta, S. Musumeci, E. Rizzarelli and S. Sammartano, *J. Chem. Soc., Dalton Trans.*, (1983) 1271; (c) G. Arena, R. Cali, V. Cucinotta, S. Musumeci, E. Rizzarelli and S. Sammartano, *Thermochim. Acta, 74* (1984) 77.

6 (a) A. Odani and O. Yamauchi, *Inorg. Chim. Acta, 66* (1982) 163; (b) O. Yamauchi and A. Odani, *J. Am. Chem. Soc., 103* (1981) 391.

7 (a) N. N. Vlasova and N. K. Davidenko, *Koord. Khim., 9* (1982) 1470; (b) S. H. Kim and R. B. Martin, *J. Am. Chem. Soc., 106* (1984) 1707; (c) K. B. Yatsimirskii, P. A. Maronik, N. K. Davidenko, E. J. Lapotina and M. A. Fedorenko, *Dokl. Akad. Nauk SSSR, 279* (1984) 654.

8 (a) S. J. Lippard, *Pure Appl. Chem., 59* (1987) 731; (b) J. Reedjik, *Pure Appl. Chem., 59* (1987) 181.

9 (a) J. P. Maquet, J. L. Butour, N. P. Johnson, H. Razaka, B. Saller, C. Vienssens and M. Wright, in *Proc. 4th Int. Symp. Platinum Coordination Complexes in Cancer Chemotherapy, Vermont, 1983*, pp. 27–37; (b) A. J. Repta and D. F. Long,in A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), *Cis-Platin Current Status and New Developments*, Academic Press, New York, 1980, Ch. 18, pp. 285–304.

10 R. F. Borch and M. E. Pleasants, *Proc. Natl. Acad. Sci. U.S.A., 76* (1979) 6611.

11 (a) S. J. Lippard and J. D. Hoeschele, *Proc. Natl. Acad. Sci. U.S.A., 76* (1979) 6091; (b) J. M. Banjar, L. S. Hnilica, P. C. Briggs, J. Stein and G. Stein, *Biochemistry, 23* (1984) 1921; (c) J. Filipski, K. W. Kohn and W. M. Bonner, *FEBS Lett., 152* (1983) 105; (d) R. B. Ciccarelli, M. J. Salomon, A. Varshavsky and S. J. Lippard, *Biochemistry, 24* (1985) 7533.

12 (a) L. A. Zwelling, S. Michaels, H. Schwartz, P. P. Dodson and K. W. Kohn, *Cancer Res., 41* (1981) 640; (b) L. A. Zwelling, M. O. Bradley, N. A. Sharkey, T. Anderson and K. W. Kohn, *Mutat. Res., 67* (1979) 271.

13 S. E. Sherman and S. J. Lippard, *Chem. Rev., 87* (1987) 1153.

14 (a) S. Kasselouri, A. Garoufis and N. Hadjiliadis, *Inorg. Chim. Acta, 135* (1987) L23; (b) S. Kasselouri, J. P. Laussac and N. Hadjiliadis, *Inorg. Chim. Acta, 166*

(1989) 239; (c) S. Kasselouri and N. Hadjiliadis, *Inorg. Chim. Acta, 168* (1990) 15; (d) F. Schwarz, B. Lippert, A. Iakovidis and N. Hadjiliadis, *Inorg. Chim. Acta, 168* (1990) 275; (e) F. J. Perch, H. Preut and B. Lippert, *Inorg. Chim. Acta, 169* (1990) 195; (f) A. Garoufis, J. Hatiris and N. Hadjiliadis, *J. Inorg. Biochem., 41* (1991) 195.

15 P. A. Maronik and N. K. Davidenko, *Russ. J. Inorg. Chem., 28* (1983) 1450.

16 T. T. Sakai, A. L. Pogolotti and D. V. Santi, *J. Heterocycl. Chem., 5* (1968) 849.

17 (a) S. G. Dhara, *Indian J. Chem., 8* (1970) 193; (b) G. Raudaschl-Sieber, B. Lippert, J. D. Hoeschele, H. E. Howard-Lock, C. J. L. Lock and P. Pilon, *Inorg. Chim. Acta, 106* (1985) 141.

18 (a) A. Iakovidis, N. Hadjiliadis, H. Schöllhorn, U. Thewalt and G. Trötscher, *Inorg. Chim. Acta, 164* (1989) 221; (b) H. Pivcova, V. Sandek, D. Noskova and J. Drobnik, *J. Inorg. Biochem., 23* (1985) 43.

19 (a) B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem., 20* (1981) 335; (b) L. S. Hollis, A. R. Amundsen and E. W. Stern, *J. Med. Chem., 32* (1989) 128; (c) G. Raudaschl and B. Lippert, *Inorg. Chim. Acta, 80* (1983) L49.

20 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A, 39* (1983) 158.

21 (a) M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidari, R. Spagna and D. Viterdo, Structure solution methods: SIR 88, *J. Appl. Crystallogr., 22* (1989) 389; (b) P. T. Beurskens, DIRDIF, Direct methods for difference structures. An automatic procedure for phase extension and refinement of difference structure factors, *Tech. Rep. 1984/1,* Crystallography Laboratory, Toernooiveld, 6525 Ed. Nijmegen, The Netherlands.

22 D. T. Cromer and J. T. Waber, *International Tables for X-ray Crystallography,* Vol. IV, Kynoch Press, Birmingham, 1974, Table 2.2A.

23 J. A. Ibers and W. C. Hamilton, *Acta Crystallogr., 17* (1964) 781.

24 D. T. Cromer, *International Tables for X-ray Crystallography,* Vol. IV, Kynoch Press, Birmingham, 1974, Table 2.3.1.

25 *TEXSAN–TEXRAY Structure Analysis Package,* Molecular Structure Coorporation, The Woodlands, TX 77381, U.S.A.

26 (a) B. Lippert, H. Schöllhorn and U. Thewalt, *J. Am. Chem. Soc., 108* (1986) 6616; (b) G. Y. H. Chu, R. E. Duncan and R. S. Tobias, *Inorg. Chem., 16* (1977) 2625; (c) J. M. Delabar and M. Najoube, *Spectrochim. Acta, Part A, 34* (1978) 129; (d) M. Tsuboi, V. Takahu and I. Harada, in J. Duchesne (ed.), *Physico-Chemical Properties of Nucleic Acids,* Academic Press, New York, 1973, Ch. 11, pp. 91–145; (e) M. Mathlouthi, A. M. Seuvre and J. L. Koenig, *Carbonhydr. Res., 146* (1986) 15.

27 R. Nakamoto, *IR and Raman Spectra of Inorganic and Coordination Compounds,* Part III, Wiley, New York, 2nd edn., 1978, pp. 232–244.

28 S. Mansy, G. Y. H. Chu, R. E. Duncan and R. S. Tobias, *J. Am. Chem. Soc., 100* (1978) 607.

29 (a) G. A. Foulds, G. C. Percy and D. A. Thornton, *Spectrochim. Acta, Part A, 34* (1978) 1231; (b) J. B. Hodgson, G. C. Percy and D. A. Thornton, *Spectrochim. Acta, Part A, 35* (1979) 949; (c) G. C. Percy and H. S. Stenton, *J. Chem. Soc., Dalton Trans.,* (1976) 2429.

30 D. M. Byler and H. Susi, *Spectrochim. Acta, Part A, 35* (1979) 1365.

31 A. Iakovidis, N. Hadjiliadis and I. S. Butler, *Spectrochim. Acta,* in press.

32 (a) Y. Kyogoku, M. Tsuboi, T. Shimanouchi and I. Watanabe, *Nature (London), 189* (1961) 120; (b) M. Mathlouthi, A. M. Seuvre and J. L. Koenig, *Carbohydr. Res., 146* (1986) 1; (c) R. Faggiani, B. Lippert, C. J. L. Lock and R. Pfab, *Inorg. Chem., 20* (1981) 2381.

33 (a) P. C. Kong and T. Theophanides, *Inorg. Chem., 13* (1974) 1981; (b) P. C. Kong and T. Theophanides, *Bioinorg. Chem., 5* (1975) 51.

34 D. M. Reily, K. Wilkowski, K. Shinozuka and L. G. Marzilli, *Inorg.Chem., 24* (1985) 37.

35 (a) R. E. Cramer and P. L. Dahlstrom, *Inorg. Chem., 24* (1985) 3420; (b) A.T. M. Marcelis, J. L. Van Der Veer, J. C. M. Zwetsloot and J. Reedjik, *Inorg. Chim. Acta, 78* (1983) 195; (c) M. D. Reily and L. G. Marzilli, *J. Am. Chem. Soc., 108* (1986) 6785; (d) K. Inagaki, F. J. Dijt, E. L. M. Lempers and J. Reedjik, *Inorg. Chem., 27* (1988) 382.

36 V. Aletras and N. Hadjiliadis, in preparation.

37 (a) R. Romeo, D. Minniti and S. Lanza, *Inorg. Chem., 18* (1979) 2362; (b) J. R. Bales, C. J. Coulson, D. W. Gilmour, M. A. Mazid, S. Neidl, R. Kuroda, B. J. Peart, C. A. Ramsden and P. J. Sadler, *J. Chem. Soc., Chem. Commun.,* (1983) 432.

38 Y. G. Breusova-Baidala, N. N. Zheligovskaya and V. I. Spitsyn, *Izv. Akad. Nauk SSSR, Ser. Khim., 6* (1974) 1239.

39 (a) V. S. Krattiger, K. H. Scheller and R. B. Martin, *Inorg. Chim. Acta, 59* (1982) 281; (b) R. B. Martin, *J. Phys. Chem., 83* (1979) 2404.

40 C. K. Johnson, *ORTEPII, Rep. ORNL-5138,* Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

41 H. Schöllhorn, U. Thewalt, G. Raudaschl-Sieber and B. Lippert, *Inorg. Chim. Acta, 124* (1986) 207.

42 B. Lippert, C. J. L. Lock and R. A. Speranzini, *Inorg. Chem., 20* (1981) 808.

43 (a) T. J. Kistenmacher, D. J. Szalda and L. G. Marzilli, *Acta Crystallogr., Sect. B, 31* (1975) 2416; (b) D. J. Szalda, L. G. Marzilli and T. J. Kistenmacher, *Inorg. Chem., 14* (1975) 2076; (c) D. J. Szalda and T. J. Kistenmacher, *Acta Crystallogr., Sect. B, 33* (1977) 865; (d) D. J. Szalda, L. G. Marzilli and T. J. Kistenmacher, *Biochem. Biophys. Res. Commun., 63* (1975) 601.