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Hydrolysis of the Peptide Bond in *N*-Acetylated *L*-Methionylglycine Catalyzed by Various Palladium(II) Complexes: Dependence of the Hydrolytic Reactions on the Nature of the Chelate Ligand in *cis*-$[Pd(L)(H_2O)_2]^{2+}$ Complexes

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Summary. Hydrolytic reactions between various palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$ in which *L* is ethylenediamine (*en*), 1,2-propylenediamine (1,2-*pn*), isobutylenediamine (*ibn*), 1,2-diaminocyclohexane (1,2-*dach*), *N*-methylethylenediamine (*Meen*), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Me_4en), *S*-methyl *L*-cysteine (*Me*S-*L*-H*Cys*), *L*-methionine (*L*-H*Met*), and 2,5-dithiahexane (*dth*) and dipeptide *N*-acetylated *L*-methionylglycine (*Me*CO*Met-Gly*) were studied by ^{1}H NMR spectroscopy. The reactions were carried out in the *pH* range 2.0–2.5 and at 50°C. In all these reactions, palladium(II) complex bound to a methionine residue effects the regioselective cleavage of the amide bond involving the carboxylic group of methionine. We found that the rate of hydrolysis and mechanism of this reaction are strongly dependent from the nature of the chelate ligand *L* in palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$.

Keywords. Palladium(II) complexes; Hydrolysis; Methionine-containing peptides.

Introduction

Many biological processes involve hydrolysis of peptides and proteins, but relatively little is known about the mechanism of this reaction. The extreme inertness

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of the amide bond makes this reaction interesting from the chemical point of view. Several proteolytic enzymes are used for cleavage [1], but very often application of enzymes is limited by their rather narrow requirements for temperature and *pH*. However, transition-metal complexes hold promise as new reagents for protein cleavage by various mechanisms. Several cobalt(III) complexes coordinate to peptides and facilitate hydrolysis, but they cleave only the N-terminal amino acid [2]. However, practical applications usually require cleavage of internal amide bonds. Studies with some iron-*EDTA* complexes that are covalently attached to amino acid side chains revealed some mechanistic features of these hydrolytic reactions, but they did not result in practical methods for analytical biochemistry [3–12]. Recently, *Kostić* and coworkers have shown that platinum(II) [13] and palladium(II) [14–21] aqua complexes can be promising reagents for hydrolytic cleavage of peptides and proteins. These complexes bind to the heteroatom in the side chain of methionine [13–17] or histidine [18–21] and promote cleavage of the amide bond involving the carboxylic group of this anchoring amino acid. The mechanism of this regioselective hydrolytic reaction catalyzed by platinum(II) and palladium(II) aqua complexes has not been completely understood yet. For clarification of this mechanism it was necessary to investigate the influence of different factors on this hydrolytic reaction, such as *pH*, temperature, steric effects of substrate, and catalyst. Recently, hydrolytic reactions between various palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$ in which *L* is a bidentate coordinated ligand and *N*-acetylated *L*-histidylglycine have been investigated [22]. In all these reactions the regioselective cleavage of the amide bond involving the carboxylic group of histidine was confirmed. Moreover, the obtained results showed that the rate of the hydrolysis decreases as the steric bulk of the palladium(II) complex increases. Giving the importance to the recent results with *cis*-$[Pd(L)(H_2O)_2]^{2+}$ and histidine-containing peptides it seems to us reasonable to investigate the effects of these palladium(II) complexes on the rate of hydrolysis and mechanism of the hydrolytic reaction of methionine-containing peptides.

The present study deals with hydrolysis of the peptide bond in *N*-acetylated *L*-methionylglycine catalyzed by various palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$ in which *L* are different chelating ligands.

Results and Discussion

Regioselective Hydrolysis of Peptide Bond in MeCOMet-Gly

In the present study hydrolytic reactions between various palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$ (*L* is ethylenediamine (*en*), 1,2-propylenediamine (1,2-*pn*), isobutylenediamine (*ibn*), 1,2-diaminocyclohexane (1,2-*dach*), *N*-methylethylenediamine (*Meen*), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Me_4en), *S*-methyl *L*-cysteine (*Me*S-*L*-H*Cys*), *L*-methionine (*L*-H*Met*), and 2,5-dithiahexane (*dth*)) and dipeptide *N*-acetylated *L*-methionylglycine (*Me*CO*Met-Gly*) were studied by ^{1}H NMR spectroscopy. The palladium(II) complexes are as shown in Fig. 1. The reactions between these palladium(II) complexes and *Me*CO*Met-Gly* were carried out at 50°C and at $2.0 < pH < 2.5$. As was shown in previous studies [18–20, 23], acidic solutions are needed to suppress the formation of hydroxo-bridged oligomeric

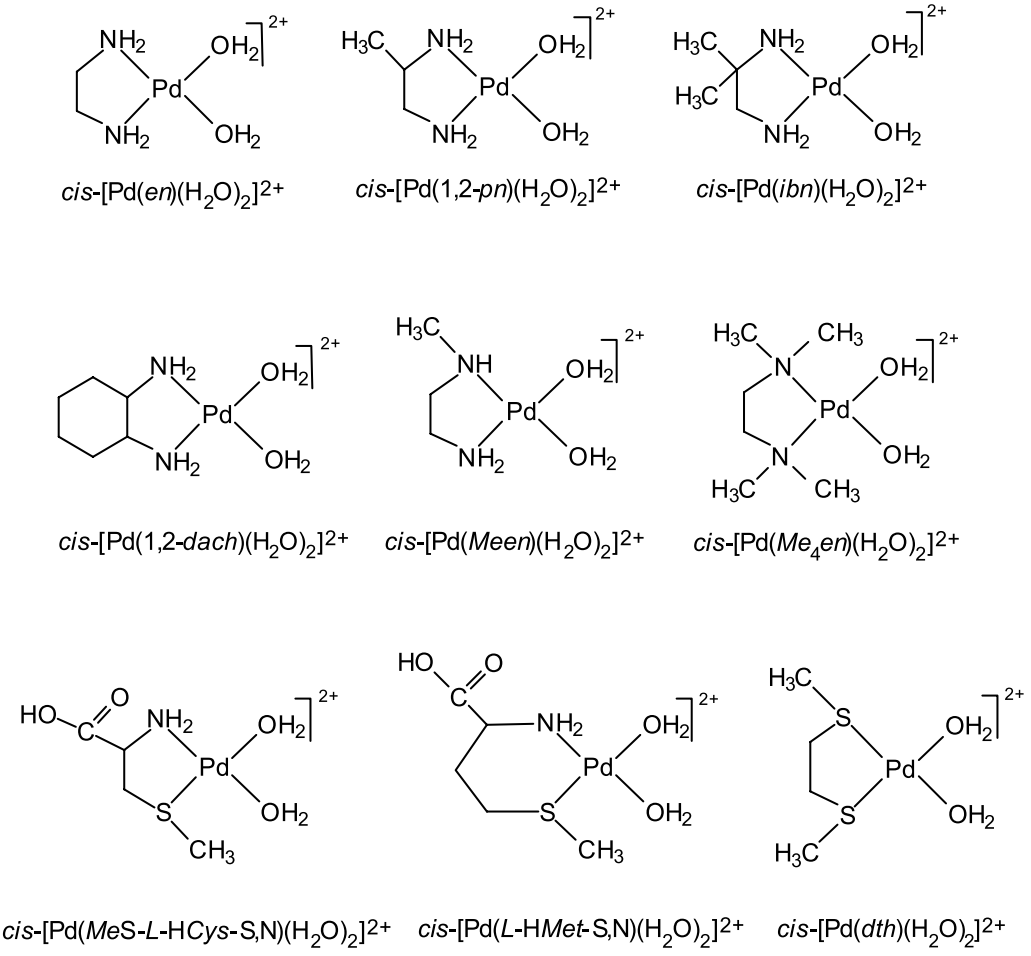
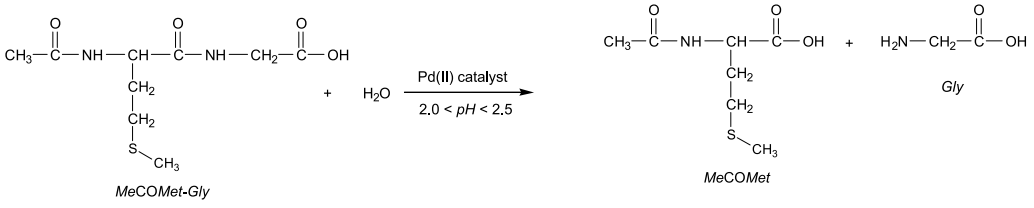


Fig. 1. Palladium(II) complexes used in the reactions with *Me*CO*Met-Gly*

palladium(II) complexes which are catalytically inactive. In all these reactions only the cleavage of the amide bond involving the carboxylic group of methionine was observed (see Scheme 1). Mixing of the palladium(II) complex with an equimolar amount of the peptide under the above described experimental conditions resulted in a spontaneous coordination of palladium(II) complex to the sulfur atom of the methionine residue. The binding of the palladium(II) to the methionine side chain is very fast and it is noticed from the simultaneous decline



Scheme 1

of the resonance at 2.11 ppm due to the S-methyl protons of the free *Me*CO*Met-Gly* and growth of the resonance at 2.54 ppm corresponding to the S-methyl protons of the peptide coordinated to palladium(II) through the sulfur atom.

Dependence of the Hydrolytic Reactions on the Nature of Ligand L in cis-[Pd(L)(H$_2$O)$_2$]$^{2+}$

The hydrolytic reactions of the methionine-containing peptides with palladium(II) complexes have been studied by *Kostić* and coworkers in the great detail [24]. From the NMR spectra they have concluded that different promoters produce different hydrolytically active palladium(II)-peptide complexes. When the promoter is $[PdCl_4]^{2-}$, the active form is a mononuclear palladium(II)-peptide complex, whereas with promoter $[Pd(H_2O)_4]^{2+}$ a binuclear complex with two sulfur atoms of the two methionine side chains as bridges and water molecules in the unspecified terminal positions was produced. It was shown that this binuclear complex is more efficient than the corresponding mononuclear complex in promoting hydrolysis of the scissile amide bond. Additionally, it was also found that with methionine-containing peptides and *cis*-[Pd(*en*)(H$_2$O)$_2$]$^{2+}$, *cis*-[Pd(*Me$_4$en*)(H$_2$O)$_2$]$^{2+}$, and *trans*-[Pd(*py*)$_2$(H$_2$O)$_2$]$^{2+}$ complexes the nitrogen coordinated ligands were replaced with water molecules, and presumably the same active complex is formed as from $[Pd(H_2O)_4]^{2+}$ [25]. In the reaction of *cis*-[Pd(*dtco*)(H$_2$O)$_2$]$^{2+}$ (*dtco* is 1,5-dithiacyclooctane having two sulfur atoms coordinated to palladium(II)) with methionine-containing peptides the above mentioned authors found that in solution a binuclear palladium(II)-peptide complex with two bidentate *dtco* ligands in the unspecified positions and two methionine side chains as bridges is present [24]. Although this binuclear complex has no aqua ligands it has been shown as catalytically active form. The catalytic ability of this binuclear complex was explained through the dissociation of one of the bridging substrate and formation of a single-bridged palladium(II)-peptide complex, which contains two aqua ligands in a favorable position and which are needed for the cleavage of the remaining bridged substrate.

The nine Pd(II) complexes in Fig. 1 differ in the chelate ligand. The palladium(II) complexes *cis*-[Pd(*en*)(H$_2$O)$_2$]$^{2+}$, *cis*-[Pd(1,2-*pn*)(H$_2$O)$_2$]$^{2+}$, *cis*-[Pd(*ibn*)(H$_2$O)$_2$]$^{2+}$, *cis*-[Pd(*Meen*)(H$_2$O)$_2$]$^{2+}$, *cis*-[Pd(*Me$_4$en*)(H$_2$O)$_2$]$^{2+}$, and *cis*-[Pd(1,2-*dach*)(H$_2$O)$_2$]$^{2+}$ have a bidentate diamine ligand. In relation to *en* and 1,2-*dach* ligands other chelated diamine ligands in these complexes contain different numbers of methyl groups at the nitrogen or carbon atom. The palladium(II) complexes *cis*-[Pd(*Me*S-*L*-H*Cys*-S,N)(H$_2$O)$_2$]$^{2+}$ and *cis*-[Pd(*L*-H*Met*-S,N)(H$_2$O)$_2$]$^{2+}$ have the S,N-coordinated amino acid as bidentate ligand. These two complexes differ in the ring size of the chelate ligand. The later *cis*-[Pd(*dth*)(H$_2$O)$_2$]$^{2+}$ complex in Fig. 1 has a bidentate ligand coordinated through two sulfur atoms. We have found that in the reactions of all palladium(II) complexes of the type *cis*-[Pd(*L*)(H$_2$O)$_2$]$^{2+}$ with *Me*CO*Met-Gly* the ^{1}H NMR resonance at $\delta = 3.96$ ppm corresponding to the glycine protons of the none hydrolyzed peptide decreased, while that at $\delta = 3.76$ ppm for free glycine increased. Upon addition of glycine to the reaction mixture its resonance is enhanced. The amounts of the unreacted peptide and the hydrolysis products were determined from the known initial concentration of *Me*CO*Met-Gly* and from integrated resonance of the free glycine. Some of the liberated glycine reacts with the catalyst to form a

Table 1. Hydrolysis of the amide bond in *Me*CO*Met-Gly* promoted by various palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$ at $2.0 \leq pH \leq 2.5$ at 50°C

Palladium(II) complex	Hydrolyzed amide bond after four hours/%
cis-$[Pd(en)(H_2O)_2]^{2+}$ *cis*-$[Pd(1,2\text{-}dach)(H_2O)_2]^{2+}$ *cis*-$[Pd(1,2\text{-}pn)(H_2O)_2]^{2+}$ *cis*-$[Pd(ibn)(H_2O)_2]^{2+}$ *cis*-$[Pd(Meen)(H_2O)_2]^{2+}$ *cis*-$[Pd(Me_4en)(H_2O)_2]^{2+}$	80–88
cis-$[Pd(L\text{-}HMet\text{-}S,N)(H_2O)_2]^{2+}$	58
cis-$[Pd(MeS\text{-}L\text{-}HCys\text{-}S,N)(H_2O)_2]^{2+}$	42
cis-$[Pd(dth)(H_2O)_2]^{2+}$	50

small amount of the bis(bidentate) complex *cis*-$[Pd(L)(Gly\text{-}N,O)]^{+}$ easily detected by ^{1}H NMR spectroscopy by the resonance at $\delta = 3.52$ ppm. Indeed, the same complex is formed upon mixing of equimolar amounts of *cis*-$[Pd(L)(H_2O)_2]^{2+}$ and glycine. Catalytic ability of each *cis*-$[Pd(L)(H_2O)_2]^{2+}$ in the investigated reactions was determined by measuring the amount of the hydrolyzed peptide during time at the same experimental conditions. The concentration of the free and the hydrolyzed peptide was determined every 15 min and all reactions were followed for ten hours. During the first four hours the amount of hydrolytic products has been increasing whereas in the later stage in all investigated reactions no significant changes were observed. The amount of the hydrolyzed peptide in these reactions after four hours is given in Table 1.

Our results showed that in the reactions between palladium(II) complexes with chelated diamine ligands (*en*, 1,2-*pn*, *ibn*, 1,2-*dach*, *Meen* and Me_4en) the rate of the hydrolysis was approximately the same and the amount of hydrolyzed peptide after 4 h was between 80–88%. The schematic presentation of the reactions between diamine-palladium(II) complexes and *Me*CO*Met-Gly* is given in Fig. 2. From the intermediate binuclear palladium(II) complex **1** bidentate coordinated diamine ligands have been displaced by water molecules and with all diamine-palladium(II) complexes presumably the same active complex **1a** is formed. The replacement of chelated diamine ligands by water molecules is very fast and this reaction is additionally supported by the *trans*-effect of the bridged sulfur atom of methionine side chain and acidic medium ($2.0 < pH < 2.5$). A sharp ^{1}H NMR singlet for methylene protons of the free *en*, *Meen*, Me_4en, *ibn* or slightly broader signal of these protons for 1,2-*pn*, all at 3.34–3.40 ppm, indicates complete detachment of these ligands from Pd(II). In the reaction between *cis*-$[Pd(1,2\text{-}dach)(H_2O)_2]^{2+}$ and *Me*CO*Met-Gly* detachment of the 1,2-*dach* ligand from Pd(II) was monitored by disappearance of the resonances at 2.48–2.58 ppm for C-1 and C-2 methine protons of 1,2-*dach* ligand coordinated to Pd(II) and the enhancement of these resonances at 3.30–3.50 ppm for free diamine ligand. The binuclear complex **1a** was also observed by *Chen at al*. in the reaction of *cis*-$[Pd(en)(H_2O)_2]^{2+}$ and *trans*-$[Pd(py)_2(H_2O)_2]^{2+}$ with *Me*CO*Met-Gly* [25]. As all the aqua ligands in complex **1a** are in the *cis* position to the substrate, any of them can be delivered to

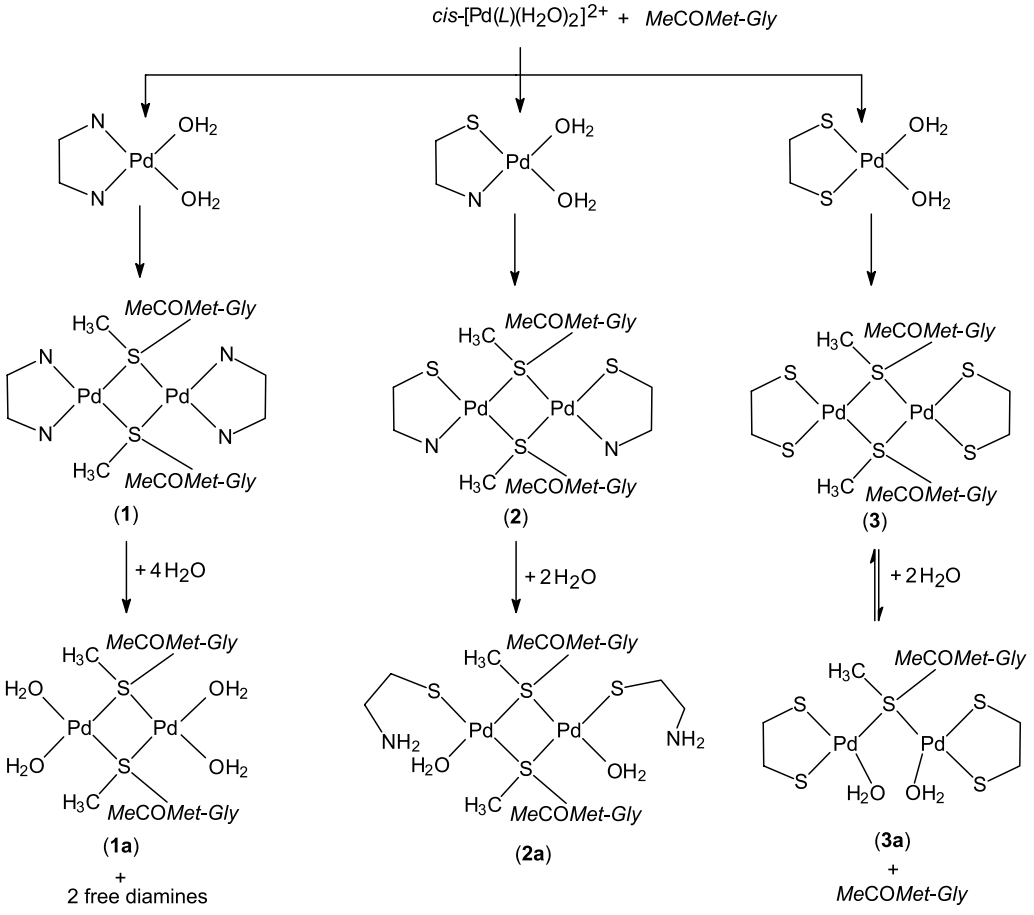


Fig. 2. Different pathways of the hydrolytic reactions between various palladium(II) complexes of the type *cis*-[Pd(*L*)$(H_2O)_2]^{2+}$ and *Me*CO*Met-Gly* at $2.0 \leq pH \leq 2.5$ at 50°C

the scissile peptide bond. Summing up we can say that all *cis*-[Pd(*L*)$(H_2O)_2]^{2+}$ complexes with *L* as diamine chelate ligand produce the same hydrolytic active form in solution. These facts should be taken in account for explanation of their approximately equal hydrolytic abilities in the reactions with methionine-containing peptides (see Table 1).

In the reaction between *Me*CO*Met-Gly* and palladium(II) complexes with S,N-coordinated amino acids *cis*-[Pd(MeS-*L*-HCys-S,N)$(H_2O)_2]^{2+}$ and *cis*-[Pd(*L*-HMet-S,N)$(H_2O)_2]^{2+}$ we assumed that hydrolytically active form is binuclear complex **2a** (Fig. 2). This complex was produced from the complex **2** by ring opening of the S,N-coordinated amino acid. This ring opening reaction was also observed between these two complexes and *Ala-His*, *Gly-His*, and *Ser-His* dipeptides [26]. In relation to the hydrolytically active complex **1a** in the complex **2a** there is only one water molecule per palladium(II). The water molecule is in the *cis* position to the scissile peptide bond of the peptide. Also, this can be the reason for less hydrolytic abilities of these complexes in relation to those with diamine chelate ligands (see Table 1). The complex *cis*-[Pd(*L*-H*Met*-S,N)$(H_2O)_2]^{2+}$ with a six-membered chelate ring is more hydrolytically powerful than the *cis*-[Pd(*Me*S-*L*-H*Cys*-S,N)$(H_2O)_2]^{2+}$ because the

later complex has a more stable five-membered chelate ring and its ring opening reaction is much slower. In the reactions between these complexes and *Me*CO*Met-Gly* the signal at 2.11 ppm due to the uncoordinated CH_3S group of *L*-H*Met* or *Me*S-*L*-H*Cys* did not appear in the ^{1}H NMR spectrum for 10 h. This is in accordance with the fact that these amino acids during this time are coordinated through the sulfur atom to Pd(II).

In the reaction between *cis*-$[Pd(dth)(H_2O)_2]^{2+}$ and *Me*CO*Met-Gly* the binuclear complex **3** (Fig. 2), as an intermediate product, having two bidentate *dth* ligands in unspecified positions, has been formed. This complex has no aqua ligands but promotes hydrolysis nevertheless. A similar binuclear complex has been found in the reaction of *cis*-$[Pd(dtco)(H_2O)_2]^{2+}$ with this peptide [24]. Hydrolytic activity of complex **3** occurred through the dissociation of one of the bridged peptides and formation of the single bridged complex **3a** with only one water molecule per palladium(II) in favorable position for cleavage of the remaining substrate ligand (Fig. 2). Hydrolytic ability of this complex is similar with those for *cis*-$[Pd(L\text{-}HMet\text{-}S,N)(H_2O)_2]^{2+}$ and *cis*-$[Pd(MeS\text{-}L\text{-}HCys\text{-}S,N)(H_2O)_2]^{2+}$ (see Table 1). This should be reasonable because their hydrolytically active complexes present in solution are structurally similar and both have only one water molecule per palladium(II) which is necessary for hydrolysis of the scissile peptide bond.

Conclusion

With all investigated palladium(II) complexes of the type *cis*-$[Pd(L)(H_2O)_2]^{2+}$ only hydrolysis of the *Met-Gly* amide bond of *Me*CO*Met-Gly* was observed. The palladium(II) complexes with chelate diamine ligands (*L*) are more effective in promoting the cleavage of the scissile amide bond than those with bidentate S,N-coordinated amino acids *L*-H*Met* or *Me*S-*L*-H*Cys* and with chelating thioether *dth* ligand. The differences in hydrolytic abilities of the investigated palladium(II) complexes are in accordance with different Pd(II)-peptide active forms present in solution.

Experimental

Distilled water was demineralized and purified to a resistance greater than 10 MΩ · cm. The compounds D_2O, DNO_3, NaOD, and $K_2[PdCl_4]$ were obtained from Aldrich Chemical Co. All common chemicals were of reagent grade. Dipeptide *L*-methionylglycine, amino acids *S*-methyl-*L*-cysteine and *L*-methionine were obtained from Sigma Chemical Co. The terminal amino group in *Me*CO*Met-Gly* was acetylated by standard methods [14]. All *pH* measurements were made at 25°C. The *pH* meter (Iskra MA 5704) was calibrated with Fischer certified buffer solutions of pH 4.00 and 7.00. The results were not corrected for the deuterium isotope effect. Elemental microanalyses for carbon, hydrogen, and nitrogen were done by the Faculty of Chemistry, University of Belgrade. Their results agreed favourably with calculated values.

Preparation of cis-[PdCl$_2$(L)] Complexes

Method A. L is ethylenediamine ($PdC_2H_8N_2Cl_2$), 1,2-propylenediamine ($PdC_3H_{10}N_2Cl_2$), isobutylenediamine ($PdC_4H_{12}N_2Cl_2$), 1,2-diaminocyclohexane ($PdC_6H_{14}N_2Cl_2$), *N*-methylethylenediamine ($PdC_3H_{10}N_2Cl_2$), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine ($PdC_6H_{16}N_2Cl_2$).

These complexes were prepared by a modification of the method of *van Eldik et al.* [27]. K_2PdCl_4 (0.1632 g, 0.50 mmol) was dissolved in 25 cm^3 of water, and to this solution an equivalent amount of the corresponding diamine ligand (*L*) was added. The *pH* of the solution was adjusted to 2–3 by the addition of 0.1 *M* HCl, which was followed by further refluxing for 5 h. If the *pH* is controlled carefully, a clear color change from brown to yellow is observed during this time. The obtained yellow solution was left overnight at room temperature. The crystals were removed by filtration, washed with a small amount of ethanol, and air-dried. Depending of the type of diamine ligand (*L*) the yield of *cis*-[$PdCl_2$(*L*)] complex was between 65–80%.

Method B. L is *S*-methyl *L*-cysteine ($PdC_4H_9O_2NSCl_2$) and *L*-methionine ($PdC_5H_{11}O_2NSCl_2$).

The complexes *cis*-[$PdCl_2$(*L*-H*Met*-S,N)] and *cis*-[$PdCl_2$(*Me*S-*L*-*Cys*-S,N)] were synthesized according to the literature procedures for the synthesis of palladium(II) and platinum(II) complexes of methionine and its derivatives [28–32]. K_2PdCl_4 (0.1632 g, 0.50 mmol) was dissolved in 3 cm^3 of water, and to this solution an equimolar amount of *L*-methionine (0.0746 g) or *S*-methyl-*L*-cysteine (0.0676 g) dissolved in 3 cm^3 of water was added. The *pH* of the mixture was adjusted to *ca.* 2 by the slow addition of 0.1 *M* HCl and then the reaction mixture was heated at 50–60°C with stirring for 1 h. The obtained solution was cooled at room temperature and then left overnight in a refrigerator. The yellow crystals of *cis*-[$PdCl_2$(*L*-H*Met*-S,N)] or *cis*-[$PdCl_2$(*Me*S-*L*-*Cys*-S,N)] complex were removed by filtration, washed with a small amount of ethanol, and air-dried. The yield was 0.1200 g (73.5%) for *cis*-[$PdCl_2$(*L*-H*Met*-S,N)] and 0.1170 g (74.9%) for *cis*-[$PdCl_2$(*Me*S-*L*-H*Cys*-S,N)].

Method C. L is 2,5-dithiahexane ($PdC_4H_{10}S_2Cl_2$).

2,5-Dithiahexane ligand was prepared as described in Ref. [33]. This ligand was used for preparation of *cis*-[$PdCl_2$(*dth*)] complex by modification of the method for preparation of the analogue Pt(II) complex [34]. A solution of K_2PdCl_4 (0.2088 g, 0.64 mmol) in 20 cm^3 of water was added slowly to *dth* (0.0785 g, 0.64 mmol) in a 50 cm^3 round-bottomed flask equipped with a dropping funnel, with stirring at room temperature. The reaction mixture was then heated at 60–70°C with stirring for 2 h. The yellow precipitate was removed by filtration, washed with cold water, and air-dried. Yield 0.1430 g (74.6%).

Preparation of cis-[Pd(L)(H$_2$O)$_2$]$^{2+}$ Complexes

All *cis*-[Pd(*L*)$(H_2O)_2]^{2+}$ complexes were prepared on the same way by using the procedure described in literature for preparation of aqua complexes from corresponding chloro complexes of Pt(II) and Pd(II) [35, 36]. The *cis*-[$PdCl_2$(*L*)] complex was treated in D_2O solution with the appropriate amount of $AgNO_3$. The Pd(II) complex and $AgNO_3$ were mixed in 1:1.95 molar ratio to avoid an excess of Ag^+ ion in final solution of the aqua complex. The mixture was stirred at room temperature in the dark for up to 24 h. The precipitate of AgCl was removed and the filtrate containing the aqua complex was stored in the refrigerator and further used for the reaction with peptide.

Reactions of Peptide with Palladium(II) Complexes

Reactions of *Me*CO*Met-Gly* with palladium(II) complexes in D_2O solutions were followed by ^{1}H NMR spectroscopy using a Bruker 250 spectrometer. Equimolar amounts of the palladium(II) complex and the peptide were mixed in an NMR tube. The final solution was 30 *mM* in each reactant. The *pH* was varied in the range of 2.0–2.5. All reactions were carried out at 50°C. The internal reference was *TSP* (sodium trimethylsilylpropane-3-sulfonate).

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