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COORDINATION COMPOUNDS

Mixed-Ligand Palladium(II) Complexes with Amino Acids, Cytosine, and Adenine

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Abstract—pH titration shows that 1 : 1 : 1 mixed-ligand complexes are formed in the systems palladium(II)–Cyt–Glu–H_2O ($\log\beta$ = 19.73) and palladium(II)–Cyt–Lys–H_2O ($\log\beta$ = 16.20). Complexes $Pd(C_5H_5N_5)(C_5H_8NO_4)Cl$, $Pd(C_5H_5N_5)(C_6H_{13}N_2O_2)Cl$, $Pd(C_4H_5N_3O)(C_6H_{13}N_2O_2)Cl$, and $Pd(C_4H_5N_3O)(C_5H_8NO_4)Cl$ are synthesized and characterized by chemical analysis, X-ray powder diffraction, and thermogravimetry. The coordination mode of amino acids, cytosine, and adenine to the palladium(II) ion is determined.

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Complexes of the platinum-group metals have been actively studied with the goal of preparing new antitumor medicines. The use of platinum(II)-based medicines is limited by side reactions. Therefore, the attention of researchers has been focused on palladium(II) compounds, which are far less toxic [1–6].

Mixed-ligand complexes of transition metals are mediators of bioreactions in living organisms and intermediates of technological processes.

Mixed-ligand complexes of palladium(II) with amino acids, purine bases, and pyrimidine bases were studied in [7–9].

We studied the interaction of palladium(II) with adenine ($C_5H_5N_5$, Ade), cytosine ($C_4H_5N_3O$, Cyt), glutamic acid ($C_5H_9NO_4$, Glu), and lysine ($C_6H_{14}N_2O_2$, Lys).

Potentiometric titration. pH titration showed that 1 : 1 : 1 mixed-ligand complexes are formed in the palladium(II)–Cyt–Glu–H_2O and palladium(II)–Cyt–Lys–H_2O systems. The reagents used were 0.01 M solutions of H_2PdCl_4, which was synthesized as described in [10], and 0.01 M solutions of cytosine, lysine, and glutamic acid. An ionic strength was adjusted at 0.1 mol/L with a 1 M KNO_3 solution. The experiments were carried out at +(0–21)°C over a wide pH range. The titrant used was a 0.1 KOH solution. The starting volume of the titrated solutions was 50 mL.

We failed to determine stability constants for palladium(II) complexes with adenine by potentiometric titration because of the low solubility of the complexes.

SCOGS software was used to calculate the stability constants of mixed-ligand complexes [11]. The ionization constants of ligands used in the calculations were determined by titrating amino acid and cytosine solutions with 0.1 M HCl and KOH as in [12]: for Cyt, pK_1 = 4.32 and pK_2 = 11.56; for Lys, pK_1 = 2.35, pK_2 = 9.08, and pK_3 = 10.54; and for Glu, pK_1 = 2.31, pK_2 = 4.46, and pK_3 = 9.72; we also used the stability constants of binary complexes calculated by the Bjerrum technique [13].

System	$\log K_1$	$\log K_2$	$\log K_3$
Pd(II)–Cyt–H_2O	10.70	8.60	
Pd(II)–Glu–H_2O	8.52	6.85	5.84
Pd(II)–Lys–H_2O	6.30	5.50	

The titration curves for the Pd(II)–Cyt–Glu–H_2O and Pd(II)–Cyt–Lys–H_2O systems lie below the titration curves for amino acids and the pyrimidine base. The stability constants of mixed-ligand complexes are as follows: $\log\beta$ (Pd(II)–Cyt–Glu) = 19.73 and $\log\beta$ (Pd(II)–Cyt–Lys) = 16.20.

Synthesis of complexes. Mixed-ligand complexes $Pd(Cyt)(Glu^-)Cl$ and $Pd(Cyt)(Lys^-)Cl$ were synthesized by mixing 0.01 M solutions of the reagents in the 1 : 1 : 1 (mol/mol) ratio. The solution was concentrated to a viscous mass on a water bath; then, it was repeatedly treated with ethanol and acetone until a green-brown precipitate appeared. The precipitate was filtered, rinsed with acetone and ether, dried to constant weight, and then analyzed.

Because palladium(II) forms sparingly soluble compounds with adenine, complexes $Pd(Ade)(Lys^-)Cl$ and $Pd(Ade)(Glu^-)Cl$ were prepared by a different procedure, as follows. A 1 : 1 mixture of 0.01 M solutions of H_2PdCl_4 and lysine was concentrated to one-third its initial volume on a water bath, then an equimolar amount of a hot adenine solution was added. A precipitate was filtered, rinsed with an acetone + ethanol

Results of chemical analysis of complexes

Compound	Mr	Found/calcd., %			
		Pd	N	C	H
$Pd(C_4H_5N_3O)(C_5H_8NO_4)Cl$ (**I**)	398.2	26.85/26.72	14.10/14.06	27.05/27.12	3.15/3.26
$Pd(C_4H_5N_3O)(C_6H_{13}N_2O_2)Cl$ (**II**)	399.1	26.75/26.66	17.60/17.54	30.02/30.07	4.42/4.51
$Pd(C_5H_5N_5)(C_6H_{13}N_2O_2)Cl$ (**III**)	422.0	25.10/25.21	23.50/23.22	31.82/31.28	4.45/4.26
$Pd(C_5H_5N_5)(C_5H_8NO_4)Cl$ (**IV**)	422.2	25.10/25.20	19.80/19.90	28.35/28.42	3.15/3.08

(1 : 2) mixture, and then stored in a desiccator until water was completely removed.

The compounds were identified and their formulas determined by chemical analysis, thermogravimetry, X-ray powder diffraction, and IR spectroscopy.

Palladium was determined gravimetrically [14]. Carbon, nitrogen and hydrogen were determined by combustion and the absorption of the products on a Carlo Erba CHNS-O EA 1108 Elemental Analyzer [15]. The results of chemical analyses are tabulated.

X-ray powder diffraction (DRON-2, monochromatic CuK_α radiation, 1/4 deg/min) implies that all compounds were individual.

Thermogravimetric analysis (MOM derivatograph, 20–1000°C, 10 K/min, Al_2O_3 reference) showed that all compounds have identical thermal curves. At 200–500°C, the melting occurs, which is followed by decomposition of complexes because of the destruction and burning up of the organic part of the molecule. The final thermolysis product is metallic palladium with minor carbon.

IR spectra (400–4000 cm^{-1}) were recorded as KBr disks on Specord 75IR and Specord M82 spectrophotometers. IR absorption spectra were assigned with reference to the assignment of the spectra of the reagents and analogues [16–18].

The IR spectra of the complexes differ from the spectra of free ligands, indicating that the ligands are coordinated to a palladium(II) ion. The similarity of the spectra of $Pd(C_4H_5N_3O)(C_5H_8NO_4)Cl$ and $Pd(C_4H_5N_3O)(C_6H_{13}N_2O_2)Cl$ implies the identical bonding of palladium(II) atoms with amino acids and cytosine in these complexes.

Some vibrational bands (at 1536, 1184, and 1099 cm^{-1}) can be assigned to the N–H bending vibrations in the α-amino group of the amino acid, which apparently interacts with the metal.

The vibrations at 1634 and 1412 cm^{-1} are likely due to the antisymmetrical and symmetrical vibrations of the COO^- group of the amino acid, which interacts with the metal; the bending vibrations of this group appear at 591 and 535 cm^{-1}.

There is a strong band at 1725 cm^{-1}; it can be assigned to the stretching vibrations of the C=O group of cytosine. this group possibly interacts with palladium(II), because the band shifts relative to the uncomplexed ligand (1704 cm^{-1} in cytosine). The changed frequencies of the stretching vibrations of the pyrimidine ring (1621, 1510, 1464, and 1393 cm^{-1} in complexes against 1601, 1504, 1472, and 1363 cm^{-1} in pure cytosine) confirms that the ligand interacts with the metal. Apparently, the heterocyclic N3 atom interacts with the metal: the in-ring C=N stretching vibrations in the complex appear at 1669 cm^{-1}, and in uncomplexed cytosine at 1633 cm^{-1}. The bending frequencies of the pyrimidine hydrogen atoms experience some shift: 1256 cm^{-1} (1240 cm^{-1}) and 969 cm^{-1} (996 cm^{-1}). The Pd–N vibrations appear about 422 cm^{-1}.

Presumably, cytosine is coordinated to palladium(II) through its heterocyclic N3 atom and the carbonyl oxygen atom (C=O). Lysine and glutamic acid are presumably bidentate due to their α-NH_2 and COO^- groups.

The spectra of mixed-ligand complexes with adenine differ from the spectra of the uncomplexed ligands. The differences are in the stretching and bending vibrations of the purine ring. For example, the C=N stretching vibrations in the heterocycle shift toward 1706 cm^{-1} (against 1673 cm^{-1} in adenine). The C=C and C–N bending vibrations in the purine ring are observed at 990–937 and 813–774 cm^{-1} (cf. 1021 and 852–871 cm^{-1} in the pure ligand).

The vibrations in the purine ring appear at 1617, 1586, 1441, and 1380 cm^{-1}; they experience a shift relative to the pure ligand (1612, 1510, 1419, 1367 cm^{-1}).

^{13}C NMR spectra of solutions of ligands, either free or complexed, were recorded with suppression of proton signals on a high-resolution Fourier-transform Bruker AC-200 pulsed spectrometer with a working proton frequency of 200.13 MHz. Chemical shifts were determined relative to external tetramethylsilane.

Analyzing the spectroscopic data, we observe changes in the chemical shifts for all ^{13}C signals from lysine in compounds **II** and **III** relative to the uncomplexed ligand. The displacement of the chemical shifts of signals from the carboxy carbon atom of lysine ($\Delta\delta C^1$ = 2.98 ppm) proves that this carboxy group is chemically bonded to a palladium(II) ion. The displacement of the chemical shift for signals from the C^3 atom ($\Delta\delta C^3$ = 2.69 ppm) indicates the involvement of the

α-NH_2 group in chemical bond with a palladium(II) ion. Inasmuch as the displacement of the chemical shifts of signals from the C^6 atom of lysine cannot be evaluated (this signal is under the DMSO signal), the participation of the ε-amino group of the ligand can be suggested circumstantially (on the basis of the displacement of the chemical shifts of the C^5 signals relative to uncomplexed lysine). The significant displacement of the chemical shift of the C^5 signal from lysine ($\Delta\delta$ = 2.10 ppm) can signify that the ε-amino group of the ligand interacts with another palladium ion.

Thus, lysine is coordinated to a metal ion through its carboxy oxygen atom and the nitrogen atom of the α-amino group; the ε-amino group of lysine participates in intermolecular bonds.

The ^{13}C-{^1H} NMR spectra of complexes **III** and **IV** show that all coordination sites of adenine are involved in bonding to the metal. The maximum changes in the chemical shifts relative to the uncomplexed ligand are observed for the C^5 and C^8 atoms of adenine (10.08 and 8.27 ppm, respectively); this observation can indicate that the preferred coordination mode of adenine to a palladium(II) ion is through the heterocyclic N7 atom (possibly, because of proton mobility, through the N9 atom). The amino group of adenine is presumably hydrogen-bonded to the water oxygen atom.

With reference to the related literature [19] and NMR spectroscopic data, we may suggest that adenine interacts with palladium(II) through its heterocyclic nitrogen atom (probably, the N7(N9) atom), while lysine interacts through its carboxy and α-NH_2 groups.

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