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# Ternary palladium(II)–glycylmethionine-nucleobase complexes: solution studies and crystal structure of the 9-methylguanine compound

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Ternary complex formation between model nucleobases and [Pd(gly-L-met)] **1** (gly-L-met = dianion of glycylmethionine, deprotonated at the amide N and at the met carboxylate terminus) has been studied by $^1$H NMR spectroscopy and potentiometry. A representative example, [Pd(gly-L-metH)(Hmgua)]$NO_3$·$H_2O$ **3** (Hmgua = 9-methylguanine), has been characterized by X-ray crystallography. Co-ordination of Pd is through the terminal amino group of the glycyl entity, the deprotonated amide nitrogen, S of the methionine, and $N^7$ of the purine nucleobase. The carboxylic acid group of methionine is protonated. In aqueous solution binding of Pd to other nucleobases occurs *via* $N^3$ in the case of 1-methylcytosine (Hmcyt) and of deprotonated 1-methyluracil, $N^7$ of 9-ethylguanine (Hegua) or $N^1$, $N^7$/$N^1$ of the guanine anion (egua). Discrete rotamers form on binding of Pd to $N^3$ of the pyrimidine nucleobases and to $N^1$ of the guanine. The gly-L-metH resonances provide no evidence for the existence of stable diastereomers, suggesting that inversion at the chiral S atom of met is fast. In contrast, both [Pt(gly-L-metH)Cl] and its ternary derivative with Hmcyt appear to be present in solution as diastereomeric mixtures. Stability constants have been determined for ternary complexes formed from **1** and [Pd(gly-L-metH)Cl], respectively, with nucleobases.

Complexes between metal ions and two different types of bioligands, namely nucleobases [or (oligo)nucleotides] and amino acids (or peptides) may be considered as models for ternary interactions in which a metal entity (M) cross-links a protein (P) and a nucleic acid [Fig. 1(*a*)]. Alternative ternary interactions include M binding to a protein, which subsequently associates with a nucleic acid [Fig. 1(*b*)], or initial binding of M to a nucleic acid which then causes a protein to bind to the metallated nucleic acid [Fig. 1(*c*]. Biologically relevant examples for all three cases are known.[1–3] Artificial chemical DNA nucleases frequently are based on metal–protein conjugates,[4] thereby representing an application of ternary complex formation in molecular biology.

Ternary complexes consisting of a metal ion, an amino acid[5,6] (or peptide[7,8]), and a nucleobase can be considered simple models for a type (*a*) interactions. The model character is, however, limited due to the fact that the observed binding patterns are relevant only to those ternary interactions that feasibly occur with nitrogen or oxygen termini of proteins, metal ions and nucleic acids, whereas most natural metal-protein complexes involve amino acid side-chain donor atoms. Dinuclear ($Pt^{II}Pd^{II}$,[9] $Pt^{III}Pt^{III}$[10]) compounds containing bridging nucleobases and amino acids or peptides are special cases of ternary complexes. Though potentially useful as heavy-metal stains in protein crystallography, these compounds are unlikely to be of biorelevance.

In continuation of our previous work on model nucleobase complexes of Pd(gly-L-his),[7e] we herewith report on glycyl-L-methionine complexes of $Pd^{II}$ with model nucleobases and make some comparison with the corresponding platinum(II) analogues. The glycyl-L-methionine dipeptide offers two tridentate metal binding patterns, involving either the amino terminus of glycine, the deprotonated amide nitrogen and the carboxylate oxygen of the methionine (N,N,O,), or the first two donor sites and the thioether sulfur instead of the carboxylate oxygen (N,N,S). Copper(II) utilizes the N,N,O donor set,[11] as do $Ge^{IV}(CH_3)_2$ and $Sn^{IV}(CH_3)_2$,[12] but $Pt^{II}$ in [Pt(gly-L-metH)Cl]·$H_2O$[13] and $Pd^{II}$ in [Pd(gly-DL-metH)Cl]·$H_2O$[14] are N,N,S co-ordinated (with gly-L-metH being the monoanion).

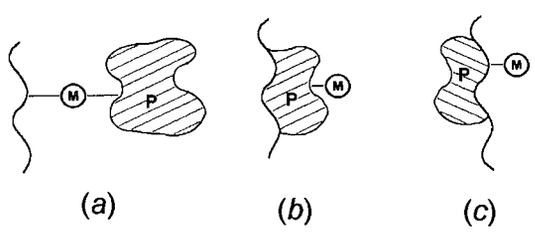


**Fig. 1** Three principal ways of ternary metal–protein–nucleic acid interactions

Interest in the co-ordination chemistry of methionine and its derivatives with $Pt^{II}$ stems, among others, from the usefulness of $[PtCl_4]^{2-}$ as a heavy-metal label for exposed methionines in proteins,[15] its possible involvement in nephrotoxicity during Cisplatin, *cis*-[$Pt(NH_3)_2Cl_2$], cancer chemotherapy,[16] and findings that $Pt(L\text{-met})_2$ is a metabolite of Cisplatin.[17] Methionine and likewise the dipeptide glycylmethionine possess two chiral centres, $C_\alpha$ and the thioether S, and therefore can exist as diastereomers. The effect of other ligands at the metal raises the question of stereochemical discrimination.

In a paper reporting the crystal structure of [Pd(gly-DL-met)Cl]·$H_2O$[14] the synthesis of three nucleobase adducts of this compound was described, yet no spectroscopic data were given.

## Experimental

Glycyl-L-methionine, Gly-L-met$H_2$ (Bachem), acetylhistidine (ahis), acetylhistamine (ahist), (Aldrich), 9-ethylguanine (Hegua, Chemogen), 9-methylguanine (Hmgua, Chemogen), uridine (Sigma), inosine (Sigma), $K_2[PdCl_4]$ and $K_2[PtCl_4]$ (Degussa) were used as supplied. 1-Methylcytosine (Hmcyt),[18] 1-methyluracil (Hmura),[19] 1-methylthymine (Hmthy),[19] 9-methyladenine (made),[20] and the binary complex [Pt(gly-L-metH)Cl][13] were prepared as described.

### Preparation

**[Pd(gly-L-met)]·2$H_2O$ 1.** Presumably polymeric [Pd(gly-L-met)]·2$H_2O$ **1** was prepared by dissolving $K_2[PdCl_4]$ (0.613

mmol) and gly-L-met$H_2$ (0.611 mmol) in water (75 $cm^3$) and keeping the solution at around pH 2 by means of 1 mmol $dm^{-3}$ KOH until it remained constant. Then 4 equivalent of $AgNO_3$ (2.45 mmol) were added and the AgCl that formed was removed after 10 min. The solution was then raised to pH 6 (KOH) and concentrated to 10 $cm^3$ by rotary evaporation. Within 24 h a yellow precipitate formed in 73% yield (Found: C, 23.9; H, 4.5; N, 8.0. Calc. for $C_7H_{16}N_2O_5PdS$: C, 24.3; H, 4.7; N, 8.1%).

**[Pd(gly-L-met)(Hegua)]·2.5$H_2O$ 2.** 9-Ethylguanine (0.636 mmol) was added to a suspension of complex **1** (0.636 mmol) in water (50 $cm^3$) and heated for 1 h at 50 °C to give a clear yellow solution (pH 4.9). After cooling to room temperature, yellow crystals precipitated (68% yield), which were filtered off (Found: C, 31.1; H, 4.8; N, 18.1. Calc. for $C_{14}H_{26}N_7O_{6.5}PdS$: C, 31.4; H, 4.9; N, 18.3%).

**[Pd(gly-L-metH)(Hmgua)]$NO_3$·$H_2O$ 3.** In analogy to **2**, the corresponding Hmgua complex was prepared and subsequently recrystallized from aqueous 1 mol $dm^{-3}$ $HNO_3$. Upon slow evaporation of the solution yellow crystals suitable for X-ray analysis were isolated in 75% yield (Found: C, 27.7; H, 3.7; N, 20.0. Calc. for $C_{13}H_{22}N_8O_8PdS$: C, 28.0; H, 4.0; N, 20.1%). X-Ray analysis showed the crystal to be anhydrous.

### Instrumentation

Proton NMR spectra were recorded on Bruker AC200 and DRX-400 spectrometers in $D_2O$ solutions containing 3-trimethylsilylpropane-1-sulfonate as internal reference. The $^{195}Pt$ NMR spectrum of [Pt(gly-L-metH)Cl] was recorded on a Bruker AC200 (42.95 MHz) spectrometer in $D_2O$, with external $Na_2[PtCl_6]$ as reference. Infrared spectra (KBr) were obtained on a Bruker IFS 113v instrument. pH Measurements were made using a Metrohm 650 instrument and a pH combination (Ag–AgCl reference) electrode. The pD values given refer to the pH-meter reading with 0.4 units added.

### Stability measurements

Protonation and stability constants of the ligands and the ternary complexes were determined potentiometrically. The compounds $K_2[PdCl_4]$ and gly-L-met$H_2$ were mixed in strictly equimolar concentration and 2 equivalents of base added to ensure complete formation of the species $[PdAH_{-1}]$ (where A stands for the gly-L-metH monoanion). This species corresponds to the amino, amide and thioether co-ordinated palladium(II) complex containing free $CO_2H$. The fourth co-ordination site is occupied by a chloride ion. The stock solution of the palladium(II) complex was mixed with the nucleobases in 1:1 and 2:1 ratios ($c_A = 4 \times 10^{-3}$ mol $dm^{-3}$) and these samples were titrated with carbonate-free KOH. Argon was bubbled through the samples to ensure the absence of oxygen and carbon dioxide and to stir them. All pH-metric measurements were carried out at 298 K and at constant ionic strength (0.2 mol $dm^{-3}$ $KNO_3$). Measurements were made with a Radiometer PHM 84 pH-meter equipped with a GK2421C combined electrode and an ABU 80 automatic burette. The pH readings were converted into hydrogen-ion concentration[21] and stability constants were calculated by means of a general computational program (PSEQUAD).[22]

### X-Ray crystallography

X-Ray data for a crystal of complex **3** (dimensions approximately 0.15 × 0.10 × 0.40 mm) were collected on a Nicolet R3m/V single-crystal diffractometer at room temperature using graphite-monochromated Mo-Kα radiation (λ = 0.710 73 Å). Unit-cell parameters were obtained from a least-squares fit to 25 randomly selected reflections in the range $15 \leqslant 2\theta \leqslant 30°$. Intensity data were collected at variable scan speed (3.5–15° $min^{-1}$ in ω) using an ω–2θ scan technique. An empirical absorption correction *via* ψ scans was applied. No correction was made for extinction.

The structure was solved by Patterson and Fourier methods and refined on *F* by full-matrix least squares applying the SHELXTL PLUS program.[23] Idealized hydrogen positions were calculated geometrically with fixed X–H bond distances (C–H 0.96, N–H 0.90 Å) and fixed isotropic *U* values. Crystallographic data and experimental details are presented in Table 1.

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 186/350.

## Results and Discussion

### Binary complexes

Despite several attempts we were not able to crystallize the binary complex [Pd(gly-L-metH)Cl] from a reaction solution containing $K_2[PdCl_4]$ and gly-L-met$H_2$ at pH 2. We therefore applied another route to generate this compound by isolating the presumably polymeric compound **1** and preparing [Pd(gly-L-metH)Cl] *in situ* (Scheme 1). It is proposed that $Pd^{II}$ in **1** is

$$K_2[PdCl_4] + \text{gly-L-met}H_2 \xrightarrow{(i)} [\text{Pd(gly-L-met}H)Cl] + 2KCl + HCl$$

$$(ii) \Big\| -4AgCl$$

$$[\text{Pd(gly-L-met}H)(H_2O)]^+$$

$$(iii) \Big\|$$

$$[\{\text{Pd(gly-L-met)}\}_n]\cdot 2H_2O \ \mathbf{1}$$

$$(iv) \Big\|$$

$$[\text{Pd(gly-L-met}H)Cl]$$

**Scheme 1** (*i*) KOH, pH 2; (*ii*) 4$AgNO_3$; (iii) KOH, pH 6; (*iv*) HCl, pH 3

surrounded by the $NH_2$ (gly), N (amide) and S (met) donor atoms and in addition by a deprotonated carboxylate oxygen of met from an adjacent molecule. A comparison of the IR spectra of [Pt(gly-L-metH)Cl] and **1** supports this view: thus the intense, characteristic band of [Pt(gly-L-metH)Cl] at 1710 $cm^{-1}$, which is due to the $CO_2$ entity, is missing in the spectrum of **1**.

The proton NMR spectrum of [Pd(gly-L-metH)Cl], generated from **1** at pD ≈ 3 in the presence of an excess of KCl and recorded at ambient temperature, is remarkably simple (Fig. 2).

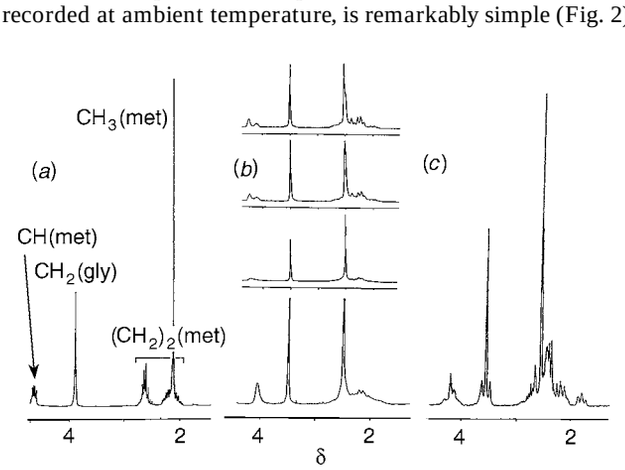


**Fig. 2** Proton NMR spectra (δ 1.5–4.5) of gly-met at pD 2.4 in $D_2O$, at 293 K (*a*), [Pd(gly-L-metH)Cl] in KCl, at pD 3 in $D_2O$ at 293, 289, 285 and 280 K (bottom to top) (*b*) and [Pt(gly-L-metH)Cl], at pD 4.8 in $D_2O$ at 293 K (*c*)

In contrast [Pt(gly-L-metH)Cl] has a more complex spectrum even at 293 K. The CH (met) and $CH_3$ (met) resonances are split in a 60:40 ratio [Fig 2(*c*)] and are assigned to two diastereomers. In the $^{195}$Pt NMR spectrum (δ − 3077 for chloride species, δ − 2733 for aqua species) no signal splitting due to diastereomers is observed at 42.95 MHz, however.* In addition, the gly $CH_2$ resonance displays a $^{195}$Pt coupling of ≈30 Hz which is not observed in the 400 MHz spectra, however. We conclude that, unlike in the platinum complex which at ambient temperature gives rise to two diastereomers (≈60:40) that are in slow exchange on the NMR timescale, inversion of the S–$CH_3$ in the palladium complex is rapid under these conditions but leads to some signal broadening. Only at lower temperature, *ca*. 280–285 K, the existence of two diastereomers, again in a 60:40 ratio, is visible: then the $CH_3$ resonance of met is split and two sets of CH resonances of met are visible, with no coupling resolved, however, in the latter case.

### Ternary complexes

**Proton NMR spectra.** The mixed gly-L-met, Hegua complex **2** was isolated form polymeric **1** and Hegua on a preparative scale. The elemental analysis data are consistent with the proposed composition [Pd(gly-L-met)(Hegua)]·2.5$H_2O$. The chemical shift of the guanine $H^8$ resonance (δ 8.30, pD 6) indicates $N^7$ co-ordination. The behaviour of **2** at neutral or slightly alkaline pH is similar to that of other palladium(II) species, Pd(dien) (dien = diethylenetriamine),[25] Pd(gly-L-his),[7e] *trans*-[$(am)_2Pt(mcyt)_2Pd]^{2+}$, (am = $NH_3$ or $NH_2Me$)[26] in that the μ-egua species as well as the egua-$N^1$ linkage isomer form, *viz*. Scheme 2. The identification of the various guanine $H^8$

$$2[\text{Pd(gly-L-met)(Hegua-}N^7\text{)}] \xrightarrow[-H^+]{KOH} [\{\text{Pd(gly-L-met)}\}_2(\text{egua-}N^1,N^7)]^- + \text{Hegua}$$

$$[\{\text{Pd(gly-L-met)}\}_2(\text{egua-}N^1,N^7)]^- + \text{Hegua} \xrightarrow[-H^+]{KOH} 2[\text{Pd(gly-L-met)(egua-}N^1\text{)}]^-$$

**Scheme 2**

resonances is straightforward on the basis of their differences in chemical shifts and the pH dependence of their formation (Fig. 3). The $^1$H NMR spectrum of **2** at ambient temperature gives no indication of the existence of discrete diastereomers: the guanine $H^8$ gives a single, sharp resonance and the gly-met resonances at higher field display no fine structure whatsoever. The guanine $H^8$ resonances of both the $N^1$ linkage isomer and $N^1$,$N^7$ bridged species are split, probably due to hindered rotation about the Pd–$N^1$ bond. Again, the $(CH_2)_2$ resonances of the met are featureless, suggesting that the inversion of the S–$CH_3$ group is still fast at ambient temperature and not responsible for signal doubling of the guanine $H^8$.

Reaction of complex **1** with Hmcyt in a weakly acidic medium gives rise to two new $H^5$ and $H^6$ doublets of the nucleobase, which are sharp and display no sign of further splitting, in addition to resonances of the free nucleobase. Differentiation between free and co-ordinated Hmcyt was accomplished by comparison with the spectra of Hmcyt at the same pD. As in the case of [Pd(gly-L-his)(Hmcyt)][7e] we attribute the two new resonances ($H^6$, δ 7.63, 7.60; $H^5$, δ 6.02, 6.01; $^3J$ = 7.4 Hz; $CH_3$, δ 3.42, 3.40) to two different rotamers, present in a 3:1 ratio. The shift range of the aromatic Hmcyt protons is consistent with $N^3$ binding. The simplicity of the spectrum at higher field [singlets for CH (met), $CH_2$ (gly), $CH_3$ (met); unstructured $(CH_2)_2$ met resonances] again rules out the existence of discrete diastereomers on the $^1$H NMR timescale.

* With $[Pt(Hamet)Cl_3]^-$ a 6 ppm splitting of the $^{195}$Pt resonance due to diastereomers has been detected at higher field strength.

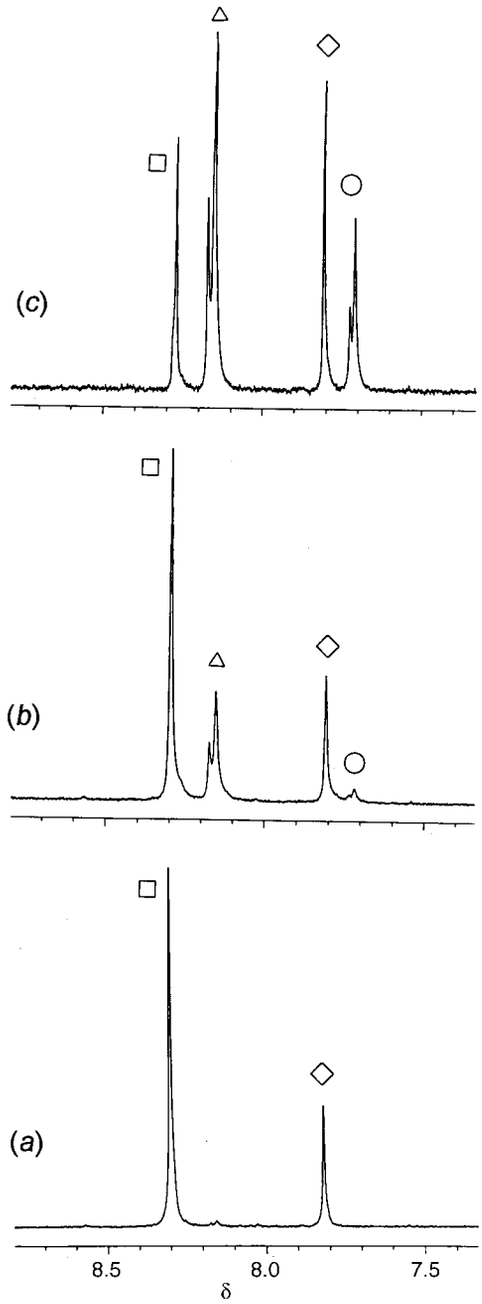


**Fig. 3** 9-Ethylguanine $H^8$ (δ 7.5–8.5) resonances of 1 : 1 mixtures of Hegua and complex **1**, $c$ = 0.033 mol $dm^{-3}$, in $D_2O$, at pD 5.6 (*a*), 7.0 (*b*) and 8.3 (*c*). The $H^8$ resonances are marked as follows: (◇) Hegua/egua; (□) Pd(Hegua-$N^7$)/Pd(egua-$N^7$); (○) Pd(egua-$N^1$); (△) $Pd_2$(egua-$N^1$,$N^7$)

The corresponding platinum species, [Pt(gly-L-met)(Hmcyt)], prepared *in situ* from [Pt(gly-L-metH)Cl], $AgNO_3$ and Hmcyt in water, displays a more complex $^1$H NMR spectrum than that of its palladium analogue. Resonances due to free and complexed Hmcyt are easily differentiated, as are those of $CH_2$ of gly. On the other hand, the met resonances are strongly overlapped and are hardly useful for any diagnostic purposes. Both $H^5$ and $H^6$ resonances of Hmcyt are more numerous than for the palladium analogue: for $H^5$ and $H^6$ of the ternary complex, three doublets are discernible, suggesting that resonances due to diasteromers are resolved for one of the two rotamers (Fig. 4).

Reaction of complex **1** with Hmura was confirmed by $^1$H NMR spectroscopy. Complex formation takes place with liberation of $H^+$ from Hmura and leads to a drop in pH. It occurs even at pD 4. The upfield shifts of the new mura resonances of $[Pd(gly\text{-}L\text{-}met)(mura)]^-$ ($H^6$, δ 7.47, d, $^3J$ = 7.5 Hz; $H^5$, δ 7.69 and 7.70, d each, pD 4–6) relative to Hmura are consistent with

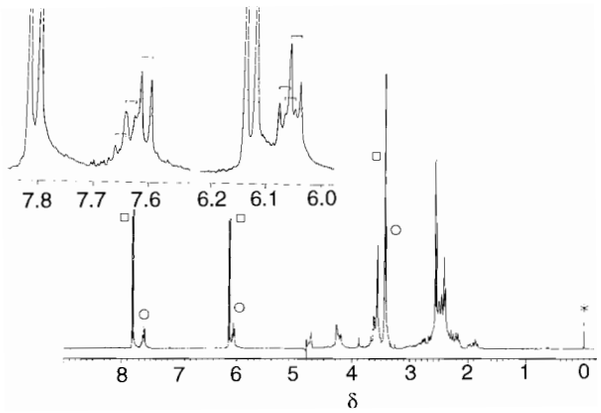


**Fig. 4** Proton NMR spectrum (400 MHz) of a 1 : 1 mixture of Hmcyt and [Pt(gly-L-metH)Cl] at pD 4.2 in $D_2O$ after 4 d at 40 °C, with the $H^5$ and $H^6$ Hmcyt resonances of the ternary complex (○) enlarged. Resonances due to free Hmcyt are indicated by (□), the internal reference by (*). The solvent signal at δ 4.8 has been suppressed

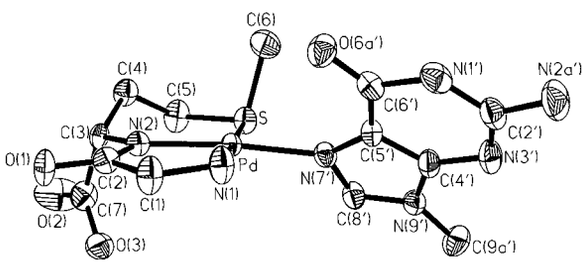


**Fig. 5** View of the cation of $[Pd(gly\text{-}L\text{-}metH)(Hmgua)]NO_3\cdot H_2O$ **3** with the atom numbering scheme

$N^3$ co-ordination. There are two distinct sets of $H^5$ doublets of Pd–mura resonances present in a 1:1 ratio. Glycylmethionine resonances are broad, without any coupling resolved. The two new $H^5$ doublets are therefore interpreted in terms of two rotamers of the ternary complex being present rather than originating from the expected two diastereomers of a single rotamer.

### Crystal structure of complex 3

Since crystals of complex **2** proved unsuitable for X-ray work the Hmgua analogue **3**, in its protonated form, was prepared. Fig. 5 gives a view of the cation $[Pd(gly\text{-}L\text{-}metH)(Hmgua)]^+$ with the atom numbering scheme and Table 2 selected interatomic distances and angles. Palladium(II) is co-ordinated to the amino group of the glycyl residue, to the deprotonated amide nitrogen of the dipeptide, to the thioether sulfur and to $N^7$ of Hmgua. It has a square-planar co-ordination geometry, with some marked deviations in angles about the metal caused by the bite of the tridentate peptide ligand. To a first approximation, the five-membered glycyl ring is planar, whereas the six-membered ring of the met entity represents an envelope with only $C(4)H_2$ markedly (0.71 Å) out of the plane. Bond lengths within the Pd(gly-L-metH) entity are not significantly different from those of [Pd(gly-L-metH)Cl],[14] except for the Pd–S distance, which is longer in the guanine adduct [2.279(1) Å] as compared to the chloride complex [2.263(1) Å]. The major difference between [Pd(gly-L-metH)Cl][14] and likewise its platinum analogue[13] and **3** is, apart from Cl being replaced by the guanine, the difference in chirality at the thioether S. In the chloride compounds both chiral centres, $C_\alpha$ and S, adopt *S* configurations, whereas in **3** a single diastereomer with *S* configurations for $C_\alpha$, yet *R* for the sulfur, is present. Thus, both in **3** and in [M(gly-L-metH)Cl] (M = Pd or Pt) uniform, yet *different* diastereomers are present. As a consequence of the *R* configuration of the thioether sulfur the $CO_2H$ and S–$CH_3$ groups are pointing in opposite directions relative to each other, almost at right angles to the plane of the envelope. In contrast, in [M(gly-L-metH)Cl] (M = Pd or Pt) the six-membered ring has a boat-like conformation with the $CO_2H$ and $CH_3$ groups on the same side of the chelate. The existence of $CO_2H$ is, apart from $NO_3^-$ being present in the crystal, also evident from the significantly different bond lengths between C=O(2) [1.213(3) Å] and C–OH(3) [1.302(2) Å].

The geometry of the Hmgua ligand is normal.[27] The Pd–N(7′) bond length [2.026(5) Å] appears to be at the upper end of those for reported palladium–oxopurine compounds,[28] possibly as a consequence of a *trans* influence of the deprotonated amide N. The guanine forms an angle of 54° with the palladium co-ordination plane. This value is not unusual, even though values in the range 70–80° appear to be more common, at least with $Pt^{II}(NH_3)_2$ compounds.[29] The orientation of the guanine is such that O(6a′) of Hmgua and $CH_3$(6) of gly-L-met, which are on the same side of the chelate plane, are pointing away from each other. The distance between these two groups is 4.62 Å.

As to intermolecular hydrogen bonding, a proton of the guanine $NH_2$ group is donated to the OH group of the $CO_2H$ group (2.95 Å; symmetry operation $-x$, $+y-\frac{1}{2}$, $-z+\frac{1}{2}+1$), which in turn donates its acidic protons to O(1) of the amide linkage (2.59 Å; symmetry operation $x+\frac{1}{2}$, $-y+\frac{1}{2}+2$, $-z+2$).

**Table 1** Crystallographic data and experimental details of the X-ray study of compound **3**

| | |
|---|---|
| Formula | $C_{13}H_{20}N_8O_7PdS$ |
| *M* | 538.83 |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| *a*/Å | 8.479(3) |
| *b*/Å | 9.558(2) |
| *c*/Å | 23.527(7) |
| *U*/Å$^3$ | 1906.7(1) |
| $D_c$/g cm$^{-3}$ | 1.877 |
| *Z* | 4 |
| μ(Mo-Kα)/cm$^{-1}$ | 10.97 |
| *F*(000) | 956.0 |
| 2θ Range/° | 2–50 |
| No. measured reflections | 3699 |
| No. independent reflections | 3382 |
| No. observed reflections | 3209 [$F > 4\sigma(F)$] |
| No. parameters | 272 |
| Final *R*, *R*′ | 0.026,[a] 0.037[b] |

[a] $\Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $R' = \Sigma w(F_o - F_c)/\Sigma w(F_o)$, $w^{-1} = \sigma^2(F) + 0.001\,793F^2$.

**Table 2** Selected bond lengths (Å) and angles (°) for compound **3**

| | | | |
|---|---|---|---|
| Pd–S | 2.279(2) | N(7′)–C(5′) | 1.381(7) |
| Pd–N(2) | 1.996(4) | N(3′)–C(4′) | 1.357(8) |
| Pd–N(1) | 2.049(5) | N(3′)–C(2′) | 1.311(8) |
| Pd–N(7′) | 2.026(5) | C(4′)–C(5′) | 1.386(8) |
| S–C(6) | 1.805(6) | O(6a′)–C(6′) | 1.223(7) |
| S–C(5) | 1.803(6) | O(1)–C(2) | 1.244(7) |
| N(2)–C(3) | 1.460(7) | O(13)–N(11) | 1.253(8) |
| N(2)–C(2) | 1.340(7) | N(1′)–C(6′) | 1.406(8) |
| N(9′)–C(8′) | 1.349(7) | N(1′)–C(2′) | 1.371(8) |
| N(9′)–C(4′) | 1.370(8) | O(3)–C(7) | 1.291(8) |
| N(9′)–C(9a′) | 1.460(7) | N(11)–O(12) | 1.219(8) |
| N(1)–C(1) | 1.467(8) | N(11)–O(11) | 1.242(9) |
| C(1)–C(2) | 1.519(8) | O(2)–C(7) | 1.216(8) |
| C(3)–C(4) | 1.533(8) | O(6′)–C(5′) | 1.414(8) |
| C(3)–C(7) | 1.524(8) | N(2a′)–C(2′) | 1.339(8) |
| N(7′)–C(8′) | 1.329(7) | C(4)–C(5) | 1.515(8) |
| | | | |
| N(1)–Pd–N(7′) | 91.8(2) | Pd–S–C(6) | 102.0(2) |
| N(2)–Pd–N(7′) | 173.1(2) | Pd–N(2)–C(2) | 116.7(4) |
| N(2)–Pd–N(1) | 82.9(2) | Pd–N(2)–C(3) | 127.5(3) |
| S–Pd–N(7′) | 85.8(1) | Pd–N(1)–C(1) | 111.4(3) |
| S–Pd–N(1) | 176.0(1) | Pd–N(7′)–C(5′) | 130.1(4) |
| S–Pd–N(2) | 99.8(1) | Pd–N(7′)–C(8′) | 122.7(4) |
| Pd–S–C(5) | 108.1(2) | | |

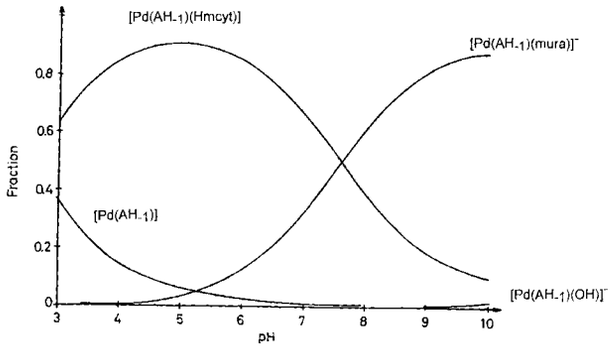


**Fig. 6** Metal-ion speciation of the systems containing $Pd^{II}$, gly-L-met, Hmcyt and Hmura in equimolar concentration (2 mmol $dm^{-3}$)

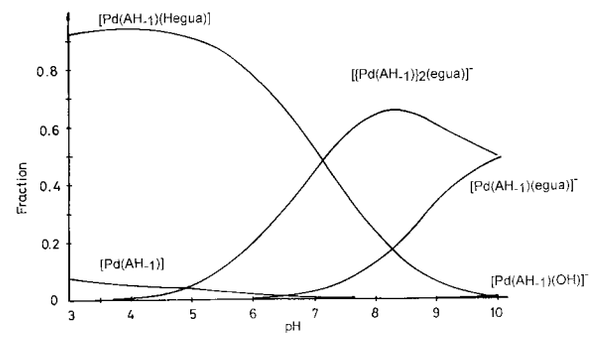


**Fig. 7** Species distribution of the complexes formed in the Pd(gly-L-met)–Hegua system in equimolar concentration (2 mmol $dm^{-3}$)

A surprisingly short intermolecular contact is seen between Pd and N(2a′) of the guanine ring (3.41 Å). Owing to the $sp^2$ hybridization of this amino N, the remaining proton (not involved in hydrogen bonding) is expected not to be directed toward the Pd, however. For this reason we do not believe that this contact represents an agostic M · · · HN interaction as seen occasionally in compounds of M = $Pd^{II}$ [30] or $Pt^{II}$.[31]

### Stability constants

Stability constants obtained for the ternary Pd(gly-L-met)–nucleobase systems are compiled in Table 3. It can be seen that uridine, Hmthy, Hmura, Hmcyt and made form only 1:1 adducts with the $PdAH_{-1}$ complex of gly-L-met. This corresponds to the co-ordination of $N^3$ nitrogen donors of uracil, thymine and cytosine and $N^1$ or/and $N^7$ of adenine.[32] The relative stability of the various complexes is demonstrated in Fig. 6, where the metal-ion speciation is plotted in the presence of two different nucleobases (Hmcyt and Hmura). Fig. 7 reveals that the ternary complexes of Hmcyt are formed in the acidic pH range, but the negatively charged nitrogen donor of the anion of Hmura is able to replace cytosine in slightly basic solutions.

In a previous paper it was demonstrated that in the case of imidazole derivatives both $N^1$ and $N^3$ nitrogens can interact with free co-ordination sites of palladium(II).[9] This results in the formation of a dimer species $(PdAH_{-1})_2(BH_{-1})$ which can be present in equimolar solution. The deprotonation of the $N^1H$ group of the imidazole moiety and the formation of the dimer species in the reaction of the mixed-metal complex *trans*-$[(MeH_2N)_2Pt(mcyt)_2PdCl]NO_3$ with ahis took place around physiological pH, while it is present only in basic solutions (pH > 9) with [Pd(gly-L-met)]. On the other hand, on the basis of the lower stability constants obtained for the ternary complexes of gly-L-met as compared to those of the PtPd complex it can be concluded that the fourth co-ordination site of palladium in $PdAH_{-1}$ peptide complexes is less effective in binding nitrogen donors and promoting ionization of the pyrrole-type $N^1H$ of imidazole.

**Table 3** Logarithms of stability constants of ternary palladium(II) complexes of gly-L-met with nucleobases (298 K, $I = 0.2$ mol $dm^{-3}$, standard deviations in parentheses)

| | Species* | | | | | |
|---|---|---|---|---|---|---|
| Ligand (B) | HB | $H_2B$ | M(HB) | MB | $M_2B$ | $M_2(BH_{-1})$ |
| $OH^-$ | | | | −8.64 | | |
| Uridine | 9.15 | — | — | 7.00(3) | — | — |
| Hmura | 9.53 | — | — | 6.97(3) | — | — |
| Hmthy | 9.95 | — | — | 7.26(3) | — | — |
| Hmcyt | 4.66 | — | — | 5.04(4) | — | — |
| made | 4.12 | — | — | 4.33(5) | — | — |
| ahis | 7.04 | 9.92 | — | 5.53(5) | — | 0.1(30) |
| ahist | 7.02 | — | — | 5.48(5) | — | −0.9(40) |
| Hegua | 9.44 | 12.65 | 14.69(8) | 6.43(5) | 12.21(8) | — |
| Inosine | 8.70 | — | 12.73(8) | 6.38(5) | 10.93(8) | — |

* 'M' stands for the $PdAH_{-1}$ species of gly-L-met and the overall stability constants refer to the equilibrium $p\mathrm{MCl} + q\mathrm{B} + r\mathrm{H} \rightleftharpoons \mathrm{M}_p\mathrm{B}_q\mathrm{H}_r + \mathrm{Cl}^-$.

Complex-formation processes of Hegua and inosine represent a different category. The data in Table 3 and the metal-ion speciation in Fig. 7 show that, consistent with the NMR and solid-state studies, both $N^7$ and $N^1$ of the purine ring can co-ordinate to the free site of palladium. It can be observed in Fig. 6 that the adduct between Hegua and the $PdAH_{-1}$ species of gly-L-met is almost completely formed in the acidic pH range even in very dilute solutions (2 mmol $dm^{-3}$). The stoichiometric composition of the complex is [Pd(AH$_{-1}$)(HB)], which corresponds to the $N^7$-co-ordinated species, while $N^1$ is protonated. The dimeric complex $[Pd(AH^{-1})]_2B^-$ is formed on increasing pH and its concentration reaches a maximum around physiological pH. The $N^1$-co-ordinated monomeric complex $Pd(AH_{-1})B^-$ is present under basic conditions, but it will predominate only in the presence of an excess of Hegua. The metal-ion speciation of the systems containing inosine is very similar to that of Hegua, and the lower stability constants obtained for the adducts of inosine can be explained by the lower p*K* values or decreased basicity of its nitrogen donors.

## Conclusion

Ternary complex formation of [Pd(gly-L-metH)Cl] and [Pd(gly-L-met)], respectively, with isolated nucleobases has been studied by $^1$H NMR spectroscopy and potentiometry. A representative example, [Pd(gly-L-metH)(Hmgua-$N^7$)]$NO_3$, has been crystallized and its structure determined by X-ray analysis. In the crystal studied a single diastereomer with *S* configuration at $C_\alpha$ and *R* configuration at the sulfur is present. In aqueous solution (ambient temperature) rapid inversion of the sulfur atom takes place, both in the binary peptide complex and the nucleobase adducts. Therefore individual diastereomers are not detected. Doubling of nucleobase resonances, as seen with $N^3$-bound Hmcyt and mura as well as $N^1$-bound Hmgua, is interpreted in terms of hindered rotation about the Pd–N (nucleobase) bond. In contrast, in [Pt(gly-L-met)Cl] and likewise in its Hmcyt derivative sulfur inversion is sufficiently slow to produce individual diastereomers. Comparison of stability constants obtained in this study with those of *trans*-$[MeH_2N)_2Pt(mcyt)_2PdCl]NO_3$,[9] $[Pd(gly\text{-}hisH_{-1})]$[7e] and $[Pd(dien)]^{2+}$[25] ternary systems reveals that charge neutralization is an important factor during complex formation. As a consequence, the ternary complexes formed with positively charged palladium(II) binary systems have higher thermodynamic stability than those of [Pd(dipeptideH$_{-1}$)] species. The decrease in stability constants is especially significant in the case of [Pd(gly-L-met)]–ahis (ahist) systems indicating that the co-ordinated sulfur donor of gly-L-met may decrease the binding ability of palladium(II) towards imidazole nitrogen donors.

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