Structural and Solution Study on Binary Peptide and Ternary Peptide–Nucleobase Complexes of Palladium(II)†

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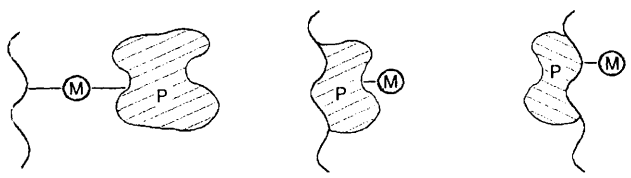
The dipeptide complex [Pd(gly-L-hisN^{α})Cl]·1.5H_2O **1** (gly-L-hisN^{α} = monoanion of glycylhistidine, deprotonated at the amide N) has been prepared and structurally characterized. Co-ordination of Pd is through the terminal amino group of the glycyl entity, N(π) of the imidazole ring of the histidine, and the deprotonated amide nitrogen. Reactions of **1** with the model nucleobases 1-methyluracil (Hmura), 1-methylcytosine (mcyt), 9-methyladenine (made), 9-ethylguanine (Hegua) and 6-methoxy-9-methylguanine (momgua) have been studied in solution by ^{1}H NMR spectroscopy. The mcyt complex, [Pd(gly-L-hisN^{α},O)(mcyt)]·3.5H_2O (gly-L-hisN^{α},O = dianion of glycylhistidine, deprotonated at the amide N and the carboxylic acid group) has been structurally characterized. Nucleobase co-ordination is *via* N^3. Proton NMR spectra of complexes of **1** with all model bases are indicative of rotamer formation and, with the purine bases, of linkage isomerism (N^7, N^1 and simultaneously with N^7/N^1). In weakly acidic, neutral or slightly alkaline media or with an excess of **1**, Hegua and, most likely, also made form complexes of Pd_3(nucleobase) stoichiometry with Pd binding through N^1 and N^7 and the third Pd linked to one of these Pd(gly-L-his) entities. As a consequence, the resonances of some of the aromatic protons of the histidine imidazole ring are shifted upfield by as much as 1 ppm. Complex stability constants have been determined by means of ^{1}H NMR spectroscopy for a number of 1:1 complexes of **1** with model nucleobases. Competition experiments carried out at pD 7.1 indicate that **1** binds to the four model nucleobases in the following preference: Hegua-N^7 ≈ mcyt-N^3 ≫ made-N^1 > made-N^7 > mura-N^3.

Binary complex formation between proteins or peptides and metal ions[1,2] as well as binary interactions between nucleic acids or nucleobases and metal ions[3] have been widely studied in recent years. Similarly, the principles of nucleic acid–protein interactions have been and still are a subject of high interest.[4] It is obvious that the biological relevance of such interactions, *e.g.* in metalloproteins, metal–DNA complexes and nucleic acid processing or packaging, provides a rationale for these studies. In contrast, the full significance of ternary interactions involving metal cations, proteins and nucleic acids simultaneously in biological processes is still vague (Fig. 1). There is, however, a growing list of examples of *direct*, metal-mediated interactions between nucleic acids (nucleobases) and proteins [Fig. 1(*a*)] as well as examples with the metal ion indirectly promoting specific nucleic acid–protein interactions [Fig. 1(*b*) and 1(*c*)]. These examples include, among others, DNA–Pt–protein cross-linking,[5] a phenomenon possibly related to the mode of action and/or toxicity of platinum antitumour drugs, the exonuclease activity of the Klenow fragment of DNA polymerase I,[6] gene regulation of metalloproteins,[7] and a range of DNA and RNA binding proteins such as zinc finger proteins,[8] various RNA polymerases,[9] gene 32 protein,[10] or damage recognition proteins.[11] The scission of DNA by bleomycin metallopeptides is also related to ternary complex formation.[12]



(*a*) (*b*) (*c*)

Fig. 1 Three principal ways of ternary metal–protein nucleic acid interactions: (*a*) metal ion (M) cross-linking protein (P) and nucleic acid; (*b*) metal ion binding to protein which in turn binds to the nucleic acid; and (*c*) metal ion binding to nucleic acid which causes binding of a protein to the nucleic acid

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1993, Issue 1, pp. xxiii–xxviii.

Rapidly growing are techniques that take advantage of nucleic acid–protein (peptide) recognition *and* the ability of a conjugated metal ion to cleave the target nucleic acid *via* metal-induced hydrolysis,[13] redox chemistry[14] or photochemistry.[15] This methodology appears to lead to highly specific metal nucleases. Binding of the active metal ion may take place in a fashion identical[16] or similar[17] to that described in this paper for Pd, which is related to the way serum albumin is believed to carry Cu^{II}.

Modelling ternary interactions at different degrees of complexity and under quite versatile aspects has been attempted in a number of cases,[18] but structural data on such complexes is still very limited.[19] As part of a study aimed at understanding the principles of ternary complex formation between metal ions, peptides and nucleobases (oligonucleotides) and possible applications, we have started to prepare simple dipeptide complexes of transition metals and derivatives of these with model nucleobases. In this paper we describe the preparation, spectroscopic properties and crystal structures of glycyl-L-histidine (gly-L-his) complexes of Pd^{II} and of ternary complexes containing model nucleobases. The binary Pd–gly-L-his complex has previously been prepared in solution[20,21] and solution studies of this compound with ATP,[21] GMP[22] and cytidine[22] have been performed.

The co-ordination properties of gly-L-his as well as related peptides containing this fragment towards transition-metal ions have been reviewed.[23] Several more recent studies[24] essentially confirm the binding patterns previously reported.

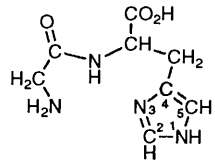
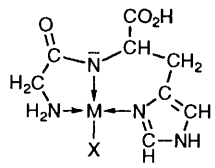
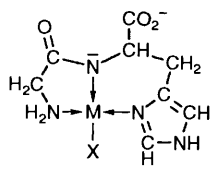
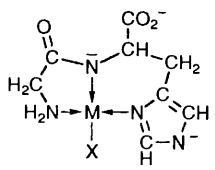
Structure	Formula	Charge of dipeptide
	gly-L-his $C_8H_{12}N_4O_3$	0
	M(gly-L-hisN$^{\alpha}$)X M($C_8H_{11}N_4O_3$)X	1–
	M(gly-L-hisN$^{\alpha}$,O)X M($C_8H_{10}N_4O_3$)X	2–
	M(gly-L-hisN$^{\alpha}$, N$^{\tau}$, O)X M($C_8H_9N_4O_3$)X	3–

Fig. 2 Schematic representations of gly-L-his (single tautomer only) and its various deprotonated, metal-complexed forms. Protonated forms of the peptide are not shown. Note that the numbering scheme of the imidazole ring of the his entity is not identical with that used in the crystal structure descriptions

Fig. 2 gives schematic views of the dipeptide and its various anionic, complexed forms relevant to this work.

Experimental

Starting Materials.—The compounds gly-L-his·HCl (Bachem), 9-ethylguanine (Hegua), (Chemogen), 6-methoxy-9-methylguanine (momgua) (Chemogen) and $K_2[PdCl_4]$ (Degussa) were used as obtained. 1-Methylcytosine (mcyt),[25] 9-methyladenine[26] (made) and 8-deuterio-9-methylalenine ([^{2}H]made)[27] were prepared as described.

Preparations.—[Pd(gly-L-hisN$^{\alpha}$)Cl]·1.5H_2O **1**. To a solution of $K_2[PdCl_4]$ (0.51 mmol) in water (40 cm^3) was added gly-L-his·HCl (0.51 mmol). After stirring the brownish reaction mixture at 22 °C for 0.5 h, the pH dropped from 3.5 to 1.5 and was kept between 1.5 and 2.5 during the next 24 h by means of 1 mol dm^{-3} KOH. The clear yellow solution was concentrated to 5 cm^3 by rotary evaporation and allowed to evaporate. After 1 d, yellow prisms of complex **1** were isolated in 64% yield and dried in air. Elemental analysis indicated partial loss of water of crystallization [Found: C, 26.9; H, 2.7; N, 15.6. Calc. for $C_8H_{12}ClN_4O_{3.5}Pd$ (hemihydrate): C, 26.5; H, 3.3; N, 15.5%].

[{Pd(gly-L-hisN$^{\alpha}$,O)}$_n$]·2.5H_2O **2**. To a solution of complex **1** (0.58 mmol) in water (20 cm^3) was added $AgNO_3$ (0.57 mmol) at room temperature, and the AgCl filtered off after 10 min. The resulting solution (pH 2.1) was brought to pH 4.3 by addition of KOH. A pale yellow precipitate formed in 81% yield (Found: C, 26.4; H, 3.8; N, 15.5. Calc. for $C_8H_{15}N_4O_{5.5}Pd$: C, 26.6; H, 4.2; N, 15.5).

[Pd(gly-L-hisN$^{\alpha}$,O)(mcyt)]·3.5H_2O **3**. Complex **1** (0.18 mmol) and mcyt (0.18 mmol) were dissolved in water (15 cm^3) and the yellow solution was brought to pH 4.5 by addition of KOH. The then colourless solution was allowed to evaporate and after several days colourless crystals separated in 80% yield and were dried in air (Found: C, 30.8; H, 4.8; N, 19.6. Calc. for $C_{13}H_{24}N_7O_{7.5}Pd$: C, 30.9; H, 4.8; N, 19.4%).

[Pd(gly-L-hisN$^{\alpha}$,O)(Hegua)]·2H_2O **4**. To a solution of complex **1** (0.20 mmol) in water (5 cm^3) was added Hegua (0.20 mmol) and the mixture stirred at 22 °C. The suspension became clear upon raising the pH to 4.6 by means of 1 mol dm^{-3} KOH. After a few minutes, a microcrystalline pale yellow product formed and was filtered off and dried in air (yield 69%). Attempts to obtain crystals suitable for X-ray diffraction by recrystallization from water or methanol failed (Found: C, 33.0; H, 4.3; N, 23.3. Calc. for $C_{15}H_{23}N_9O_6Pd$: C, 33.9; H, 4.4; N, 23.7%).

[Pd(gly-L-hisN$^{\alpha}$,O)(momgua)]·0.5momgua·4.5H_2O **5**. To a solution of complex **1** (1.11 mmol) in water (90 cm^3) was added momgua (1.11 mmol) and the pH raised to 4.5 by means of 0.1 mol dm^{-3} KOH. Slow evaporation of the solution gave yellow, well soluble crystals of **5** in 21% yield. Elemental analysis was consistent with the presence of seven molecules of water of crystallization (Found: C, 31.0; H, 5.1; N, 22.8%), but preliminary X-ray analysis showed 4.5H_2O only.

Instrumentation.—Proton NMR spectra were recorded on a Bruker AC FT spectrometer (200 MHz) in D_2O solutions containing sodium 3-trimethylsilylpropane-1-sulfonate as internal reference. For correlation spectroscopy (COSY) the Bruker microprogram COSYPDHGAU was applied. Assignment of the histidine imidazole resonances by phase-sensitive two-dimensional COSY proved difficult because cross-peaks frequently were too close to the diagonal. In a number of cases individual spin systems were identified by selective one-dimensional COSY.[28] Selectivity was achieved by off-resonance excitation applying a train of rectangular pulses, each incremented in its width and phase (phase-modulated saw-teeth pulse[29]). This particular technique is equivalent to on-resonance excitation by Gaussian pulses, but does not require a selective exciter unit. Values of pD were determined by use of a glass electrode and addition of 0.4 to the meter reading; pH* values, as used in pK_a determinations, are uncorrected. The FTIR spectra were taken with a Bruker IFS 113v spectrometer as KBr pellets.

X-Ray Crystal Structure Analysis.—Pale yellow crystals of complexes **1** and **3** were sealed in glass capillaries. Data were collected on a CAD4 Enraf-Nonius diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å). The details pertaining to data collection and refinement are listed in Table 1. The unit-cell parameters were obtained and refined by using 25 randomly selected reflections in the range θ 11–16°. Three standard reflections, measured at regular intervals, showed no systematic variation in intensity for either structure. Reflections having $I > 3\sigma(I)$ were corrected for Lorentz-polarization factors. An empirical absorption correction, based on the ψ scan, was applied to the data for **3**, but neglected for **1** because of the small crystal dimensions and μ value.

The structures were solved by conventional Patterson and Fourier methods and refined through full-matrix least-squares methods. Oxygen atoms of water molecules O(W1)–O(W3) in complex **1** were refined isotropically. Final refinements, with unit weights, led to R and R' values reported in Table 1.

In all the compounds a Fourier difference synthesis showed the presence of extra peaks attributed to oxygen atoms of water molecules. An occupancy factor of 0.5 for O(W1)–O(W3) in compound **1** and O(W4) in **3** was assigned on the basis of the respective electron-density peaks in the Fourier maps.

The contributions of hydrogen atoms were included in the final refinement at calculated positions (C–H 0.95 Å) with B = 1.3B_{eq} of the atom to which they are attached.

Neutral-atom scattering factors were taken from ref. 30. All calculations were carried out on a Micro VAX 2000 computer, with the Enraf-Nonius SDP package.[31] Final non-hydrogen positional parameters are listed in Tables 2 and 3.

Table 1 Crystallographic data and details of refinements for compounds **1** and **3**

	1	**3**
Formula	$C_8H_{11}PdClO_3N_4 \cdot 1.5H_2O$	$C_{13}H_{17}PdN_7O_4 \cdot 3.5H_2O$
M	380.07	504.78
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$ (no. 4)	$P2_1$ (no. 4)
a/Å	8.389(5)	9.206(2)
b/Å	13.934(5)	10.021(1)
c/Å	11.589(5)	10.472(3)
β/°	111.08(2)	90.62(1)
U/Å^3	1264(1)	966.1(4)
D_c/g cm^{-3}	2.00	1.74
Z	4	2
Crystal dimensions/mm	0.50 × 0.45 × 0.13	0.40 × 0.20 × 0.15
μ(Mo-Kα)/cm^{-1}	16.8	10.0
F(000)	756	514
2θ range/°	2–56	2–60
No. measured reflections	3383	3092
No. independent reflections [$I \geqslant 3\sigma(I)$]	1934	2621
No. parameters	319	261
Final R, R'	0.045, 0.049	0.032, 0.036

Table 2 Atomic positional parameters with estimated standard deviations (e.s.d.s) in parentheses for compound **1**

Atom	x	y	z
Pd	0.040 5(1)	0.250	−0.006 26(9)
Cl	−0.217 1(5)	0.173 8(4)	−0.098 2(4)
O(1)	0.370(1)	0.439 6(9)	0.223(1)
O(2)	0.300(1)	0.394 4(7)	−0.127 8(8)
O(3)	0.578(1)	0.390 0(7)	−0.032 3(9)
N(1)	−0.048(2)	0.324(1)	0.108(1)
N(2)	0.251(1)	0.320 7(8)	0.079 8(9)
N(3)	0.147(1)	0.178 0(8)	−0.107(1)
N(4)	0.188(2)	0.089(1)	−0.249(1)
C(1)	0.080(2)	0.394(1)	0.181(1)
C(2)	0.247(2)	0.385(1)	0.164(1)
C(3)	0.415(2)	0.308 4(9)	0.065(1)
C(4)	0.444(2)	0.202(1)	0.039(1)
C(5)	0.316(2)	0.163(1)	−0.076(1)
C(6)	0.343(2)	0.107(1)	−0.162(2)
C(7)	0.069(2)	0.131(1)	−0.214(1)
C(8)	0.422(2)	0.369(1)	−0.040(1)
Pd(B)	0.080 1(1)	0.140 2(1)	0.318 33(9)
Cl(B)	−0.183 1(6)	0.196 3(5)	0.306 2(4)
O(1B)	0.403(2)	−0.021 3(8)	0.215(1)
O(2B)	0.384(2)	−0.023(1)	0.517(1)
O(3B)	0.626(2)	0.047(1)	0.603(1)
N(1B)	−0.025(2)	0.051(1)	0.173(1)
N(2B)	0.293(1)	0.085 5(8)	0.312 2(9)
N(3B)	0.203(2)	0.222 4(9)	0.465(1)
N(4B)	0.266(2)	0.307(1)	0.631(1)
C(1B)	0.103(2)	0.005(1)	0.136(1)
C(2B)	0.280(2)	0.022(1)	0.225(1)
C(3B)	0.463(2)	0.105(1)	0.402(1)
C(4B)	0.490(2)	0.210(1)	0.437(1)
C(5B)	0.373(2)	0.242(1)	0.508(1)
C(6B)	0.411(3)	0.295(1)	0.612(1)
C(7B)	0.140(2)	0.263(1)	0.542(1)
C(8B)	0.489(2)	0.036(1)	0.516(2)
O(W1)*	0.122(3)	−0.149(2)	0.338(1)
O(W2)*	−0.048(4)	0.008(3)	−0.480(3)
O(W3)*	0.175(5)	−0.085(3)	0.615(3)

* Isotropically refined with occupancy factor of 0.5.

Table 3 Atomic positional parameters with e.s.d.s in parentheses for compound **3**

Atom	x	y	z
Pd	0.206 41(4)	0.250	0.340 63(3)
O(1)	0.115 0(5)	−0.042 7(5)	0.595 3(4)
O(2)	−0.091 5(5)	−0.172 9(4)	0.268 0(4)
O(3)	0.143 8(5)	−0.136 4(5)	0.284 7(5)
N(1)	0.309 2(5)	0.258 5(7)	0.514 4(4)
N(2)	0.103 5(5)	0.098 6(5)	0.423 2(4)
N(3)	0.098 0(5)	0.227 3(4)	0.175 3(4)
N(4)	0.036 6(6)	0.215 9(5)	−0.026 4(5)
C(1)	0.292 5(6)	0.130 8(6)	0.579 3(6)
C(2)	0.159 9(6)	0.054 4(6)	0.532 5(5)
C(3)	−0.021 3(6)	0.027 4(5)	0.372 0(5)
C(4)	−0.112 2(6)	0.120 4(6)	0.285 8(6)
C(5)	−0.035 2(6)	0.161 1(6)	0.167 2(6)
C(6)	−0.071 8(7)	0.154 1(7)	0.041 3(6)
C(7)	0.133 3(6)	0.257(1)	0.058 2(5)
C(8)	0.015 6(7)	−0.104 3(6)	0.303 0(5)
O(2c)	0.501 5(4)	0.248 4(8)	0.219 2(5)
N(1c)	0.542 0(5)	0.459 2(5)	0.152 7(5)
N(3c)	0.326 2(5)	0.402 2(5)	0.258 9(5)
N(4c)	0.150 0(5)	0.561 4(5)	0.292 8(5)
C(1c)	0.683 8(7)	0.419 4(8)	0.100 5(8)
C(2c)	0.458 2(6)	0.364 2(6)	0.210 6(6)
C(4c)	0.279 0(6)	0.530 3(5)	0.250 3(5)
C(5c)	0.369 5(7)	0.627 6(6)	0.191 6(6)
C(6c)	0.497 2(7)	0.588 7(6)	0.142 3(6)
O(W1)	−0.354 4(5)	−0.119 7(6)	0.122 0(5)
O(W2)	0.357 7(6)	−0.211 1(7)	0.497 7(6)
O(W3)	0.404 3(6)	−0.010 6(6)	0.233 6(8)
O(W4)*	0.398(1)	0.521 4(9)	0.554(1)

* Occupancy factor = 0.5.

Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters, and remaining bond lengths and angles.

Results and Discussion

Binary Complexes.—The complex-forming properties of the dipeptide glycyl-L-histidine (gly-L-his) with transition-metal ions has been the subject of a series of studies for more than 30 years.[20–24,32] Typically, gly-L-his acts as a tridentate ligand forming metal chelates with the amine nitrogen (N^{am}), N^{α} and N^{π} (N^3 in Fig. 2), occasionally complemented by intermolecular binding to a carboxyl oxygen O^{carb}. Crystallographically confirmed examples are those of Cu^{II},[33] Au^{III},[34] and the here described palladium compounds. An alternative tridentate chelating binding pattern *via* N^{am}, N^{α} and O^{carb} appears to be realized considerably less frequently,[35] as is a binding mode with N^{am}, O^{carb} chelation and simultaneous N^{τ} (N^1 in Fig. 2) bridging.[36] The use of N^{am}, N^{α}, N^{τ} and N^{π} in a cyclic, tetranuclear complex as postulated before[20,37] has recently been confirmed by us using X-ray crystallography.[34]

The palladium(II) complex **1** has previously been reported,[20–22] although not isolated. It forms in a rather acidic

medium (pH < 2), meaning that the pK_a of the peptide amide NH [38] is lowered upon metal co-ordination by more than 12 log units. The reaction leading to formation of **1** has to be carried out at low pH in order to avoid formation of secondary products at higher pH.

After removal of the co-ordinated chloro ligand of complex **1** by means of $AgNO_3$, a poorly soluble product **2** of composition [Pd(gly-L-hisN$^{\alpha}$,O)]·2.5H_2O forms, even in moderately acidic solution (pD ≥ 3). Changes in the IR spectra when going from **1** to **2**, *e.g.* loss of ν(C=O) at 1710 cm^{-1} (**1**) or of ν(OH) at 3500 cm^{-1} (**1**), point toward deprotonation of the histidine CO_2H entity rather than of the still available second imidazole ring position. A polymeric arrangement with a carboxylate oxygen being the fourth ligand of Pd is feasible on the basis of model building.

^1H *NMR Spectra of* gly-L-his *and of Complex* **1**.—The ^1H NMR spectra of both the dipeptide and its palladium complex **1** have been reported, as has the distribution of the rotamer population.[21] pD-Dependent spectra were used to determine pK_a values. These are for deprotonation of the free peptide: 2.6 for CO_2H, 7.1 for the imidazolium ring, and 8.1 for the terminal NH_3^+ group, in fair agreement with published data.[24a] Neither deprotonation of the imidazole ring (estimated 14–15) [39] nor of the peptide NH (estimated 14–17 [23]) was observed.

pD-Dependent spectra (pD 2–6.5, NaCl added, shifts of his CH and CH_2 resonances) of complex **1** gave a $pK_a \approx 4.0$ for deprotonation of the CO_2H group, which means that deprotonation of the amide group and subsequent co-ordination of Pd^{II} effectively increase the basicity of the carboxylate group by a factor of 10–20. Deprotonation of the imidazole ring (N^{τ}) in **1**, which occurs with $pK_a \approx 9.6$,[20] was not detected by ^1H NMR spectroscopy due to severe complication of spectra recorded at strongly alkaline pH.

Even in moderately acidic solution (pD ≥ 2.5) the formation of novel, unidentified species was observed, with at least five aromatic his protons in the range δ 6.5–7.5. The intensities of these resonances was higher with the aqua species, which was prepared from complex **1** upon addition of $AgNO_3$.

Although aware of the possibility that in addition to the postulated polymeric compound **2** and the cyclic, tetranuclear complex, a μ-hydroxo species might exist in solution [equation (1)] (in equilibrium with the corresponding gly-L-hisN$^{\alpha}$,O

$$2[Pd(\text{gly-L-his}N^{\alpha})(H_2O)]^+ \longrightarrow [(\text{gly-L-his}N^{\alpha})Pd(OH)Pd(\text{gly-L-his}N^{\alpha})]^+ + H_3O^+ \quad (1)$$

forms), we have not been able to demonstrate its existence. From comparison with $[Pd(dien)(H_2O)]^{2+}$ (dien = diethylenetriamine), for which a pK_a of 7.74 has been determined,[40] it appears likely that the pK_a of an aqua ligand in [Pd(gly-L-hisN$^{\alpha}$)$(H_2O)]^+$ or [Pd(gly-LhisN$^{\alpha}$,O)(H_2O)] is >7.7, hence its formation in moderately acidic solution is not significant.

Solution Studies of Ternary Complexes.—Both model building and the results of crystal structure determination of complex **3** suggest a few features relevant to *all ternary* gly-L-his, nucleobase complexes. First, the imidazole ring of histidine and in particular the H^2 proton prevent any rapid rotation of the nucleobase about the Pd–N(nucleobase) bond. Therefore, rotamers, whether formed through real rotation or *via* a dissociative process, are expected to be present in solution. Secondly, the H^2 proton of the imidazole ring of histidine is always above the nucleobase π system and therefore is expected to undergo a substantial upfield shift in the ^1H NMR spectrum. This effect has previously been reported by Kozlowski and co-workers.[22]

(*i*) 1-*Methylcytosine compound.* The complex [Pd(gly-L-hisN$^{\alpha}$,O)(mcyt)]·3.5H_2O **3** forms in weakly acidic solution. At ambient temperature, both H^5 and H^6 doublets of the mcyt ligand (H^5 more pronounced than H^6) are split in the ^1H NMR spectrum (60:40), indicating the presence of two rotamers and hence hindered rotation about the Pd–N^3 cytosine bond. Heating to 362 K causes the two sets of resonances to collapse due to fast nucleobase rotation. The resonances of both aromatic protons of the imidazole ring of histidine are likewise doubled (for H^2 more pronounced than for H^5) at ambient temperature and his H^2 has undergone a 0.6 ppm upfield shift as compared to complex **1**.

(*ii*) 1-*Methyluracil compound.* The reaction of complex **1** with 1-methyluracil (Hmura) is pH dependent. In the absence of any other nucleobase, marked reaction occurs even in a weakly acidic medium (pH 6) which is well below the pK_a of Hmura (≈9.7). The ^1H NMR spectrum of the anionic complex [Pd(gly-L-hisN$^{\alpha}$,O)(mura)]$^-$ is consistent with the presence of two rotamers at ambient temperatures (55:45). The H^5 resonances of Hmura and H^2 resonances of his are particularly well separated for the two rotamers.

(*iii*) *Guanine compounds.* The complex [Pd(gly-L-hisN$^{\alpha}$,O)(Hegua)]·2H_2O **4** forms under conditions comparable to those of **3**. In contrast to **3**, the ^1H NMR spectrum at ambient temperature displays a single, sharp guanine H^8 resonance. This could either be a consequence of fast rotation about the Pd–N bond or no rotation at all. Co-ordination at N^7 is inferred from the chemical shift of the guanine H^8 (δ 8.27); for N^1 binding the resonance should be considerably more upfield.[41] Formation of an intramolecular hydrogen bond between O^6 of guanine and NH_2 of the glycyl residue, which is possible only for one rotamer, could account for no rotation. The ring-current effect of Hegua in **4** is big enough to shift the resonance of H^2 of the imidazole ring upfield to collapse with H^5 (δ 6.97). The two resonances are separated (δ 7.05, 7.03) only in a more acidic medium (pD 2.9). In the case of the analogous guanosine and 5′-GMP compounds, which were not isolated but studied in solution only, the separation between the H^2 and H^5 resonances of the imidazole entity of histidine was somewhat more pronounced, 0.09 and 0.05 ppm, respectively (pD 4–5), but still considerably smaller than with the mcyt complex **3**.

When the pD is raised above 5 the ^1H NMR spectrum of complex **4** (or a 1:1 mixture of **1** and Hegua, pD 2–3) becomes more complicated (Fig. 3). As far as the aromatic guanine and histidyl protons are concerned, seven new guanine H^8 signals and at least 14 new doublets due to histidine protons are observed. Except for the original H^8 guanine resonance of **4**, which starts moving upfield above pH* 7.5 as a consequence of deprotonation at guanine N^1, none of the new guanine H^8 resonances displays any notable pH dependence in the range 5 ≤ pH* ≤ 9. The assignment of the guanine H^8 resonances, as used in Fig. 3, is on the basis of spectra recorded at different pD values of mixtures of **1** and Hegua at 1:1, 2:1 and 3:1 ratios, *r*. At *r* = 1:1, free Hegua is formed from **4** at higher pD (≥5), as identified by its chemical shift. Of the six remaining H^8 resonances, two (δ 7.77 and 7.71) are due to two rotamers of the N^1 linkage isomer Pd(Hegua-N^1). As expected, the H^8 resonances of this species occur furthest upfield and increase in intensity with pD. Two other resonances, at δ 8.17 and 8.10, which have similar linewidths to those of Pt(Hegua-N^1), are due to two rotamers of the dinuclear Pd_2(egua-N^1,N^7) species (no or fast rotation about Pd–N^7, slow rotation about Pd–N^1). The positions of these two signals between those of Pd(Hegua-N^7) **4** and Pd(egua-N^1) are in agreement with expectations.[41] The two remaining H^8 resonances at δ 8.37 and 7.93 are assigned to two rotamers of a Pd_3(egua) species since they represent *the* predominant guanine resonances (>80% of total H^8 intensity) at Pd: Hegua = 3:1, pD 7, even though there is hardly any free palladium dipeptide **1** detectable in solution. Thus in neutral or weakly alkaline solution, **4** rearranges according to equation (2).

$$\underset{\mathbf{4}}{Pd(\text{Hegua-}N^7)} \longrightarrow \left\{ \begin{array}{l} Pd_2(\text{egua-}N^1,N^7) + H^+ \\ Pd(\text{egua-}N^1) + H^+ \\ Pd_3(\text{egua}) + H^+ \\ \text{Hegua} \end{array} \right\} \quad (2)$$

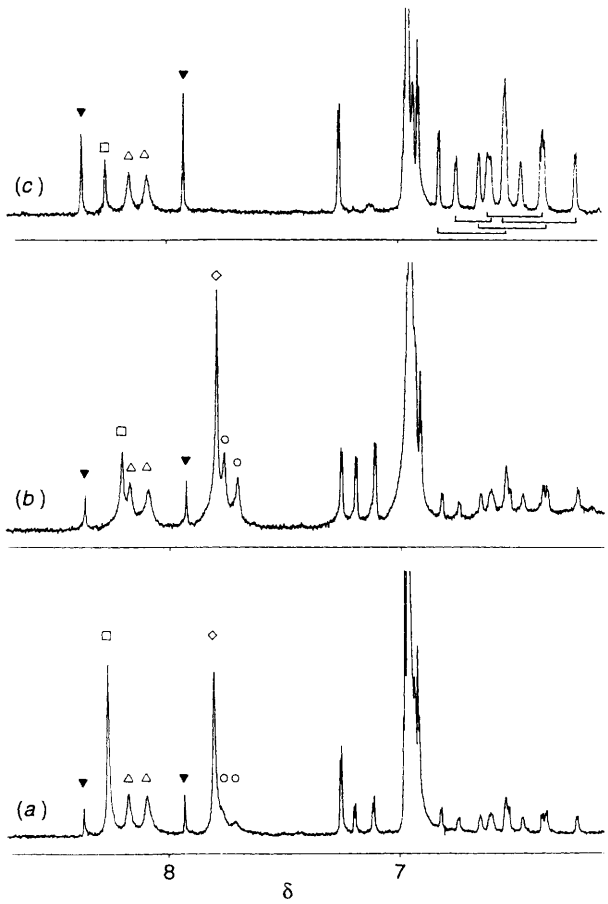


Fig. 3 9-Ethylguanine H^8 (δ 7.7–8.4) and histidine H^2,H^5 resonances (δ 6.2–7.3) of complex **1** and Hegua (*a*) 1:1, c = 0.025 mol dm^{-3} each, D_2O, pH* 7.6; (*b*) 1:1, c = 0.025 mol dm^{-3} each, D_2O, pH* 8.7, and (*c*) 2:1, c_{Pd} = 0.05 mol dm^{-3}, D_2O, pH* 7.7. With **1**:Hegua = 3:1 (not shown), resonances due to Pd_3(egua) predominate. Of the aromatic his resonances, those between δ 6.2 and *ca.* 6.9 are due to Pd_3(equa). Ten of the 11 aromatic his resonances have been correlated using one-dimensional COSY (*c*). The H(8) resonances are marked as follows: (◇) Hegua/egua; (□) Pd(Hegua-N^7)/Pd(egua-N^7); (○) Pd(egua-N^1); (△) Pd_2(egua-N^1,N^7); (▼) Pd_3(egua)

Both Pd_2 and Pd_3 species are also formed from complex **4** by addition of extra Pd in a weakly acidic, neutral, or basic medium. It is not possible, at present, unequivocally to propose a structure for Pd_3(egua). Two possibilities can be foreseen. (*a*) Formation of Pd_3(egua-N^1,N^7,X), with X possibly being N^3, as in the $(NH_3)_3Pt^{II}$–egua system.[42] Unambiguous proof, a considerable downfield shift of the CH_2 of the ethyl group upon metal binding at N^3,[42] was not achieved, possibly because of superposition by the solvent peak at δ 4.9 (*cf.* CH_2 peak in $[\{Pt(NH_3)_3\}_3$(egua-N^1,N^3,N^7)]$^{5+}$ at δ 5.7, however). (*b*) Alternatively, rearrangement of palladium entities or addition of Pd could lead to a situation in which a palladium entity adds to an *already bound* Pd(gly-his) *via* a deprotonated donor site, *e.g.* O of the carboxylate or even the histidine N^τ site (with H^+ moving to CO_2^- then). This would imply that even at pH ≈ 7 the glycylhistidine moiety of Pd(gly-L-his) bound to guanine competes with guanine binding sites for Pd. We tentatively favour possibility (*b*). In Fig. 4 schematic representations of possible Pd_3(egua) species are given.

Correlating guanine H^8 and histidine imidazole resonances, the latter can be categorized as follows: Pd(Hegua-N^7), δ *ca.* 6.9–7.0; Pd(egua-N^1), 7.1–7.2 and *ca.* 6.9–7.0; Pd_2(egua-N^1,N^7), 7.26 and *ca.* 6.9–7.0; Pd_3(egua), 6.24–*ca.* 6.9. As to aromatic histidyl resonances of Pd_3(egua), 11 doublets are differentiated. Of these, 10 sets can be correlated applying selective one-dimensional COSY (Fig. 3). If one assumes co-ordination of Pd

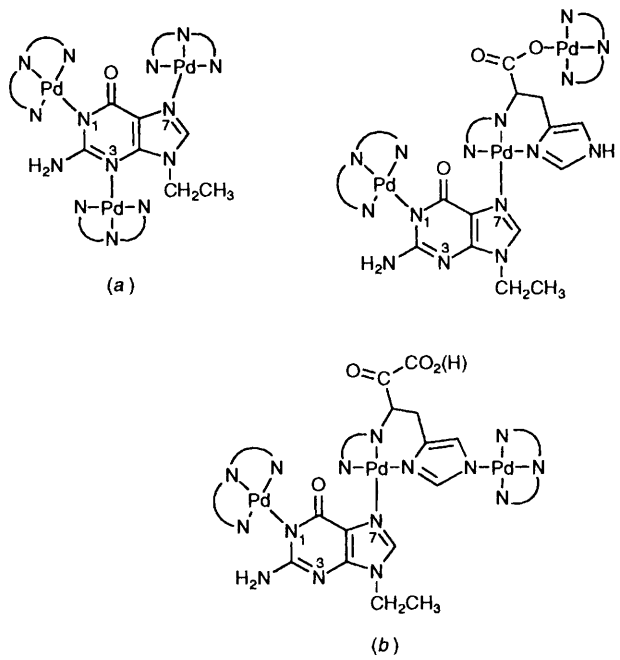


Fig. 4 Possible structures for Pd_3(equa) species: (*a*) binding of palladium dipeptide *via* N^1,N^3,N^7; (*b*) third Pd binding to an already co-ordinated Pd *via* histidyl carboxylate (top) or imidazole N (bottom). Only binding of third Pd to N^7-bound palladium entity is shown; alternatively, the third Pd might add to the N^1-bound entity

to three different donor sites of guanine, (*a*), or alternatively an arrangement as in (*b*) (Fig. 4), and allows for slow rotation about *one* Pd–N bond only (*e.g.* N^1), 2 × 2 × 3 = 12 doublets are expected. It is our hope eventually to isolate and characterize structurally the Pd_3(egua) compound.

Reaction with 6-methoxy-9-methylguanine (momgua) was carried out in an attempt to obtain a crystalline guanine derivative of complex **1**. The ^1H NMR spectrum of the crystalline products was consistent with the presence of co-ordinated *and* free momgua (*e.g.* H^8 of free ligand at δ 8.31, of compound δ 8.63; pD 3.0). The resonances of H^2 and H^5 of the imidazole ring are separated by 0.1 ppm (δ 7.06 and 6.96). X-Ray crystallography of **5** (preliminary results due to poor crystal quality not given) confirms ^1H NMR and elemental analysis data. Free guanine molecules (with half occupancy, oriented parallel to the crystallographic *b* axis) stack with co-ordinated guanines at a mean distance of 3.5 Å.

(*iv*) *9-Methyladenine (made) compounds.* By far the most complicated ^1H NMR spectra of mixtures of complex **1** with a single nucleobase were obtained with made. In 1:1 mixtures, usually 17–18 adenine resonances (H^2 and H^8) were observed in the range δ 8–9 at moderately acidic pH. A representative example is given in Fig. 5. Applying 8-deuterio-9-methylalenine in all parallel experiments, the H^2 and H^8 adenine resonances are readily distinguished. In addition, variation of the Pd:made ratio allows an identification of 1:1 and 2:1 complexes, and the pH* dependence of the chemical shifts of all resonances (Fig. 6) permits the assignment of the adenine binding sites, taking into account characteristic pK_a values of platinum(II) complexes of made.[43,44] Eighteen adenine H^2 and H^8 resonances are assigned to the following nine species: free 9-methyladenine ($Hmade^+$), two rotamers of the N^1 linkage isomer, two rotamers of the N^7 linkage isomer, and four rotamers due to the dinuclear μ-made species. Relative intensities of the aromatic adenine protons indicate that the two rotamers of the N^7 linkage isomer occur in a 1:1 ratio, while for the N^1 linkage isomers one of the two rotamers is favoured by *ca.* 2:1 over the other. Protonation of Pd(made-N^7) takes place with a pK_a ≈ 2.05 and that of Pd(made-N^1) is estimated to be

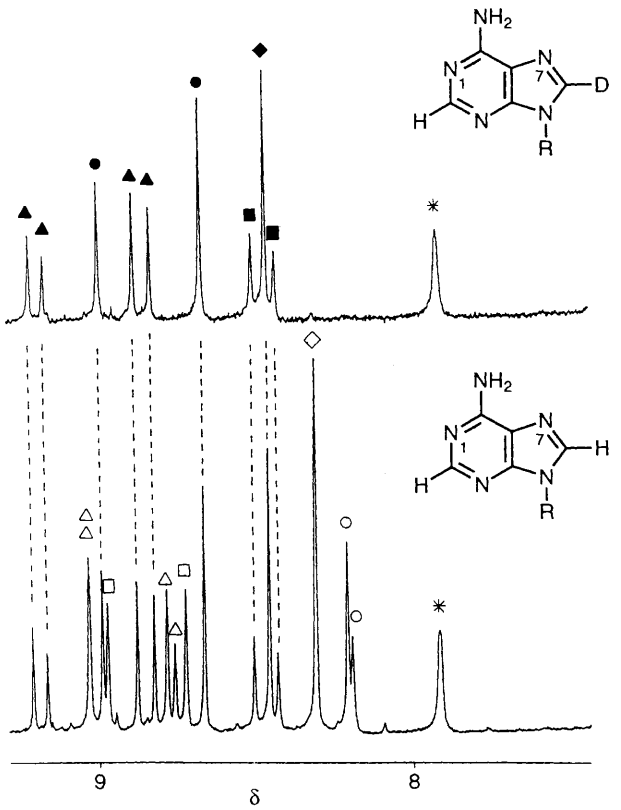


Fig. 5 Proton NMR spectra (D_2O, pH* 2.2, 0.05 mol dm^{-3} each, δ range 7.5–9.5) of a 1 : 1 mixture of complex **1** with [^{2}H]made (top) and with made (bottom). Adenine resonances of the upper spectrum are due to H^2 protons only; the lower spectrum contains both H^2 and H^8 resonances. Assignment of resonances is on the basis of their pH* dependence (*cf.* Fig. 6). Resonances are assigned as follows: made/Hmade$^+$, (◇) H^8, (◆) H^2, Pd(made-N^1), (○) H^8, (●) H^2; Pd(made-N^7), (□) H^8, (■) H^2; Pd_2(made-N^1,N^7), (△) H^8, (▲) H^2. The resonance with an asterisk is due to H^2 (imidazole) of **1**

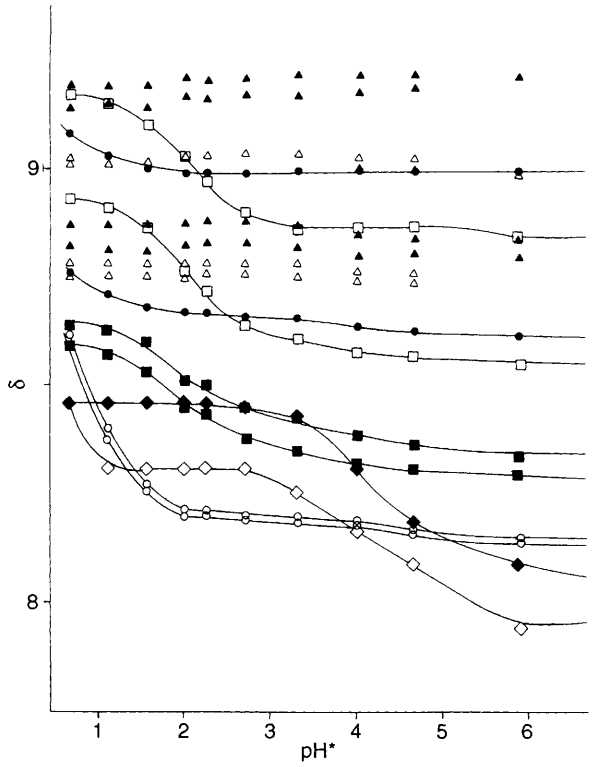


Fig. 6 The pH* (uncorrected) dependence of adenine resonances in the system complex **1** + made (1 : 1). Symbols used to assign individual resonances are as in Fig. 5. Signals due to the unidentified species X [Pd_3(made)?, *cf.* text] are not included

$pK_a \leqslant 1$. For some of the species, an additional slight pH dependence of adenine resonances is seen around pH 4, which probably reflects protonation/deprotonation of the histidine carboxylate entity. On the basis of signal intensities, the species distribution in a strongly to moderately acidic medium (pD 1–4) is Pd(made-N^1) ≈ Pd_2(made-N^1,N^7) > made/Hmade$^+$ > Pd(made-N^7). In a weakly acidic medium (pD 5–6) the amount of the μ-made species decreases at the expense of a new species X with relative proportions being Pd(made-N^1) > made > Pd(made-N^7) > Pd_2(made-N^1,N^7) > X. Signals due to X increase with pH and/or by increasing relative palladium concentration. With Pd : made = 2 : 1, pH ≈ 6.6, at least four adenine resonances at δ 9.21 and 8.67 (H^2) as well as 8.98 and 8.69 (H^8) can be assigned to this species which then represent the most intense made signals.

Since this spectral change is accompanied by the appearance of a large number of new histidyl doublets in the δ range 6–7 (one occurs as high as δ 6.00!), we propose that X is the analogue of the Pd_3 species in the 9-ethylguanine system discussed above. It is consistent with this view that in a 1 : 1 mixture of complex **1** and made, free **1** starts disappearing at pH* > 4, even though formation of Pd_2(made-N^1,N^7) decreases while free made is still available. Thus, as in the guanine system, Pd(gly-L-his), self-condensation favourably competes with Pd(gly-L-his) binding to the nucleobase made under the conditions of our experiment.

As far as the aromatic histidine resonances in the **1**–made system are concerned (Fig. 7), one- and two-dimensional COSY spectra permit identification of a number of pairs of imidazole protons.

(*v*) *Stability constants.* Stability constants were estimated in acidic solution (pD 1–3) applying ^{1}H NMR spectroscopy for the reactions (3) and (4) with L = mcyt, Hegua and L′ =

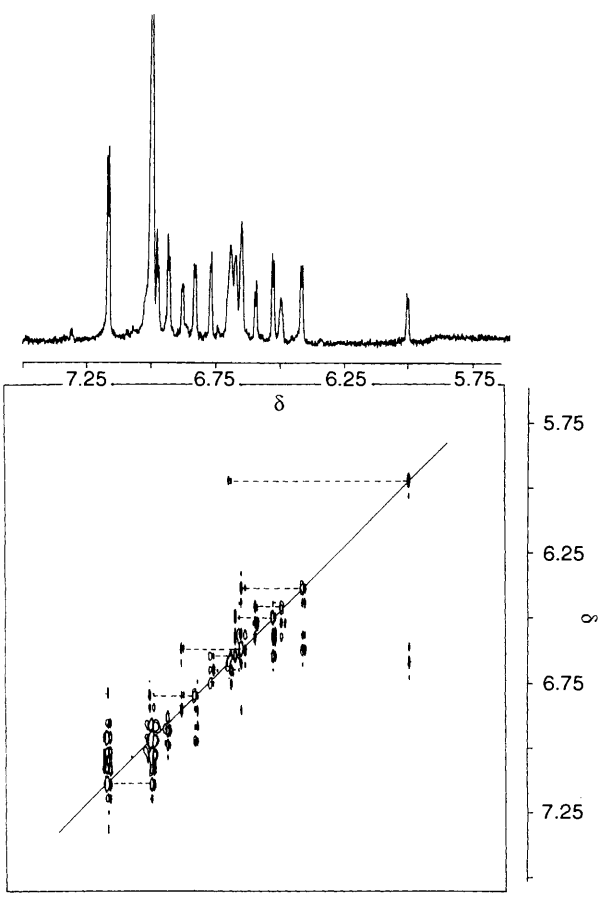


Fig. 7 One- (top) and two-dimensional COSY spectra (bottom) of imidazole histidine ^{1}H resonances of a 1 : 1 mixture of complex **1** and made (pD 7.8, 0.05 mol dm^{-3} each). Most of the doublets in the δ range 6–7, grow in with increasing pH and/or an excess of **1** and are assigned to species X. Several sets of aromatic histidine protons can be identified

$$[Pd(gly\text{-}L\text{-}hisN^{\alpha})Cl] + L \rightleftharpoons [Pd(gly\text{-}L\text{-}hisN^{\alpha})L]^{+} + Cl^{-} \quad (3)$$

$$[Pd(gly\text{-}L\text{-}hisN^{\alpha})Cl] + HL' \rightleftharpoons [Pd(gly\text{-}L\text{-}hisN^{\alpha})(L')] + H^{+} + Cl^{-} \quad (4)$$

Hmura. Standardized stability values[45] were calculated from relative intensities of co-ordinated and free nucleobases at a given (acidic) pH and converted into stability constants, taking into account the hydrogen-ion affinities (pK_a values) of the nucleobases (pK_a Hmcyt$^+$, 4.9; Hmura, 9.7; Hegua$^+$, 3.2). The log K values, which are, 6.9, 4.8 and 4.3 for mura-N^3, egua-N^7 and mcyt-N^3 compounds, respectively, follow the order of complexes of (dien)Pd^{II} with nucleosides established by Martin,[40,46] but are clearly lower. Both the lower positive charge of Pd^{II}(gly-L-hisN$^{\alpha}$) as compared to Pd^{II}dien, the presence of Cl$^-$, and/or steric aspects may account for the decrease in complex stability in our system.

(*vi*) *Competition experiments.* Preliminary competition experiments were carried out by mixing complex **1** with equimolar concentrations of two, three, or four nucleobases and followed by ^{1}H NMR spectroscopy. As expected, the species distribution is pD dependent. A typical example with c = 0.0245 mol dm^{-3} for **1** and the four model nucleobases mcyt, made, Hmura and Hegua at pD 7.1 is shown in Fig. 8. Under these conditions, pronounced binding of Pd takes place at guanine N^7 and cytosine N^3 only, with some minor binding also occurring at adenine N^1 and N^7: Hegua-N^7 ≈ mcyt-N^3 ≫ made-N^1 > made-N^7 > mura-N^3. Binding to mura-N^3 is not detectable yet, but becomes increasingly important as the pD is increased above 7.4. Binding to egua-N^1, which is expected to take place under these conditions as well, is not unambiguously detectable due to overlap with H^6 resonances of the Pd(mcyt) rotamers.

In conclusion, the stability order of complex **1** towards the four model nucleobases used in this study at pD 7.1 is different from that of (dien)Pd^{II} towards the corresponding nucleosides

Table 4 Selected co-ordination bond lengths (Å) and angles (°) and relevant geometric parameters for compounds **1** and **3**

	1 (X = Cl)		
	molecule A	molecule B	**3** [X = N(3c)]
Pd–N(1)	2.02(1)	2.02(1)	2.044(4)
Pd–N(2)	1.951(9)	1.96(1)	1.991(5)
Pd–N(3)	1.98(1)	2.00(1)	2.002(4)
Pd–X	2.297(4)	2.298(5)	2.072(5)
N(1)–Pd–N(2)	83.5(5)	82.0(5)	82.1(2)
N(1)–Pd–N(3)	175.2(4)	175.0(5)	175.2(2)
N(1)–Pd–X	91.9(4)	92.1(4)	95.4(2)
N(2)–Pd–N(3)	92.4(5)	93.1(5)	93.1(2)
N(2)–Pd–X	175.3(4)	174.0(3)	176.2(2)
N(3)–Pd–X	92.3(3)	92.8(4)	89.4(2)
Deviations[a]/Å	±0.02(1)	±0.02(1)	±0.019(6)
Pd[b]	0.019(1)	0.001(1)	0.032(1)
α[c]	—	—	83.1(1)
β[d]	21.8(9)	17.(1)	22.5(5)

[a] Of co-ordination donors from their mean plane. [b] Deviation from mean plane of donor atoms. [c] Dihedral angle (°) between palladium co-ordination and nucleobase mean planes. [d] Dihedral angle (°) between palladium co-ordination and imidazole mean planes.

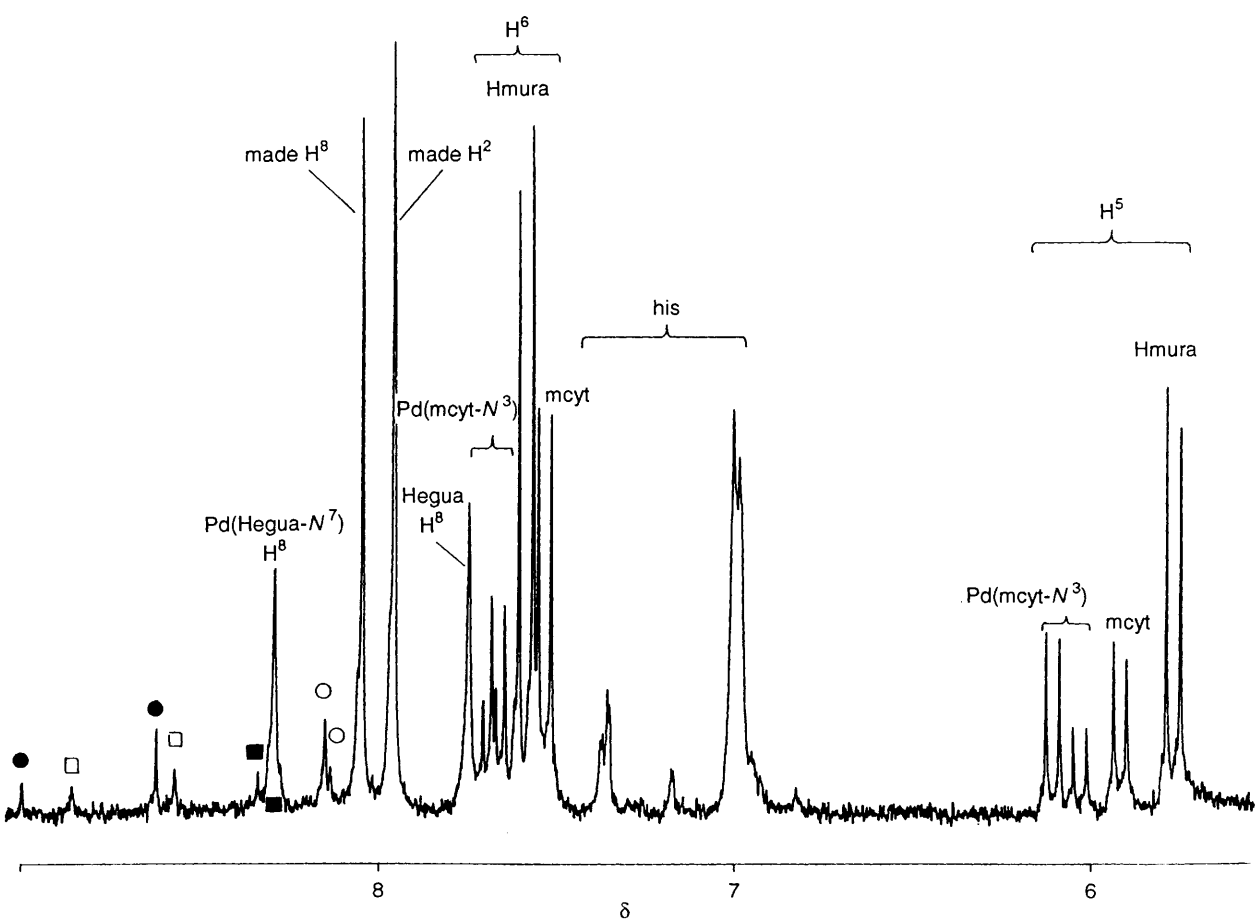


Fig. 8 Proton NMR spectrum (D_2O, pD 7.1, aromatic protons only) of a 1 : 1 : 1 : 1 : 1 mixture of complex **1**, Hegua, made, Hmura and mcyt. The assignment of resonances is made from comparison of 1 : 1 mixtures of **1** and the respective nucleobase made. Resonances of palladium complexes are assigned as follows: Pd(made-N^1), (○) H^8, (●) H^2; Pd(made-N^7), (□) H^8, (■) H^2. Individual his resonances are not assigned

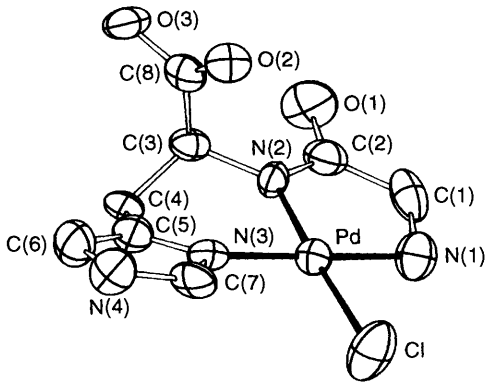


Fig. 9 An ORTEP drawing and atom numbering scheme of molecule A of complex **1** (50% probability thermal ellipsoids). The same scheme applies also to molecule B

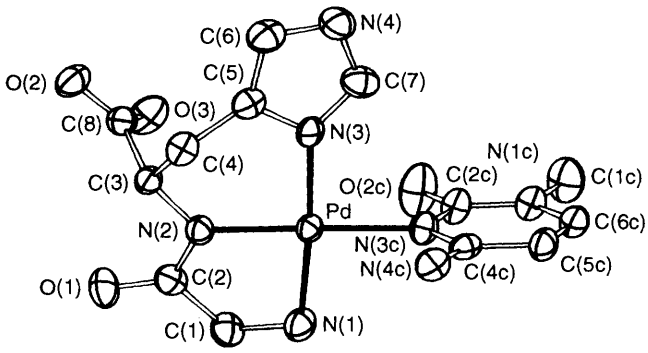


Fig. 10 An ORTEP drawing and atom numbering scheme of complex **3** (50% probability thermal ellipsoids)

and nucleotides[40] in that N^3 binding of **1** to mcyt is not disfavoured to the same extent as to Hegua-N^7 and mura-N^3. Additional work is planned further to substantiate these data.

Crystal Structures.—The ORTEP[47] plots, with the non-hydrogen atom numbering, of complexes **1** and **3** are depicted in Figs. 9 and 10. Of the two crystallographically independent molecules in **1**, A and B, only the former is shown in Fig. 9. Relevant geometrical parameters are given in Table 4.

The gly-L-his acts as tridentate ligand, co-ordinating Pd through the amino group [N(1)], the deprotonated peptide [N(2)], and the N(3) site of the imidazole ring in both complexes. The fourth co-ordination position is occupied by Cl^- in **1**, and by mcyt in **3**. The co-ordination of Pd is almost planar in all the three complexes (Table 4). The mean plane of the nucleobase makes a dihedral angle, α, with the palladium co-ordination plane of 83.1° in **3**.

To our knowledge, these are the first palladium complexes with gly-L-his so far structurally characterized. The way of chelation of the dipeptide is very similar to that recently reported in $[Au^{III}(gly\text{-}L\text{-}hisN^{\alpha},O)Cl]^{+}$ [34] as well as in copper(II) analogues.[23] The first example of a palladium(II) dipeptide complex investigated by X-ray crystallography, (cytidine)(glycyl-L-tyrosinato)palladium(II), was reported some years ago.[19f] In this complex, the dipeptide co-ordinates Pd through the amino group, the deprotonated peptide N and the oxygen of the tyrosine carboxylic group. Three-co-ordination through two N and one O atom donors (ON_2 chelation), already reported for $[Sn^{IV}(gly\text{-}L\text{-}hisN^{\alpha},O)Et_2]$,[35] is the only one possible for the glycyl-L-tyrosinate anion. On the contrary, for gly-L-his it represents an alternative way to the N_3 chelation found in the present compounds. It is to be noted that the Pd–N(cytidine) distance of 2.087(7) Å is very similar to that of 2.072(5) Å found in **3**.

The main geometrical difference between the N_3 and ON_2 chelations is that the latter implies the formation of two five-membered rings involving Pd, the former one six- and one five-membered ring. Since the five-membered ring closure demands angles at Pd significantly less than 90° (Table 4), the palladium co-ordination geometry for N_3 chelation requires less-strained angles than those of ON_2. This suggests for Pd a preferential chelation of type N_3.

In complex **3** the Pd–N(3c)–C(2c) and Pd–N(3c)–C(4c) angles are significantly different being 115.1(4) and 123.5(4)°, respectively, whereas C(2c)–N(3c)–C(4c) is 121.4(5)°. The trend of these values is similar to that found in other mcyt complexes.[19g]

The molecules of complex **1** are bound in the crystal through hydrogen bonds, between O(1) (molecule A) and H–O(3B) at $1 - x, \frac{1}{2} + y, 1 - z$ [2.51(1) Å] and between O(3)–H (A) and O(1B) at $1 - x, \frac{1}{2} + y, -z$ [2.49(1) Å], forming chains of alternated molecules A and B along the *c* axis. Other contacts, involving carboxyl and imino groups of A and B molecules and the disordered water molecules, are detected, the shortest being O(2B)···O(W3) [2.56(3) Å]. Crystals of **3** are built up of discrete complex and water molecules of crystallization. The shortest contact of 2.816(7) Å involves O(2) and N(4) of the unit at $-x, y - \frac{1}{2}, -z + 1$. Relatively short contacts are formed by the N(1) amino group, O(2c) and the carboxyl O atoms with water molecules [2.75(1)–2.898(7) Å].

Acknowledgements

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