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Ternary Complexes of *cis*-$(NH_3)_2Pt(II)$ with Model Nucleobases (1-Methylcytosine, 9-Methylguanine) and N- and O-bound Amino Acids (gly, ala)

FRANK SCHWARZ, BERNHARD LIPPERT*

Fachbereich Chemie, Universität Dortmund, D-4600 Dortmund (F.R.G.)

AKIS IAKOVIDIS and NICK HADJILIADIS*

Department of Chemistry, University of Ioannina, Ioannina 45-110 (Greece)

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Abstract

The formation and properties of isomeric complexes of *cis*-$(NH_3)_2Pt(II)$ containing the model nucleobase 1-methylcytosine, 1-MeC, and the amino acid glycine, glyH, are reported. Depending on the pH, different protonation states of amino acid and nucleobase are present. In acidic medium, *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$ initially forms with glyH *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(glyH\text{-}O)]^{2+}$ (**2b**) which slowly at pH 2–3 and faster at pH 4–5 converts into *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(gly\text{-}N)]^{+}$ (**1a**). **1a** is protonated to give the glyH-*N* species with a $pK_a \simeq 2.8$ and deprotonated at the NH_2 group of 1-MeC with a $pK_a \simeq 12.5$–13. Deprotonation of **2b** was not detected up to pH 6, at which point conversion **2b** → **1a** was complete. **1a** was prepared and isolated as the nitrate salt via two different routes, starting either from the gly chelate *cis*-$[(NH_3)_2Pt(gly\text{-}N,O)]^{+}$ or from *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$. Only the second way led to both O- and N-bound glycine complexes. In the absence of glyH, *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$ undergoes a condensation reaction initially to the μ-hydroxo complex *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(OH)Pt(1\text{-}MeC)(NH_3)_2]^{3+}$ (**6**) and slowly to a bis(1-methylcytosinato) bridged diplatinum(II) complex, *cis*-$[(NH_3)_2Pt(1\text{-}MeC^-)_2Pt(NH_3)_2]^{2+}$. Analogues of **1a** with 9-methylguanine (9-MeGH) instead of 1-MeC as well as mixed 1-MeC, alanine and mixed 9-MeGH, alanine complexes have also been prepared and isolated.

Introduction

It is generally believed today that the antitumor activity of *cis*-diamminedichloroplatinum(II), *cis*-DDP, is related to its interaction with cellular DNA and the subsequent interference with DNA replication and/or transcription in cancer cells [1]. This view does not, however, imply that reactions with biomolecules other than DNA do not take place and that reaction with proteins or peptides are insignificant. In fact, there is evidence that a large fraction of *cis*-DDP eventually becomes protein bound [2] and some of the second generation Pt drugs behave similarly [3]. It has been hypothesized that *cis*-DDP toxicity is related to its ability to inactivate proteins [4] and a protective effect of the tripeptide glutathione against *cis*-DDP toxicity appears to be established today [5].

Considering the highly condensed structure of chromatin-DNA in eucaryotic cells it is not all that surprising that histone–DNA cross-links have been detected both with *cis*-DDP and the inactive *trans*-isomer [6]. Similarly, cross-linking between DNA and non-histone proteins has been detected in Pt treated mouse L1210 and HeLa cells, respectively [7]. Cross-links between DNA and regulatory DNA binding proteins or DNA and DNA processing enzymes appear to be yet another potentially significant possibility.

While interactions of Pt(II) with amino acids and peptides in general [8] and of *cis*-$(NH_3)_2Pt(II)$ in particular [9] have been studied, also with regard to a possible use as antitumor agent [10], ternary complexes of Pt(II) containing amino acids *and* nucleobases have received relatively little attention as yet [11].

The systematic study of mixed amino acid, nucleobase metal complexes in general is of considerable interest concerning the possible role of metal ions in protein–nucleic acid association [12]. Principles of such interactions are beginning to emerge [13].

In this report, we describe preparative and spectroscopic results on ternary interactions of *cis*-$(NH_3)_2Pt(II)$ with model nucleobases and amino acids.

*Author to whom correspondence should be addressed.

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Experimental

Isolation of Compounds

cis-$[(NH_3)_2Pt(1\text{-MeC})Cl]Cl$ [14], *cis*-$[(NH_3)_2Pt(gly)]NO_3$ [9] and *cis*-$[(NH_3)_2Pt(1\text{-MeC})(ala)]NO_3$ [9] were prepared as described.

cis-$[(NH_3)_2Pt(1\text{-MeC})(gly\text{-}N)]NO_3 \cdot 2H_2O$ (**1a**) was prepared via two routes. (i) *cis*-$[(NH_3)_2Pt(gly)]NO_3$ (0.6 mmol), dissolved in 3 ml of water, and 1-MeC (1.2 mmol), dissolved in 7 ml of water, were combined and kept at 45 °C for 2 days. Column chromatography (Sephadex G10) gave **1** in 40% yield, eluting with the early fractions. (ii) Alternatively, *cis*-$[(NH_3)_2Pt(1\text{-MeC})Cl]Cl$ was converted into the aqua complex by $AgNO_3$ treatment, filtered from AgCl, the solution (pH 4) brought to pH 7.7 and 2 eq. of glyH was added. After 4 days at 50 °C, the reaction mixture was passed over Sephadex G10 and **1a** was eluted after glyH and mixtures of **1a** and unreacted glyH. Occasionally, some $NaNO_3$ coeluted with **1a**. The yield was approximately 40–50%. According to IR and ^1H NMR spectra, the two compounds obtained via (i) and (ii) are identical. *Anal.* Calc. for $C_7H_{17}N_7O_6Pt$: C, 15.97; H, 3.49; N, 18.63. Found: C, 15.90; H, 3.28; N, 18.64%. The isomeric complex with O-bound glycine (**2**), which was detected in solution (see 'Results and Discussion'), was not isolated.

cis-$[(NH_3)_2Pt(9\text{-MeGH})(gly\text{-}N)]NO_3$ (**3a**) was prepared in analogy to **1b** (route (i), pH 7.5). After cooling to 0 °C and filtration of unreacted 9-MeGH, the solution was concentrated to 3 ml volume and passed over Sephadex G10. **2b** eluted in the early fractions and was contaminated with some unidentified byproduct. Recrystallization of **3a** from dilute HNO_3 (pH 2.0) gave small, starlike crystals of *cis*-$[(NH_3)_2Pt(9\text{-MeGH})(glyH\text{-}N)](NO_3)_2$ (**3b**) in 34% yield. *Anal.* Calc. for $C_8H_{18}N_{10}O_9Pt$: C, 16.19; H, 3.06; N, 23.61. Found: C, 16.3; H, 3.1; N, 23.8%.

cis-$[(NH_3)_2Pt(1\text{-MeC})(ala\text{-}N)]NO_3 \cdot H_2O$ (**4**) and *cis*-$[(NH_3)_2Pt(9\text{-MeG})(ala\text{-}N)]NO_3 \cdot H_2O$ (**5**) were prepared according to route (i). **4** proved to be contaminated with an impurity (H value off by 0.56%) which did not show up in the ^1H NMR spectrum, however. *Anal.* Calc. for $C_9H_{19}N_9O_6Pt$ (**5**): C, 19.22; H, 3.77; N, 22.42. Found: C, 19.35; H, 3.75; N, 21.95%.

cis-$[(NH_3)_2(1\text{-MeC})Pt(OH)Pt(1\text{-MeC})(NH_3)_2]X_3aq$ (**6**) was obtained from a freshly prepared solution of *cis*-$[(NH_3)_2Pt(1\text{-MeC})(H_2O)]X_2$, brought to pH = 6 by addition of 0.5 eq. of NaOH and allowed to evaporate for 2–3 days at room temperature. Yield 20–30%, depending on the concentration of the solution. Colorless crystals of the NO_3 salt rapidly lose water of crystallization in air. A sample kept in air analyzed as the 2.5-hydrate. *Anal.* Calc. for $C_{10}H_{32}N_{13}O_{14.5}Pt_2$ (**6a**): C, 12.55; H, 3.38; N, 19.04; O, 24.25. Found: C, 12.48; H, 3.40; N, 18.92; O, 24.22. The ClO_4 salt analyzed as a monohydrate. *Anal.* Calc. for $C_{10}H_{29}N_{10}O_{16}Cl_3Pt_2$ (**6b**): C, 11.53; H, 2.81; N, 13.45; Cl, 10.21. Found: C, 11.28; H, 2.84; N, 13.28; Cl, 10.50%.

Spectroscopy

^1H NMR spectra (D_2O, TSP as internal reference) were recorded on the following instruments: Jeol JNM-FX 60 (60 MHz), Varian EM 390 (90 MHz) and Bruker AM 300 (300 MHz). pD values were obtained by adding 0.4 to the pH meter reading. NaOD and/or DNO_3 was added to adjust the pH*. For the determination of pK_a values, the uncorrected pH* values were used. The pH titrations were performed by means of a pH meter (Metrohm) and a glass electrode. The Raman spectrum of **6a** was recorded on a Coderg PH 1 with krypton-laser excitation (647.1 nm, 330 mW).

Results and Discussion

Formation

Mixed nucleobase, amino acid complexes of *cis*-DDP were prepared via two routes.

(i) Reaction of amino acid anion chelates with nucleobase B

$$cis\text{-}[(NH_3)_2Pt(amac\text{-}N,O)]^+ + B \rightleftharpoons cis\text{-}[(NH_3)_2Pt(amac\text{-}N)(B)]^+ \quad (1)$$

(ii) Reaction of *cis*-$[(NH_3)_2Pt(B)(H_2O)]^{2+}$ with anionic amac and/or neutral amacH

$$cis\text{-}[(NH_3)_2Pt(B)(H_2O)]^{2+} + amac(H) \longrightarrow cis\text{-}[(NH_3)_2Pt(B)(amac)]^+ / [(NH_3)_2Pt(B)(amacH)]^{2+} \quad (2)$$

The model nucleobase B = 1-methylcytosine (1-MeC) was applied in most cases, occasionally also 9-methylguanine (9-MeGH).

Ternary complexes prepared via route (i) inevitably contained the amino acid anion bound to Pt through the NH_2 terminus, while route (ii) yielded products with the Pt coordinated via the amino or the carboxylate group, depending on the pH and the reaction time (see below). There was evidence that route (i) also led to complete displacement of the amino acid and formation of the bis(nucleobase) complex [15], while (ii) yielded an intermediate, *cis*-$[(NH_3)_2BPt(OH)PtB(NH_3)_2]^{3+}$ (B = 1-MeC) before addition of gly(H) (see below).

Complexes with N-bound Amino Acid

Figure 1 gives 300 MHz ^1H NMR spectra of *cis*-$[(NH_3)_2Pt(1\text{-MeC})(gly\text{-}N)]^+$ in D_2O, pD = 3.4 and 4.6, respectively. 1-MeC resonances show the usual pattern (doublets for H5 and H6, singlet for N-CH_3),

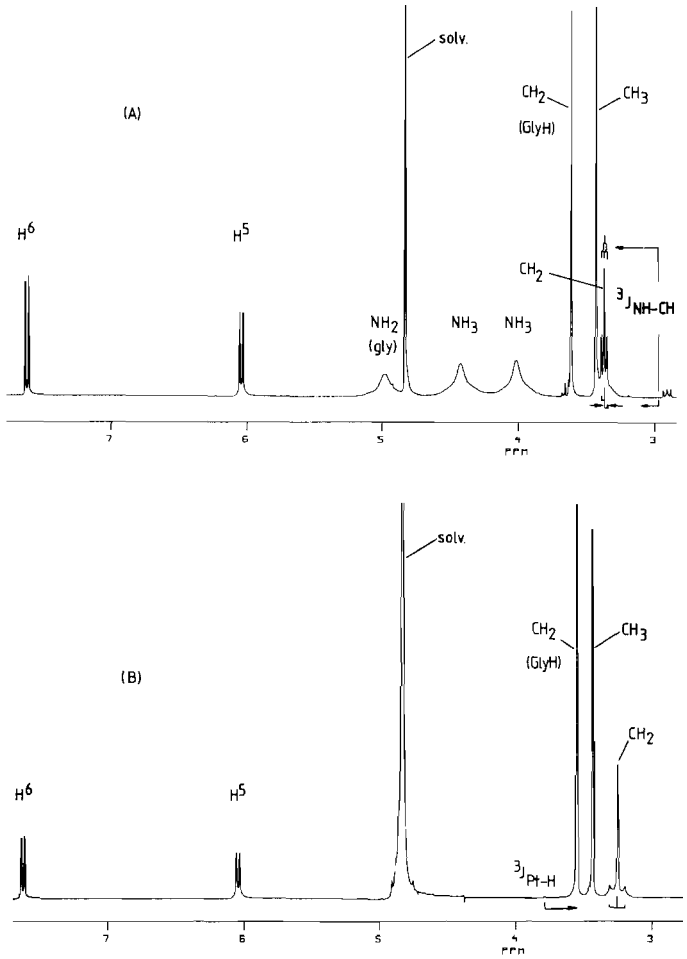

Fig. 1. 300 MHz ^{1}H NMR spectra (D_2O) of mixtures of glyH and **1a**: (A) pD 3.4 with CH_2 resonance of gly ligand displaying NH–CH coupling, (B) pD 4.6 after complete isotopic exchange (NH → ND) with CH_2 resonance of gly ligand displaying ^{195}Pt–^{1}H coupling of 34.5 Hz.

while the CH_2 resonance of the glycine ligand displays either a 1:2:1 triplet structure (acidic medium, $^3J \simeq 6.5$ Hz) or a singlet (**1a**, weakly acidic or basic medium). The same is true for the mixed glycine, 9-methylguanine complex. The triplet structure is due to coupling of CH_2 with NH_2 protons and is irreversibly lost once H → D exchange is complete. In the 90 MHz spectrum, the glycine CH_2 resonance of **1a** usually shows ^{195}Pt satellites of $^3J \simeq 34.5$ Hz, in agreement with reports by Appleton *et al.* [16]. Occasionally, even in the 300 MHz spectrum and after complete NH → ND exchange, ^{195}Pt satellites of the glycine CH_2 resonance could be observed (Fig. 1(B)), but due to relaxation phenomena [17], intensities of the satellites were considerably lower as compared to expectations. ^{195}Pt coupling is also observed for H5 of 1-MeC ($^4J \simeq 14.5$ Hz) and for H8 of 9-MeGH ($^3J \simeq 24$ Hz) when spectra are recorded at 90 MHz.

Chemical shifts of the ^{1}H NMR resonances of the mixed glycine, 1-MeC complex show a marked pH dependence, as examplified for **1** in Fig. 2. The chemical shift/pH* (uncorrected pH) dependence in the range 0.5–13.6 provides evidence for the following equilibria of the species containing N-bound glycine:

$$[(NH_3)_2Pt(\text{glyH-}N)(1\text{-MeC})]^{2+} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{\mathbf{1b}}{}$$

$$[(NH_3)_2Pt(\text{gly-}N)(1\text{-MeC})]^{+} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{\mathbf{1a}}{}$$

$$[(NH_3)_2Pt(\text{gly-}N)(1\text{-MeC}^-)] \quad (3)$$
$$\mathbf{1c}$$

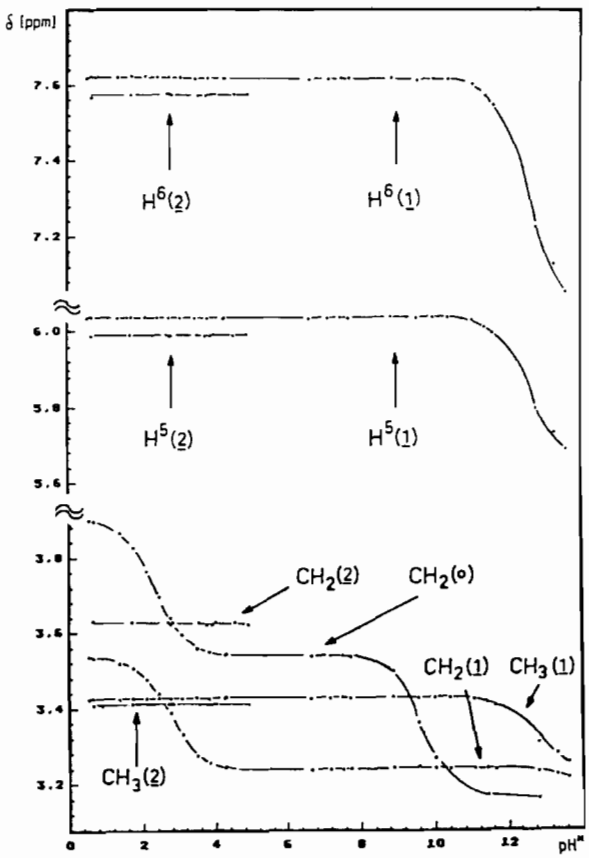

Fig. 2. pH* (uncorrected) dependence of chemical shifts of glycine (0), *cis*-$[(NH_3)_2Pt(1\text{-MeC})(gly\text{-}N)]^+$ (1) *cis*-$[(NH_3)_2Pt(1\text{-MeC})(glyH\text{-}O)]^{2+}$ (2) and the respective protonated/deprotonated forms.

pK_a values of the two equilibria are 2.8 (**1b** ⇌ **1a**) and 12.5–13 (**1a** ⇌ **1c**). pK_a values for the equilibria

$$^{\oplus}NH_3\text{–}CH_2\text{–}COOH \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} {}^{\oplus}NH_3\text{–}CH_2\text{–}COO^{\ominus} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} NH_2\text{–}CH_2\text{–}COO^{\ominus}$$

determined by the same method, are 2.3 and 9.6, respectively, in good agreement with literature values obtained in a different way [18]. Thus, on Pt(II) binding to the NH_2 terminus of glycine, the acidity of neutral glycine increases dramatically, by a factor of $10^{6.8}$. Our value is similar to those reported for *cis*- and *trans*-$[Pt(NH_3)_2(glyH)_2]^{2+}$ [19].

Interestingly, the 1-MeC ligand in **1** also shows a marked increase in acidity with deprotonation occurring above pH* 11. Although we have observed deprotonation and simultaneous platination of the exocyclic amino group of 1-methylcytosine before [20, 21], in no case of Pt(II) binding [22] have we found a similar acidification of *c.* 4 log units (cf. pK_a of 1-MeC ≃ 16.7 [23]) in a simple Pt(II) compound

TABLE 1. Chemical shifts $\Delta\delta$ [a] of amino acid protons relative to those of $[(NH_3)_3Pt(amac\text{-}N)]^+$

	CH	CH_2	CH_3	Reference
$[(NH_3)_3Pt(gly\text{-}N)]^+$		±0		24
$[(NH_3)_2Pt(gly\text{-}N,O)]^+$		+0.24		9a
$[Cl_2Pt(gly\text{-}N,O)]^-$		+0.21		24
1b		−0.12		this work
3a		−0.25		this work
$[(NH_3)_3Pt(ala\text{-}N)]^+$	±0		±0	24
$[(NH_3)_2Pt(ala\text{-}N,O)]^+$	+0.34		+0.03	9a
$[Cl_2Pt(ala\text{-}N,O)]^-$	+0.39		0.0	24
4	+0.33		−0.08	this work
5	+0.31		−0.12	this work

[a] In ppm relative to TSP, positive (negative) values indicate downfield (upfield) shifts.

of 1-MeC *without* subsequent metal binding at this site. From model building we conclude that the carboxylato group of the gly ligand could form a strong intramolecular hydrogen bond with the exocyclic amino group of the 1-MeC ring, thus possibly enhancing the acidity of the other proton at N(4).

A comparison of chemical shifts of glycine-CH_2 resonances in **1b** and the mixed gly,9-MeGH complex **3a** with those in the two chelates *cis*-$[(NH_3)_2Pt(gly\text{-}N,O)]^+$ [9a] and *cis*-$[Cl_2Pt(gly\text{-}N,O)]^-$ [24] as well as the related $[(NH_3)_3Pt(gly\text{-}N)]^+$ [24] (Table 1) shows those of the mixed gly, nucleobase complex to be highest upfield. This undoubtedly reflects the shielding effect of the nucleobase π-electron system. A comparison with compounds in the ala system (see also Table 1) shows the same trend there as far as the CH_3 resonances of the ala side chains are concerned. The α-protons, on the other hand, apparently are pointing away from the heterocyclic ring and experiencing a downfield shift. These findings are consistent with general concepts on hydrophobic ligand–ligand interactions [25, 26].

Complex with O-bound Glycine

When *cis*-$[(NH_3)_2Pt(1\text{-MeC})(H_2O)]^{2+}$ was reacted with glyH in moderately acidic medium (pD 2–4), rapid formation of a species **2b** different from that of **1a** (**1b**) was observed. Resonances of **2** are markedly different from those of **1** (see Fig. 2). In particular, the CH_2 resonance of **2b** neither shows ^{195}Pt nor ^1H coupling with NH_2 protons as does **1a**. Species **2b** is assigned to the O-bound isomer of **1b**, *cis*-$[(NH_3)_2Pt(glyH\text{-}O)(1\text{-MeC})]^{2+}$. Its solution behavior and ^1H NMR spectroscopic properties are similar to the O-bound glyH species reported by Appleton *et al.* [16]. Formation of **2** from *cis*-$[(NH_3)_2Pt(1\text{-MeC})(D_2O)]^{2+}$ and glyH (1.5 eq.) proved pH- and time-dependent. For example, at pD 3.6, c_{Pt} = 0.15 M, 22 °C, **2** is formed in 55% yield within 12 h and 70% within 24 h. While initially only

unreacted *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(D_2O)]^{2+}$ and a small amount (≃2%) of *cis*-$[(NH_3)_2Pt(1\text{-}MeC^-)_2Pt(NH_3)_2]^{2+}$ (characteristic ^1H NMR resonances at 6.86 ppm, H6, d, $^3J = 7.3$ Hz; 5.72 ppm, H5, d; 3.26 ppm, N-CH_3, s [20]), is observed, at a larger stage also resonances due to species **1** (**1a** ⇌ **1b**, averaged) are detected, e.g. 19% after 24 h under conditions mentioned above. The distribution of species is altered when, after an initial reaction time (typically 12–24 h), the pD was altered in order to monitor the chemical shifts of resonances of **2** as a function of pH* (uncorrected) as included in Fig. 2. It was found that (i) the percentage of **2b** rapidly decreased at the expense of that of **1b** (**1a**) with increasing pH*, (ii) species **2** was no longer detectable at pH* ≥ 6.2, (iii) the pH* dependence of resonances of **2** showed no sign of acid/base equilibrium in the range $0.7 <$ pH* < 6.2, and (iv) that at least one, possibly two additional yet unidentified species are formed (Fig. 3, traces IV and V). These findings indicate that the pK_a for the equilibrium

$$\underset{\mathbf{2b}}{cis\text{-}[(NH_3)_2Pt(glyH\text{-}O)(1\text{-}MeC)]^{2+}} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{\mathbf{2a}}{cis\text{-}[(NH_3)_2Pt(gly\text{-}O)(1\text{-}MeC)]^{+}} \quad (5)$$

must be ≥7–8, hence that Pt coordination via an oxygen of the carboxylic group of the glyH zwitterion must have only a slight acidifying effect on glyH. It probably is the consequence of a rather weak Pt(glyH-O) bond. The thermodynamically more stable bond is undoubtedly that via the amino group. The interconversion **2b** → **1b** (**1a**), which conceivably could occur in an intra- or intermolecular fashion, represents an interesting aspect for coordination chemistry and will be studied further. As far as implications for Pt(II) binding to peptides of proteins are concerned, these findings suggest that the carboxylate terminus of a peptide or protein, unlike the amino terminus, is not a preferred Pt(II) binding site under physiological pH conditions. We are, of course, aware that side chains of peptide and proteins contain additional potential donor sites for Pt complexation.

A μ-Hydroxo Bridged Bis(1-MeC) Complex

In an attempt to come up with an explanation for traces IV (V) in the ^1H NMR spectra shown in Fig. 3, we reinvestigated [27] the solution behavior of *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$. Although we are now certain that the set(s) of resonances in question are not due to the dinuclear μ-OH bridged complex *cis*-$[(NH_3)_2(1\text{-}MeC)Pt(OH)Pt(1\text{-}MeC)(NH_3)_2]^{3+}$, we wish to report on it.

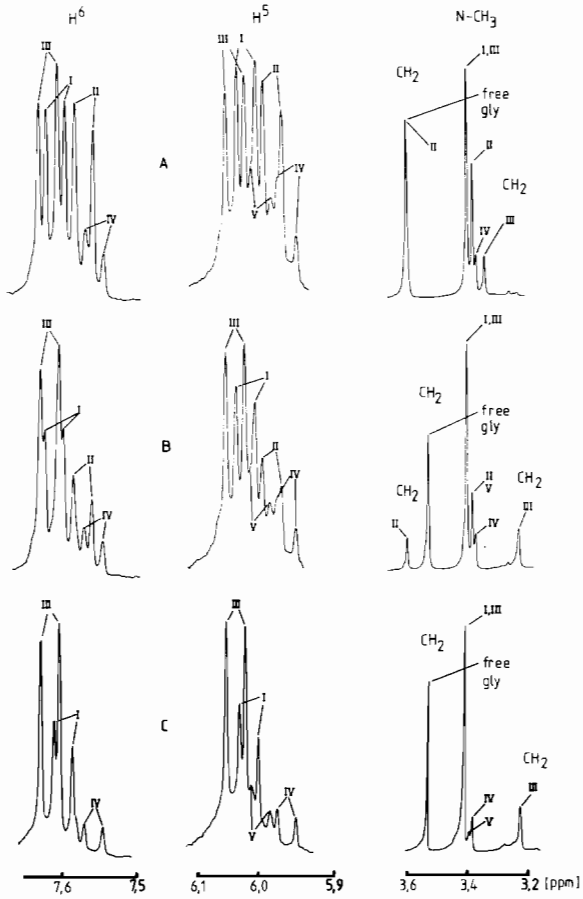

Fig. 3. Sections of ^1H NMR spectra (300 MHz, D_2O) of mixtures of *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(D_2O)]^{2+}$ and glyH (1:2): (A) pD 3.5, after 1 day at 22 °C, (B) 30 min after (A) with NaOD added to give pD 4.5, (C) 30 min after (B) with NaOD added to give pD 6.2, with the following species identified: *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(D_2O)]^{2+}$ (I), *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(glyH\text{-}O)]^{2+}$ (**2**) (II), *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(gly\text{-}N)]^{+}$ (**1a**) (III). Signals IV and V are due to yet unidentified species.

cis-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$ is a weak acid according to

$$cis\text{-}[(NH_3)_2Pt)(1\text{-}MeC)(H_2O)]^{2+} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} cis\text{-}[(NH_3)_2Pt(1\text{-}MeC)(OH)]^{+} \quad (6)$$

with a pK_a of 5.9 as deduced from NaOH titration of a freshly prepared solution of the aqua complex. Both the aqua and the hydroxo complex have been isolated and characterized by X-ray crystallography before [27]. When *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$ was treated with 0.5 eq. of NaOH, and the solution allowed to slowly evaporate, crystals of composition $[Pt_2(NH_3)_4(1\text{-}MeC)_2(OH)]X_3 \cdot aq$ (**6**) ($X = NO_3^-$ or ClO_4^-) were obtained in reasonable yield. The condensation reaction

$$2cis\text{-}[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+} + OH^- \longrightarrow 6 + 2H_2O \quad (7)$$

apparently also takes place in the absence of added OH^-, viz.

$$2cis\text{-}[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+} \longrightarrow 6 + H_3O^+ \quad (8)$$

albeit with low yield. We conclude this from the fact that on ageing, a solution of *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(H_2O)]^{2+}$ displays a slight drop in pH and a simultaneous drop in overall NaOH consumption.

The dinuclear, μ-OH bridged structure of **6** is based on the following arguments. (i) The 1-MeC resonances (H6, 7.637 ppm; H5, 6.008 ppm) in the ^1H NMR spectrum of **6** do not represent an average between the mononuclear aqua and hydroxo complexes. Distinct resonances are observed for **6** and the two species of equilibrium (6). (ii) Both 1-MeC ligands in **6** are equivalent on the NMR time scale, hence must have an identical binding pattern. (iii) The Raman spectrum of **6** (H_2O, pH 6.05) is consistent with one set of 1-MeC ligands present, with intense ring modes (1262, 794 cm^{-1}) characteristic of N3 coordination. (iv) Elemental analysis data of two different salts unambiguously show the presence of three counter ions. (v) $[Pt(dien)(H_2O)]^{2+}$, which also has a pK_a of 5.9, behaves in a similar way [28].

As previously pointed out [29], two possible arrangements (open and stacked) exist in principle for **6**. Variable temperature ^1H NMR spectra in the narrow range of 5–30 °C in D_2O were inconclusive in that they showed only a slight (0.03 ppm) upfield shift (as expected for ring stacking) with decreasing temperature. Finally, we note that in a slow reaction (days), **6** is partially converted into the dinuclear, 1-methylcytosinato bridged complex *cis*-$[(NH_3)_2Pt(1\text{-}MeC^-)_2Pt(NH_3)_2]^{2+}$ (head–tail) [20], which eventually crystallizes from solution and can be isolated in low yield. It is possible that formation of this compound in the reaction of *cis*-$[(NH_3)_2Pt(1\text{-}MeC)(D_2O)]^{2+}$ with glyH in moderately acidic medium (see above) also takes place via **6**.

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