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The reactions of $[Au(dien)Cl]^{2+}$ with L-histidine-containing dipeptides. Dependence of complex formation on the dipeptide structure

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Reactions between the monofunctional $[Au(dien)Cl]^{2+}$ complex with L-histidine-containing dipeptides, L-histidyl-glycine (L-His-Gly), and glycyl-L-histidine (Gly-L-His) were studied by ^1H NMR spectroscopy. All reactions were performed in aqueous solution at $3.50 \leq pD \leq 5.50$ at ambient temperature. In reaction of $[Au(dien)Cl]^{2+}$ with L-His-Gly, only **1** with N3-monodentate coordinated dipeptide was formed. The reaction was completed within 3 min and the complex was very stable during several days with no release of dien from Au(III). However, in the reaction of $[Au(dien)Cl]^{2+}$ with Gly-L-His, depending on the pD, different Au(III)-dipeptide complexes were observed. When this reaction was carried out at $3.50 \leq pD \leq 4.50$, only **4** with tridentate coordination of the dipeptide via the amino, deprotonated amide, and N3 imidazole nitrogen were observed after 4 days. However, during this time, at $4.50 < pD \leq 5.50$, two Au(III)-dipeptide products, **5** which represents an imidazole-bridged species along with the already described **4**, were observed. The formation of these complexes proceeds through intermediates, **2** and **3** with N3-monodentate and N_P,N3-bidentate coordinated dipeptide, respectively, and with complete loss of dien.

Keywords: Gold(III)-dien complex; L-Histidyl-glycine; Glycyl-L-histidine; Proton NMR spectroscopy

1. Introduction

Following the discovery of the anticancer properties of cisplatin [1–3], special attention was devoted to gold(III) complexes [4–10] as possible alternatives to antitumor-active platinum(II) complexes due to the fact that both Pt(II) and Au(III) possess the same d^8 electronic configuration and form square-planar complexes. The possible involvement of gold(III) complexes in cancer treatment initiated an interest in interactions of Au(III) with different bioligands, such as peptides and proteins [11–21]. The most important amino acid in the study of interactions of metal ions with peptides and proteins is L-histidine, since it is found in the active sites of several metalloenzymes [22–24] and of metal transport proteins [25]. Only a few gold(III) complexes with L-histidine-containing peptides have previously been described, those of glycyl-L-histidine (Gly-L-His), [Au(Gly-L-His-N_A,N_P,

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N3)Cl]Cl·3H_2O [15], [Au(Gly-L-His-N_A,N_P,*N3*)Cl]NO_3·1.25H_2O [16], [Au(Gly-L-His-N_A, N_P,*N3*)Cl]NO_3 [16], and [Au(Gly-L-His-N_A,N_P,*N1*,*N3*))$_4$·10H_2O [15], that of the dipeptide L-alanyl-L-histidine (L-Ala-L-His), [Au(L-Ala-L-His-N_A,N_P,*N3*)Cl]NO_3·2.5H_2O [16] and of the tripeptide glycyl-glycyl-L-histidine (Gly-Gly-L-His), [Au(Gly-Gly-L-His-N_A,N_{P1}, N_{P2},*N3*)]Cl·H_2O [17]. These complexes crystallized from a 1 : 1 reaction mixture of $[AuCl_4]^-$ and the corresponding peptide at low pH (1.50–2.00) and their square-planar geometries were determined by X-ray analyses [15–17]. From these investigations, it was concluded that the N3-anchored Au(III) is very effective in displacing the amide proton at pH < 2.00 and the next step of this reaction was the very fast coordination of this metal ion to the deprotonated nitrogen of the amide bond(s) and to the terminal amino group, leading to chelation of the L-histidine-containing peptide [15–17]. This chelation reaction contributes to stabilization of the +3 oxidation state of gold and to its protection from reduction [13, 14].

The present paper reports an ^{1}H NMR investigation of the reactions of $[Au(dien)Cl]^{2+}$ (dien is diethylenetriamine tridentate coordinated to Au(III)) with the L-histidine-containing dipeptides L-His-Gly and Gly-L-His in aqueous solution at $3.50 \leq pD \leq 5.50$ and at 25 °C. The data obtained from this study were compared with those for the reactions of $[AuCl_4]^-$ and $[M(dien)(H_2O)]^{2+}$ complexes (M = Pt(II) and Pd(II)) with different L-histidine-containing peptides [15, 16, 26–29].

2. Experimental

2.1. *Materials*

Distilled water was demineralized and purified to a resistance of greater than 10 MΩ cm^{-1}. The compounds D_2O, DCl, KOD, H[$AuCl_4$]·3H_2O, diethylenetriamine (dien), the amino acid glycine (Gly), and glycineamide ($GlyNH_2$) were purchased from the Sigma-Aldrich Chemical Co. Hydrochloric acid, sodium hydroxide, and sodium chloride were obtained from Zorka Pharma, Šabac. The dipeptides L-histidyl-glycine (L-His-Gly) and glycyl-L-histidine (Gly-L-His) were obtained from Bachem A.G. All chemicals were of analytical reagent grade. The amino group in the glycine was acetylated by a standard method [30].

2.2. *Synthesis of the [Au(dien)Cl]Cl$_2$ complex*

[Au(dien)Cl]Cl_2 was prepared by a modification of a published procedure [31, 32]. To a solution of H[$AuCl_4$]·3H_2O (354 mg, 0.9 mmol) in water (2 cm^3) was added slowly, under stirring, a solution containing dien (0.26 cm^3, 2.35 mmol) and 6 M HCl (1.20 cm^3, 7.05 mmol) in a 1 : 3 molar ratio, respectively. The yellow precipitate, which formed immediately, redissolved after addition of a solution of NaOH (160 mg, 4 mmol) to the reaction mixture. The resulting yellow solution was stirred for 2 h at 0 °C and then left standing in the dark at room temperature to evaporate slowly. Yellow crystals of [Au(dien)Cl]Cl_2 that formed after two days were removed by filtration and washed with a small amount of ethanol. The yield was 227 mg (62%). The purity of the complex was checked by elemental microanalyses, ^{1}H NMR spectroscopy, and UV–Vis spectrophotometry. The obtained data were in accord with those reported previously for [Au(dien)Cl]Cl_2 [33, 34].

2.3. *NMR measurements*

All ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer at 200 and 50.3 MHz, respectively, using 5 mm NMR tubes kept at 25 °C. Sodium 3-(trimethylsilyl)propionate (TSP) was used as an internal reference. Both the ^{1}H and ^{13}C chemical shifts are reported in ppm.

Fresh solutions of $[Au(dien)Cl]^{2+}$ and the corresponding dipeptide (L-His-Gly and Gly-L-His) were prepared separately in D_2O at an initial concentration of 60 mM and then mixed in an NMR tube in 1 : 1, 2 : 1, and 1 : 2 molar ratios, respectively. To investigate the effect of chloride concentration on the formation of the Au(III)-dipeptide complex, reaction between equimolar amounts of $[Au(dien)Cl]^{2+}$ and L-His-Gly was performed at pD 5.00 and at 25 °C in the presence of sodium chloride, with the Cl^{-} concentration varying from 0.01 to 1.00 M.

2.4. *pH measurements*

All pH measurements were performed at ambient temperature. The pH meter (Iskra MA 5704) was calibrated with Fischer certified buffer solutions of pH 4.00. The reported pD values were corrected for the deuterium isotopic effect by adding 0.45 units to the pH meter reading [35]. However, in conceptual references to acidity and basicity, the common symbol pH was used.

3. Results and discussion

3.1. *Reaction of $[Au(dien)Cl]^{2+}$ with L-His-Gly*

When $[Au(dien)Cl]^{2+}$ was incubated with an equimolar amount of L-His-Gly dipeptide at $3.50 \leq pD \leq 5.50$, and 25 °C, **1** with N3-monodentate coordinated dipeptide was the only NMR-detectable species in solution (figure 1). Formation of **1** was very fast and the investigated reaction was complete within 3 min. This complex was stable during several days and no release of dien from Au(III) was observed. The formation of **1** was evidenced by appearance of new resonances in the ^{1}H NMR spectrum at 8.22 and 7.22 ppm, corresponding to the C2H and C5H imidazole protons, respectively (figure 1 and table 1). These chemical shifts are slightly shifted upfield with increasing pD ($\Delta\delta = 0.16$ for C2H and 0.12 ppm for C5H). The chemical shifts of these protons are consistent with those previously reported for N3-bound isomers obtained in reactions of $[M(dien)(H_2O)]^{2+}$ (M = Pt(II) and Pd(II)) with L-histidine-containing peptides (Gly-His, His-Ala, His-Gly-Ala, Pro-Gly-Ala-His, and His-Pro-Gly-Ala-His) [26–29]. However, the presently investigated selective binding of $[Au(dien)Cl]^{2+}$ to N3 imidazole nitrogen of the L-His-Gly dipeptide is in contrast with reactions of $[M(dien)(H_2O)]^{2+}$ with the above-mentioned peptides, in which both N3- and N1-imidazole-bound isomers are formed [26–29].

The pD dependence of dipeptide consumption and complex **1** formation are shown in figure 2(a). The concentrations of **1** and free L-His-Gly present in solution after 3 min were calculated from the integrated resonances of the C2H and C5H protons for the free and those for N3-bound dipeptide (see figure 1 and table 1). The observed chemical shifts for **1** are an average of those of the two species, at each pD value. The percentage of the

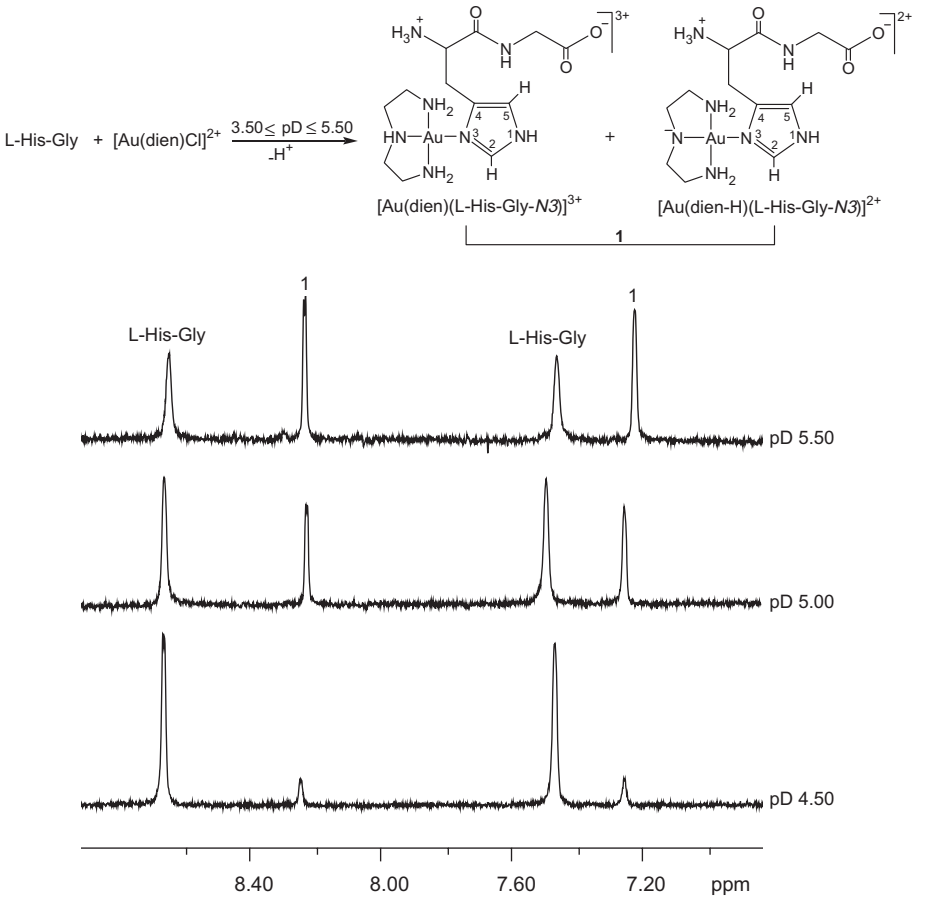

Figure 1. Schematic presentation of the reaction between $[Au(dien)Cl]^{2+}$ and L-His-Gly and proton NMR spectra in the imidazole region (C2H and C5H) recorded after 3 min. The observed chemical shifts for **1** are an average of those of the two species, at each pD value.

N3-bound L-His-Gly dipeptide increased with increasing pD, which can be attributed to deprotonation of the secondary nitrogen of the dien ligand, resulting in formation of a more reactive $[Au(dien\text{-}H)Cl]^{+}$ complex (dien–H means that the secondary nitrogen of this tridentate coordinated ligand is deprotonated) [32, 33]. The pK_a of this deprotonation reaction is 4.00 in 0.5 M ClO_4^- or 4.70 in 0.5 M Cl^- [32, 33]. Deprotonation of the secondary amine affected multiplets for the methylene dien protons at 2.93–3.16 and 3.52–3.65 ppm (pD 4.50) were shifted upfield to 2.32–2.65 and 3.34–3.52 ppm, respectively (pD 5.50). These chemical shifts are in accord with those previously observed in study of $[Au(dien)Cl]^{2+}$ in solution by ^1H NMR spectroscopy [34]. Difference in reactivity between $[Au(dien\text{-}H)Cl]^{+}$ and $[Au(dien)Cl]^{2+}$ can be attributed to greater *trans* influence of N^- than of NH [32]. This statement was supported by crystallographic results of these two complexes, confirming that the Au–Cl bond is longer in $[Au(dien\text{-}H)Cl]^{+}$ [2.330(10)] than in $[Au(dien)Cl]^{2+}$ [2.273(8) Å] [32]. On the basis of this structural information, we could have expected an increase in the rate of chloride substitution for $[Au(dien\text{-}H)Cl]^{+}$ with respect to $[Au(dien)Cl]^{2+}$.

Table 1. Characteristic ^{1}H NMR chemical shifts observed in reactions of L-His-Gly and Gly-L-His dipeptides with $[Au(dien)Cl]^{2+}$. All spectra were recorded in D_2O solutions containing TSP as the internal reference.

	Characteristic ^{1}H NMR chemical shifts δ, ppm; J_{AB}, Hz)				
		Imidazole protons			
Dipeptide/Au(III)-dipeptide complex	pD	C2H(*s*)	C5H(*s*)	Gly	dien (*m*)[a]
L-His-Gly	4.50	8.67	7.47	3.88 (*q*, J_{AB} = 17.40)	
[Au(dien)(L-His-Gly-*N3*)]$^{3+}$ (**1**)[b]	4.50	8.22	7.22	3.88 (*q*, J_{AB} = 17.40)	2.93–3.16; 3.52–3.65
Gly-L-His	4.50	8.60	7.27	3.83 (*q*, J_{AB} = 18.90)	
[Au(dien)(Gly-L-His-*N3*)]$^{3+}$ (**2**)	4.50	8.17	7.05	3.83 (*q*, J_{AB} = 18.90)	2.80–3.04; 3.43–3.59
[Au(dien-*N,N'*)(Gly-L-His-N_B*N3*)]$^{3+}$ (**3**)	4.50	8.24	7.33	3.83 (*q*, J_{AB} = 18.90)	2.80–3.04; 3.14–3.26; 3.43–3.59
[Au(Gly-L-His-N_A,N_B*N3*)Cl] (**4**)	4.50	8.54	7.24	4.00 (*q*, J_{AB} = 20.14)	
[Au(Gly-L-His-N_A,N_B*N3*)Cl]$NO_3 \cdot 1.25H_2O$ [16]	2.40	8.56	7.31	4.01 (*q*, J_{AB} = 20.00)	
Au(III)-imidazole bridged oligomer (**5**)	5.50	7.39; 7.21	7.14; 6.78	3.96–4.06 (*m*)	
[Au(Gly-L-His-N_A,N_B*N1,N3*)]$_4 \cdot 10H_2O$ [15]	5.50	7.38; 7.20	7.14; 6.79		

[a]The multiplet of the methylene protons of free dien ligand is at 3.22–3.29 ppm (pD 4.50).
[b]The chemical shifts for **1** are an average of those of the two species, at each pD value.

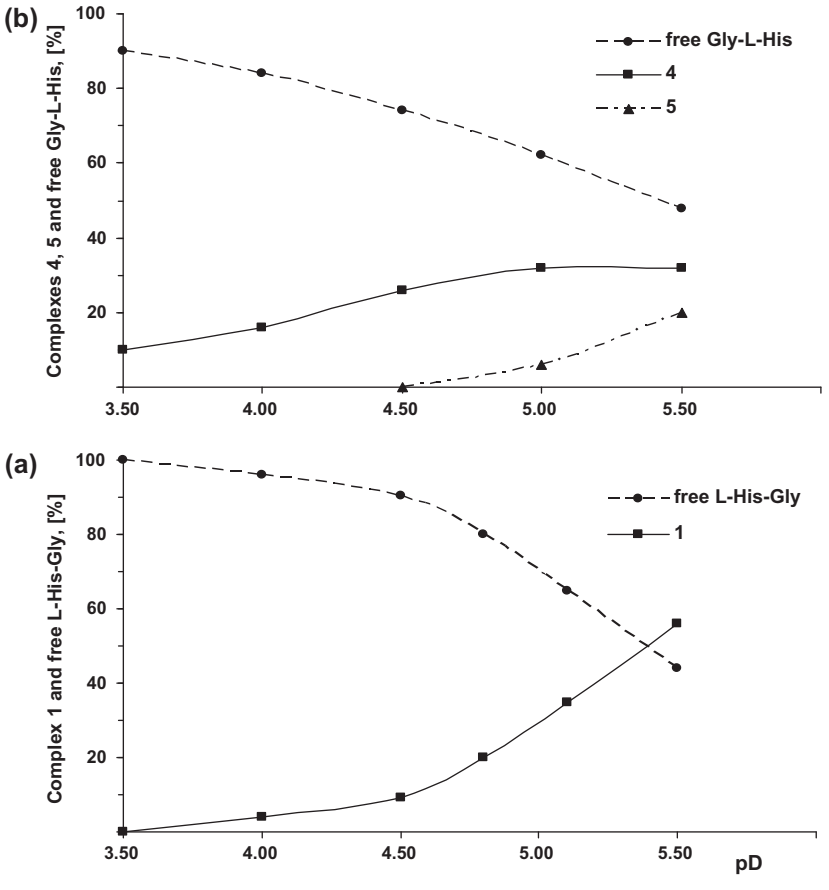

Figure 2. pD dependence of the Au(III)-dipeptide complex formation [%] for reactions of $[Au(dien)Cl]^{2+}$ with an equimolar amount of L-His-Gly (a) and Gly-L-His (b) dipeptides. The concentrations of complexes were determined after 3 min for **1**, and after 4 days for **4** and **5**.

$[Au(dien)Cl]^{2+}$ and the corresponding dipeptide were mixed in 2 : 1 and 1 : 2 molar ratios, respectively. The ^{1}H NMR spectrum run in the first 3 min of reaction was almost identical with that obtained during reaction between equimolar amounts of these reactants, confirming that binding of $[Au(dien)Cl]^{2+}$ proceeds only through monodentate coordination of the dipeptide via the N3 imidazole nitrogen of the L-histidine residue.

The influence of the chloride concentration on the amount of **1** formed in reaction between equimolar amounts of gold(III) complex and the L-His-Gly dipeptide at pD 5.00 was investigated (figure 3). The amount of **1** markedly decreased with increasing chloride concentration. Moreover, no formation of **1** was observed in the ^{1}H NMR spectrum after this reaction was performed in the presence of 1.00 M NaCl, confirming that competitive chloride coordination to $[Au(dien)]^{3+}$ significantly reduces the amount of **1**.

Possible coordination of deprotonated carboxylate oxygen ($pK_{a1} = 2.32 \pm 0.02$) [36] to $[Au(dien)]^{3+}$ was investigated by ^{13}C NMR measurements. No change in the chemical shift for the carboxylate carbon of the free dipeptide at 177.03 ppm was observed, even after prolonging the reaction time to 10 days. In addition, absence of coordination of carboxylate oxygen to Au(III) was supported by ^{1}H NMR measurements for the reaction of $[Au(dien)Cl]^{2+}$

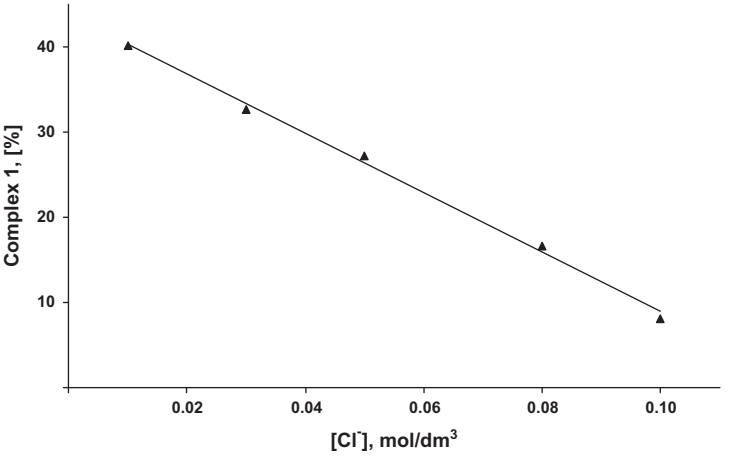

Figure 3. The influence of chloride concentration on **1** formation in reaction between equimolar amounts of $[Au(dien)Cl]^{2+}$ and L-His-Gly at the pD 5.00 and at 25 °C.

with *N*-acetylated glycine (Ac-Gly). No change in the chemical shift of $GlyCH_2$ protons was observed during several days of reaction. Complexes in which L-histidine-containing peptides (Gly-His, His-Ala, His-Gly-Ala, Pro-Gly-Ala-His and His-Pro-Gly-Ala-His) are coordinated through carboxylate oxygen have never been formed during reactions with $[Pd(dien)(H_2O)]^{2+}$ [26–29]. Formation of stable complexes in which these peptides are coordinated via carboxylate oxygen to Pt(II) was previously reported only for reactions with $[Pt(dien)(H_2O)]^{2+}$ in strongly acidic solutions [26–29].

For confirmation that binding of the terminal amino group to the $[Au(dien)Cl]^{2+}$ complex did not occur, a separate ^1H NMR experiment for reaction between this complex and glycineamide ($GlyNH_2$) was performed in the investigated pD range. No change in the chemical shift for the $GlyCH_2$ protons was observed even after reaction for several days. This finding is in agreement with that previously reported for reaction of $[Au(dien)Cl]^{2+}$ with tripeptide glycyl-glycyl-glycine (Gly-Gly-Gly), when it was stated that the NH_2 group of the tripeptide was the only Au(III)-binding site at pH > 5.00 [18].

3.2. *Reaction of $[Au(dien)Cl]^{2+}$ with Gly-L-His*

When an equimolar amount of $[Au(dien)Cl]^{2+}$ was mixed with Gly-L-His dipeptide at $3.50 \leq pD \leq 5.50$ at 25 °C, two ^1H NMR detectable Au(III)-dipeptide complexes, **2** and **3**, were observed in the first 60 min (figure 4). These reaction products were distinguished by observation of the differences in the chemical shifts of the C2H and C5H imidazole protons between **2** or **3** and free dipeptide under the same experimental conditions (figure 5 and table 1). The chemical shifts for the imidazole protons of **2** are similar to those for **1**, indicating that the same monodentate coordination mode of Gly-L-His and L-His-Gly dipeptides, respectively, occurred in these two complexes. The bidentate coordination of Gly-L-His in **3** caused the opening of one Au(III)-dien ring that could be detected in the ^1H NMR spectrum by appearance of a new multiplet at 3.14–3.26 ppm. This multiplet is positioned between multiplets at 2.80–3.04 and 3.43–3.59 ppm due to the methylene protons of tridentate-coordinated dien and its chemical shifts are almost identical with those for free dien

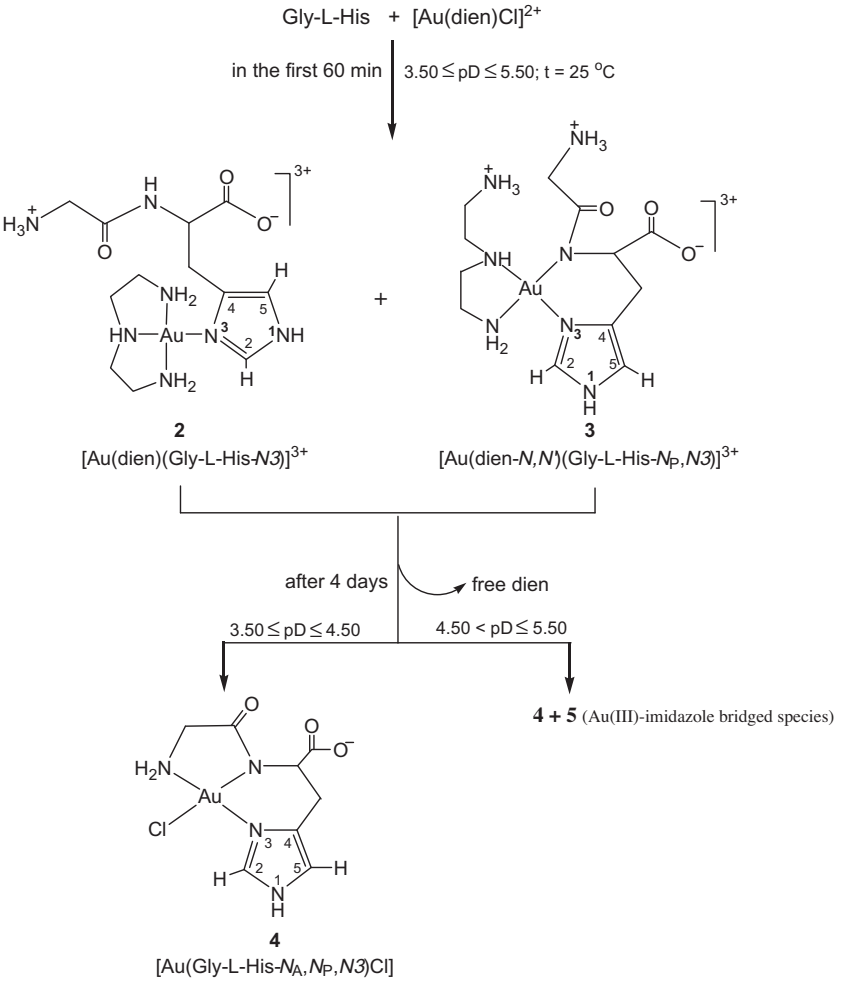

Figure 4. Schematic presentation of the reaction between $[Au(dien)Cl]^{2+}$ and Gly-L-His. Coordination of Au(III) through terminal amino, deprotonated amide and imidazole nitrogen are designated as N_A, N_P, and *N3*, respectively.

(see table 1). When reaction between $[Au(dien)Cl]^{2+}$ and Gly-L-His was prolonged for a further 48 h, new complexes **4** and **5** were observed in the ^{1}H NMR spectrum. However, during this time, the previously detected resonances for **2** and **3** decreased in intensity and completely disappeared after 4 days. The formation of **4** and **5** is strongly dependent on pD value of the reaction (figures 4 and 5). When the reaction was carried out at $3.50 \leq pD \leq 4.50$, only **4** was observed after 4 days. In this complex, Gly-L-His dipeptide is a tridentate ligand binding to Au(III) through the terminal amino group of glycine, N_A, the deprotonated amide nitrogen, N_P, and the N3 nitrogen of the imidazole ring. The same complex was previously obtained in reaction between this dipeptide and $[AuCl_4]^-$ at pH 1.50 and square-planar geometry of $[Au(Gly\text{-}L\text{-}His\text{-}N_A,N_P,N3)Cl]NO_3 \cdot 1.25H_2O$ was determined by the application of ^{1}H NMR spectroscopy and X-ray crystallography [16]. The proton NMR chemical shifts of this complex are identical with those presently reported for **4** (table 1). The tridentate

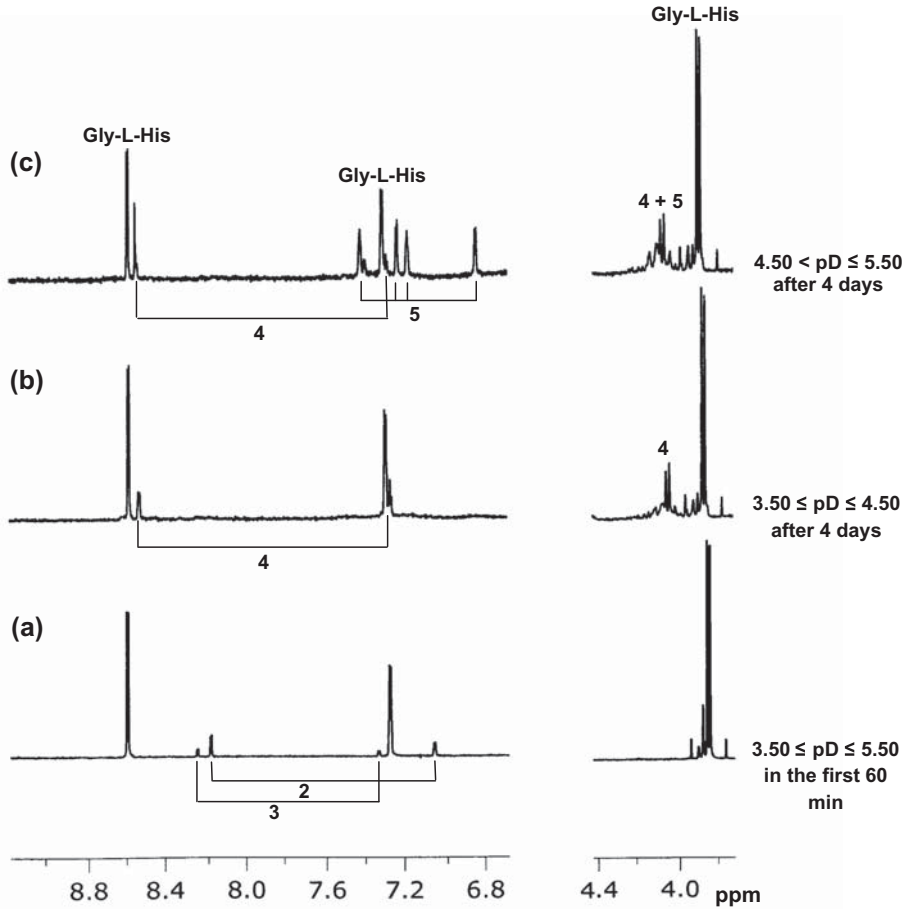

Figure 5. Parts of proton NMR spectra for reaction between equimolar amounts of $[Au(dien)Cl]^{2+}$ and Gly-L-His recorded at pD 4.50 (a and b) and 5.50 (c).

coordination of Gly-L-His caused release of dien from $[Au(dien)Cl]^{2+}$, which can be easily detected in the ^1H NMR spectrum. Intensities of two multiplets of the methylene dien protons due to the coordinated ligand decreased and a new multiplet at 3.22–3.29 ppm appeared (table 1). Upon addition of dien to the reaction mixture, the resonances of this multiplet were enhanced. The amount of **4** was determined from the known initial concentration of Gly-L-His and from the integrated resonance of the C2H proton of **4**; 10% of this complex was formed after 2 days and 26% when the reaction was carried out at pD 4.50 during 4 days (figure 2(b)). However, when the reaction between $[Au(dien)Cl]^{2+}$ and Gly-L-His was performed at $4.50 < pD \leq 5.50$, a new complex **5** along with the already described **4** appeared in solution after 4 days (figure 4). By comparison of the chemical shifts of the C2H and C5H imidazole protons of **5** with those previously reported for the cyclic tetramer $[Au(Gly\text{-}L\text{-}His\text{-}N_A,N_P,N1,N3)]_4 \cdot 10H_2O$ [15], we assume that **5** is also an imidazole-bridged oligomeric species (table 1). This assumption is supported by the fact that chloride in the fourth coordination site of **4** can be easily replaced by the deprotonated N1 imidazole nitrogen of the second monomeric $[Au(Gly\text{-}L\text{-}His\text{-}N_A,N_B N3)]^+$ [15]. Tetramer structures

have been described for Gly-L-His complexes of Ni(II) and Pd(II) formed between pH 9.00 and 10.00 [37]. $[Au(dien)Cl]^{2+}$ can coordinate to imidazole N1 of [Au(Gly-Gly-L-His-N_A, N_{P1},N_{P2},*N3*)]$^+$ at pH values as low as 3.50 [38]. The total amount of **5** was calculated by applying the method already explained for **4** and it was found that about 20% of this complex formed at pD 5.50 after 4 days (figure 2(b)). In order to confirm that **5** represents a Au(III)-imidazole bridged species, we performed an additional experiment. Solution containing $[Au(dien)Cl]^{2+}$ and Gly-L-His dipeptide at pD 7.00 was left at room temperature for several days in the dark. The reddish-brown precipitate formed under these conditions was dissolved in D_2O and the ^1H NMR spectrum of this precipitate was almost identical with that for the cyclic tetramer [Au(Gly-L-His-N_A,N_P,*N1,N3*)]$_4$·10H_2O [15]. No influence of excess of $[Au(dien)Cl]^{2+}$ or Gly-L-His on the coordination mode of this dipeptide was observed. However, the rate of this reaction was increased by increasing amount of reactants.

4. Conclusions

At $3.50 \leq pD \leq 5.50$ and at 25 °C, $[Au(dien)Cl]^{2+}$ selectively binds to N3 imidazole nitrogen of the dipeptide containing an N-terminal histidine, L-His-Gly. This reaction was completed within 3 min and the resulting complex was stable for several days with no release of dien from Au(III). Reaction of this gold(III) complex with the dipeptide containing a C-terminal histidine, Gly-L-His, depends on the pD value with different Au(III)-dipeptide complexes observed. This study contributes to better understanding of the quite complicated mechanism of reactions between antitumor-active gold(III) complexes and biomolecules, such as histidine-containing peptides.

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