Ternary α-Amino Acid-Palladium(II) Complexes with Ligand-Ligand Hydrogen Bonding

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Histidinate(His)-containing ternary α-amino acid–palladium(II) complexes have been studied by synthetic and spectroscopic methods. The following complexes with imidazolate (im), L- and D-His, L-asparaginate (L-Asn), and L-glutaminate (L-Gln) have been isolated as crystals: $[Pd(im)_2]\cdot 0.5H_2O$; [Pd(L-His)(D-His)]·H_2O; [Pd(L-Asn)-(L-His)]·$2H_2O$; [Pd(L-Gln)(L-His)]·$2H_2O$. The ternary systems involving palladium(II), L-His, and an amino acid L-AA with an OH or a $CONH_2$ group (AA=Asn, Gln, serinate, threoninate, or homoserinate) exhibit absorption maxima at 300—311 nm with ε 310—440 and negative and positive circular dichroism (CD) peaks at 307—328 nm and ≈300 nm, respectively. ^{13}C and ^1H NMR spectra gave the amounts of the *cis* and *trans* isomers of Pd(His)-(AA) in solution and confirmed that Pd(His)(AA) has an N_3O donor set in the coordination plane. Whereas the CD magnitude additivity holds for the ternary systems Pd(L-His)(B) with B=glycinate, L-alaninate, or L-valinate and the systems with L-histidine methyl ester (L-HisOMe) and L-AA, Pd(L-HisOMe)(L-AA), the magnitudes for Pd(L-His)(L-AA) deviate significantly from those estimated on the basis of the additivity. The CD magnitude anomaly as well as the geometrical and rotational isomer populations calculated from the ^1H NMR spectra establishes the existence of the ligand-ligand interaction between the carboxylato group of His and the hydroxyl or amido group of AA in solution.

With the recognition of the importance of non-covalent interactions in biological processes,[1] weak intramolecular interactions between coordinated ligands have recently attracted considerable attention. Intramolecular aromatic ring stacking between 2,2′-bipyridine, 1,10-phenanthroline, or tryptophan and the base moiety of nucleosides or nucleotides in the ternary complexes of copper(II), zinc(II), *etc.* has been detected in solution[2–9] and revealed by X-ray analysis of a crystalline copper(II) complex.[10] Electrostatic ligand-ligand interactions in the ternary α-amino acid–copper-(II) complexes have received substantial experimental support,[11–14] and the recent NMR spectroscopic study provides conclusive evidence for their existence in the corresponding palladium(II) complexes.[15] On the other hand, histidinate(His)-containing ternary amino acid–copper(II) complexes with asparaginate (Asn), glutaminate (Gln), citrullinate, serinate (Ser), homoserinate (Hmser), or threoninate (Thr) (abbreviated as AA hereafter) have been inferred to involve hydrogen bonding between the carboxylato group of His and the polar side group of AA.[16] Preferential crystallization of Cu(L-Asn)(L-His) from the solution containing Cu(II), L-Asn, and DL-His in the ratio of 1 : 1 : 1.5 has led to nearly complete optical resolution of histidine,[16,17] which is in support of the stereoselectivity due to the interaction. The molecular structures of [Cu(L-Asn)(L-His)(H_2O)]·$3H_2O$ and [Cu(L-Asn)(L-His)] disclosed by X-ray analysis[18] exhibit difference in the side chain conformation of L-Asn, indicating the side chain flexibility and its accessibility to the histidine carboxylato group axially coordinated to copper(II). Probably because hydrogen bonds are too weak in aqueous solution to affect the stability constants, however, analysis of the solution equilibria in water[16] and in 20% dioxane–water[19] failed to show any effects of the bonding.

As an extention of the studies on copper(II) complexes, we now carried out synthetic and spectroscopic investigations of the corresponding histidinate- and cysteate-($CySO_3H$)-containing ternary palladium(II) systems in order to obtain convincing information on the ligand-ligand interaction in the ternary systems Pd(His)(AA) in solution.

Experimental

Materials. DL-Histidine methyl ester dihydrochloride was prepared according to the literature.[20] L-1-Methylhistidine, L-histidine methyl ester dihydrochloride, and D- and DL-histidine hydrochloride were purchased from Sigma. All the other amino acids were obtained from Nakarai. Disodium hexachloropalladate(II) and palladium(II) chloride were from Mitsuwa and Kishida, respectively. The deuterated solvents, D_2O, CD_3OD, and DCl in D_2O were obtained from Merck. The chemicals used were of highest grade available.

Syntheses. *[Pd(L-His)(D-His)]·H_2O*: To a solution of palladium(II) chloride (0.36 g, 2.0 mmol) in 2 M HCl (2 ml; 1 M=1 mol dm^{-3}) was added an aqueous solution of DL-histidine hydrochloride (0.84 g, 4.0 mmol), and the pH of the mixture was adjusted at 6—7 with aqueous NaOH. Colorless crystals were collected and recrystallized from water. Found: C, 33.16; H, 4.23; N, 19.97%. Calcd for $C_{12}H_{16}N_6O_4Pd\cdot H_2O$: C, 33.31; H, 4.19; N, 19.42%.

[Pd(im)$_2$]·0.5H_2O: An aqueous solution of imidazole (0.27 g, 4.0 mmol) was added to a solution of palladium(II) chloride (0.36 g, 2.0 mmol) in 2 M HCl (2 ml). The pH of the resulting mixture was adjusted at ≈7 with aqueous NaOH, when almost colorless crystals separated. Found: C, 28.64; H, 2.77; N, 22.15%. Calcd for $C_6H_6N_4Pd\cdot 0.5H_2O$: C, 28.88; H, 2.83; N, 22.45%.

[Pd(L-Gln)(L-His)]·2H_2O: Palladium(II) chloride (0.36 g 2.0 mmol) in 2 M HCl (2 ml) was mixed with aqueous solutions of L-histidine hydrochloride (0.42 g, 2.0 mmol) and L-glutamine (0.59 g, 4.0 mmol), and the pH of the resulting solution was adjusted at 5—6 with aqueous NaOH. The solution was then concentrated *in vacuo* to a small volume at room temperature and kept in a refrigerator for a few days to give yellowish crystals after removal of slightly soluble Pd(L-Gln)$_2$. Found: C, 29.46; H, 4.65; N, 15.85%. Calcd for $C_{11}H_{17}N_5O_5Pd\cdot 2H_2O$: C, 29.91; H, 4.79; N, 15.85%.

[Pd(L-Asn)(L-His)]·2H_2O: The complex was prepared in the manner described for Pd(L-Gln)(L-His). Found: C,

28.62; H, 4.09; N, 16.65%. Calcd for $C_{10}H_{15}N_5O_5Pd \cdot 2H_2O$: C, 28.08; H, 4.48; N, 16.37%.

Instruments. Absorption spectra were recorded in the range 230—430 nm on a Union Giken SM-401 high sensitivity recording spectrophotometer. CD spectra were measured in the range 260—420 nm with a JASCO MOE-1 spectropolarimeter. ^1H NMR spectra at 90 MHz were obtained at 34 °C with a Hitachi R-22 NMR spectrometer equipped with a Hitachi A 1600A signal averaging analyzer internally locked and a Hitachi R-900 Fourier transform NMR spectrometer (90 MHz). ^{13}C NMR spectra at 22.63 MHz were recorded at 34 °C on a Hitachi R-900 Fourier transform spectrometer with D-lock and digital resolution of 0.02 ppm. The probe temperature was measured with a thermocouple.

Spectral Measurements. *Absorption and CD Spectra*: Absorption and CD spectra were measured at room temperature for the systems involving Pd(II), His, and AA in the ratio of 1:1:1 at pH 6.5—7.0 at a Pd(II) concentration of 1×10^{-3}—2×10^{-3} M. The samples were prepared from disodium tetrachloropalladate(II) freshly dissolved in water and 0.02 M aqueous solutions of amino acids, the pH values being adjusted with aqueous NaOH (0.05 M) and hydrochloric acid (0.01 M).

NMR Spectra. The samples were prepared in deuterated solvents (pD 5—7) in the manner described above. The palladium(II) concentrations were *ca.* 0.04—0.2 M for ^1H and 0.1—1.0 M for ^{13}C NMR spectral measurements. All carbon chemical shifts were measured relative to dioxane as an internal reference.

Results

Syntheses. Isolation of the crystalline binary copper(II) complex of L-histidine has been a challenge to a number of investigators, and only the *meso* complex, Cu(L-His)(D-His), has been successfully crystallized and analyzed crystallographically.[21] With palladium(II), the corresponding *meso* complex was obtained as crystals, whereas the active complex was obtained as a gelatinous precipitate just as the platinum(II) complex.[22] As regards the ternary complexes, only Pd(L-Asn)(L-His) and Pd(L-Gln)(L-His) were isolated as crystals by using Pd(II), His, and AA in the ratio of 1 : 1 : 2. The ternary complexes with Ser, Thr, and Hmser could not be obtained as analytically pure crystals probably owing to contamination with the binary complexes $Pd(AA)_2$, and are in contrast with the corresponding copper(II) complexes which have been isolated as crystals in previous studies.[16,17]

Spectral Properties. *Absorption and CD Spectra*: At neutral pH the ternary systems Pd(L-His)(L-AA) exhibit an absorption band centered at 300—311 nm with ε 310—440, whose pattern appears to involve a shoulder and a peak ascribable to $Pd(L\text{-His})_2$ and $Pd(L\text{-AA})_2$, respectively (Table 1). The CD spectra of the Pd(L-His)(L-AA) systems have a negative maximum at 307—328 nm with a positive shoulder at ≈300 nm and sometimes a weak positive peak at ≈380 nm. In the absence of ligand-ligand interactions within complex molecules, the CD magnitude additivity has been shown to hold for the copper(II) and palladium(II) complexes with two amino acids[11,12,15] or a peptide with two or three amino acid residues,[23,24] where the magnitudes, $\Delta\varepsilon_{calcd}$, can be estimated by summing up the experimental magnitude assigned to each molecule or residue of the amino acids constituting the systems. Thus, for ternary palladium(II) systems with amino acids L-A and L-B devoid of interacting side groups, Pd(L-A)(L-B), $\Delta\varepsilon_{calcd}$ given by Eq. 1 corresponds well with the observed value:[15]

$$\Delta\varepsilon_{calcd} = \frac{1}{2}(\Delta\varepsilon_{Pd(L\text{-}A)_2} + \Delta\varepsilon_{Pd(L\text{-}B)_2}), \quad (1)$$

where $\Delta\varepsilon_{Pd(L\text{-}A)_2}$ and $\Delta\varepsilon_{Pd(L\text{-}B)_2}$ refer to the magnitudes exhibited by the binary complexes $Pd(L\text{-A})_2$ and $Pd(L\text{-B})_2$, respectively. Because the ligand fields are supposedly different in the histidinate-containing systems from those of the systems with the other amino acids owing to the imidazole ring, we used Eq. 2 for Pd(L-His)(L-AA):

$$\Delta\varepsilon_{calcd} = \Delta\varepsilon_{Pd(DL\text{-}His)(L\text{-}AA)} + \Delta\varepsilon_{Pd(L\text{-}His)(DL\text{-}AA)}. \quad (2)$$

The estimated values given by Eq. 2 are in good agreement with the experimental ones for the systems with glycinate (Gly), L-alaninate (L-Ala), or L-valinate (L-Val) in place of L-AA (Table 1). On the other hand, polar side chains of Ser, Thr, Hmser, Asn, and Gln affect the magnitudes, decreasing the relative magnitudes $\Delta\varepsilon/\Delta\varepsilon_{calcd}$. This is reminiscent of the magnitude anomaly due to the electrostatic ligand-ligand interaction in the ternary copper(II) and palladium(II) systems with an acidic and a protonated basic amino acid and related systems,[11–13,15] and serves as an indication

Table 1. Absorption and CD spectral data for L-His-containing ternary systems

System	pH	Absorption spectrum		CD spectrum		Relative magnitude[a]
		λ_{max} / nm	ε	λ_{max} / nm	$\Delta\varepsilon$	$\Delta\varepsilon/\Delta\varepsilon_{calcd}$
Pd(L-His)(Gly)	7.1	305	310	328	−0.15	1.00
Pd(L-His)(L-Ala)	7.1	311	380	324	−0.10	0.93
Pd(L-His)(L-Val)	7.0	305	420	319	−0.47	0.96
Pd(L-His)(L-Ser)	6.9	305	410	321	−0.11	0.58
Pd(L-His)(L-Thr)	7.1	306	400	315	−0.29	0.90
Pd(L-His)(L-Hmser)	7.1	305	430	323	−0.10	0.64
Pd(L-His)(L-Asn)	6.8	300	400	307	−0.12	0.64
Pd(L-His)(L-Gln)	7.0	305	430	325	−0.15	0.74

a) Calculated according to Eq. 2. The $\Delta\varepsilon$ values were measured at λ_{max} of Pd(L-His)(L-AA).

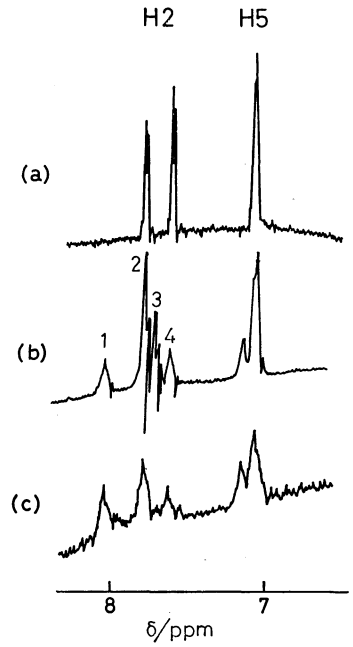


Fig. 1. ^{1}H NMR spectra of the imidazole moiety at pD 5.0 in the systems Pd(L-His)$_2$ (a), Pd(Dmgly)(L-His) (b), and Pd(Gly)(L-His) (c). The numbered signals in (b) correspond to *cis*-Pd(Gly)(L-His) (1), *cis*-Pd(L-His)$_2$ (2), *trans*-Pd(Gly)(L-His) (3), and *trans*-Pd(L-His)$_2$ (4), the geometry referring to the amino groups.

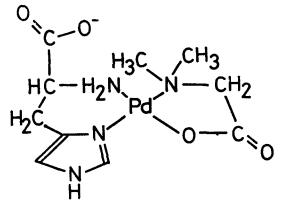


Fig. 2. Preferred coordination structure of Pd(Dmgly)-(L-His).

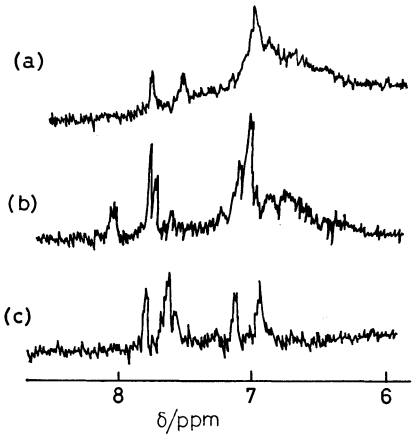


Fig. 3. ^{1}H NMR spectra of the imidazole moiety at pD >7 in the systems 1 : 1.33 Pd(II)-L-His (a), Pd(L-Ala)(L-His) (b), and Pd(L-Ala)(L-1-methylhistidinate) (c).

of side chain interactions between the carboxylato group of L-His and the hydroxyl or amido group of L-AA in the present cases.

NMR Spectra: The signal assignments were made on the basis of the substituent effects, the peak areas, and the chemical shifts observed for the amino acids in the absence of palladium(II).[25] The ^{1}H NMR spectra of Pd(L-His)$_2$ and Pd(Histam)$_2$ (Histam=histamine) show two separate peaks of the C^2 proton of the imidazole nucleus (Fig. 1). The signals exhibit splittings due to coupling with the C^5 proton. Since the imidazolyl groups contained in *cis*-Pt(L-His)$_2$[22] and *cis*-Pd(imH)$_2$Cl$_2$[26] (imH=imidazole) have been reported to give the corresponding peaks at lower fields than those observed for the *trans* forms, the signals at lower fields for Pd(L-His)$_2$ and Pd(Histam)$_2$ are also assigned to the *cis* isomers. In this connection, the spectrum of the ternary system containing *N*,*N*-dimethylglycinate (Dmgly), Pd(Dmgly)(L-His), shows only the lower field peak of the imidazole moiety in contrast to the two peaks in Pd(Gly)(L-His) (Fig. 1). The difference is probably attributed to the steric repulsion between the C^2 proton and the methyl groups in Pd(Dmgly)(L-His) and may thus point to the structure involving a *cis* arrangement with respect to the amine nitrogens (Fig. 2). Binary complexes of amino acids with the glycinate-like coordination exhibit spectra apparently due to single 1 : 2 species, indicating that the interconversion between geometrical isomers is fast as compared with the NMR time scale. The ternary systems with L-Ala, on the other hand, have four peaks of the C^2 proton, and those which are unaffected by the presence of L-AA can be assigned to *cis*- and *trans*-Pd(L-His)$_2$ involved in the system Pd(L-His)(L-AA) in solution.

At the Pd(II)/L-His ratios of >0.5 at pD 7.0, the binary system gives additional broad peaks at δ 6—8, which are also detected in the spectra of the ternary systems at pD>7 (Fig. 3). Since the ternary system involving L-1-methylhistidinate and L-Ala does not show such broad peaks, they may be associated with the coordination to palladium(II) of the deprotonated pyrrole nitrogen of His, such as is observed with Pd(im)$_2$ where both imidazole nitrogens are coordinated.

The ^{13}C chemical shift differences between free and coordinated amino acids at constant pD, shown in Table 2, reveal that coordination to Pd(II) causes downfield shifts of 11 ppm at the carbonyl carbon of L-Ala and L-Thr and 3 ppm at that of L-His. The imidazole moiety suffers larger irregular shifts indicative of its coordination. The ^{1}H NMR spectral pattern exhibited by the methyl group of L-Ala in Pd(L- or D-His)(L-Ala) corresponds well with that in Pd(Histam)-(L-Ala), while the patterns of all the protons of L-Hmser undergo changes on going from Pd(Histam)(L-Hmser) to Pd(L-His)(L-Hmser) and Pd(D-His)(L-Hmser), suggesting the side chain conformational changes of L-Hmser (Fig. 4). Glutamate involved in place of His in the ternary systems show different patterns of the β- and γ-CH$_2$ groups; Glu in the system Pd(D-Glu)(L-Thr) suffers considerable spectral changes while that in Pd(L-Glu)(L-Thr) shows patterns which are slightly different from those of Pd(L-Glu)$_2$ and Pd(L-Glu)-(L-Ala).

Discussion

Palladium(II)–Amino Acid Bonding Modes. The

TABLE 2. ^{13}C COMPLEX SHIFTS OF BINARY AND TERNARY SYSTEMS[a]

System	Assignment[b]	Complex shifts/ppm									
		L-His[c]						L-Ala or L-Thr			
		C=O	α-C	β-C	C^2	C^4	C^5	C=O	α-C	β-C	CH_3
Pd(L-His)$_2$	*cis*	3.3	−1.1	4.1	2.4	5.2	−3.5				
	trans	3.3	−1.1	4.7	2.7	5.5	−3.5				
Pd(L-His)(L-Ala)		3.0	−0.4	3.0	1.4	4.6	−3.5	11.0	4.3		2.9
Pd(L-His)(L-Thr)		3.0	−0.4	3.0	1.5	4.4	−3.5	11.3	3.5	1.6	−0.9

a) In ppm downfield at pD 5.0. Complex shifts are defined as the chemical shift differences between the complexed and free amino acids. b) Complex shifts of the peaks assigned to *cis* and *trans* isomers in the system Pd(L-His)$_2$. c) The carbons C^2, C^4, and C^5 refer to those of the imidazole nucleus.

TABLE 3. ABSORPTION AND CD SPECTRAL DATA FOR L-HisOMe-CONTAINING TERNARY SYSTEMS

System	pH	Absorption spectrum		CD spectrum		Relative magnitude[a] $\Delta\varepsilon/\Delta\varepsilon_{calcd}$
		λ_{max}/nm	ε	λ_{max}/nm	$\Delta\varepsilon$	
Pd(L-HisOMe)(L-Ala)	6.7	304	340	345	−0.042	1.00
Pd(L-HisOMe)(L-Val)	5.0	306	320	324	−0.31	0.98
Pd(L-HisOMe)(L-Ser)	6.9	305	360	343	−0.003	1.0
Pd(L-HisOMe)(L-Thr)	6.7	305	360	371	0.030	1.00
Pd(L-HisOMe)(L-Hmser)	7.0	304	370	339	−0.042	1.00
Pd(L-HisOMe)(L-Gln)	7.0	304	370	336	−0.084	1.04

a) $\Delta\varepsilon_{calcd}=\Delta\varepsilon_{Pd(L\text{-}HisOMe)(DL\text{-}AA)}+\Delta\varepsilon_{Pd(DL\text{-}HisOMe)(L\text{-}AA)}$. The values were measured at λ_{max} of Pd(L-HisOMe)(L-AA).

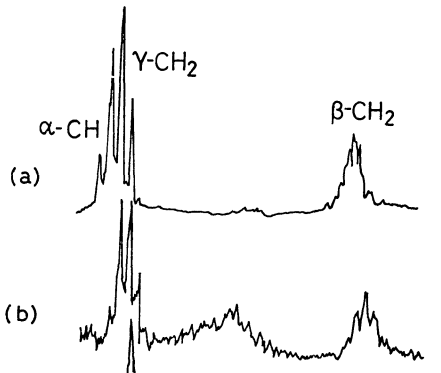


Fig. 4. ^1H NMR signal patterns of homoserinate at pD 7.0 in the systems Pd(Histam)(L-Hmser) (a), Pd(L-His)-(L-Hmser) (b), and Pd(D-His)(L-Hmser) (c).

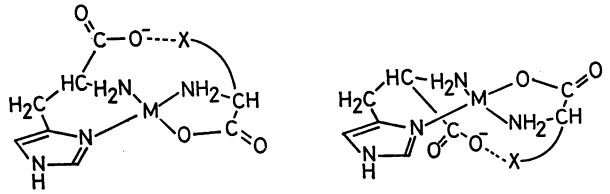
^{13}C NMR complex shifts found in the Pd(L-His)$_2$ system indicate that His coordinates to palladium(II) through the amine and imidazole nitrogens, while the glycinate-like coordination in Pd(L-AA)$_2$ is confirmed by the absorption and CD spectra[23] as well as the ^{13}C complex shifts (Table 2).[15] The spectral data also show that the ternary complexes, Pd(His)(AA), have an N_3O donor set that corresponds with the set in Cu(L-His)-(L-Thr)[27] and Cu(L-Asn)(L-His)[18] disclosed by X-ray analysis. In solution the geometrical isomers of Pd(His)$_2$ and Pd(Histam)$_2$ exist in approximately the same amounts, and this suggests that the two imidazole rings in the *cis* isomers are slightly distorted from the coordination plane in analogy with the arrangements in *trans*-Pd(Histam)$_2$Cl$_2$[28] and *trans*-Cu(L-His)(D-His),[21] since the steric repulsion between the C^2 protons of the two imidazoles in the *cis* position should otherwise be considerable and tend to favor the *trans* isomers greatly.

Intramolecular Hydrogen Bonding in Ternary Complexes. His-containing Systems: Ligand-ligand interactions between the side chains in ternary copper(II) and palladium(II) complexes have been found to give rise to CD magnitude anomaly in the d-d region due to increased asymmetry.[11-13,15] The L-His-containing ternary palladium(II) complexes with L-AA (AA=Ser, Thr, Hmser, Asn, or Gln) exhibit this anomaly in the $d_{xy}\rightarrow d_{x^2-y^2}$ transition,[15] which is considered to indicate the structural changes in the xy-plane. Direct evidence establishing that the carboxylato group of His is essential for the CD magnitude anomaly is provided by the CD spectra of the systems containing L-histidine methyl ester (L-HisOMe) instead of L-His, Pd(L-HisOMe)-(L-AA), where participation of the carboxylato group in the ligand-ligand interaction is blocked by esterification and as a consequence the relative magnitudes are expectedly close to unity (Table 3). Whereas the signals due to the methyl group of L-Ala in Pd(L-Ala)-(L- or D-His) remain the same as in Pd(L-Ala)(Histam), the presence of the carboxylato group of His in the ternary systems Pd(L-Gln)(L- or D-His) and Pd(L- or D-His)(L-Hmser) affects the ^1H NMR spectral patterns of L-Gln and L-Hmser, respectively. This implies the conformational changes of the amino acid side chains and possibly the effects of the ligand-ligand interaction

Table 4. Fractions of *cis*-isomers in ternary systems[a]

System	Temp °C	$r_{L\text{-His}}$[b]	$r_{L\text{-His}}$[c]	$\frac{r_{L\text{-His}}}{r_{D\text{-His}}}$
1 : 1 : 1 Pd(II)–His–L-Ala	34	0.33	0.35	0.9
1 : 1 : 2 Pd(II)–His–L-Ala	34	0.35	0.34	1.0
1 : 1 : 1 Pd(II)–His–L-Thr	34	0.18	0.13	1.4
1 : 1 : 2 Pd(II)–His–L-Thr	34	0.24	0.16	1.5
1 : 1 : 2 Pd(II)–His–L-Ala	8	0.33	0.32	1.0
1 : 1 : 2 Pd(II)–His–L-Thr	8	0.20	0.16	1.3
1 : 1 : 1 Pd(II)–His–L-Gln	8	0.40	0.24	1.7

a) The fraction is defined as the ratio of the *cis* isomer to the total isomers in the system. b) The fractions for the L-Hi-scontaining systems. c) The fractions for the D-His-containing systems.



M(L-His)(L-AA) M(D-His)(L-AA)

M = Pd(II) ; X = -OH, -$CONH_2$

Fig. 5. Geometrical isomers expected from steric requirements for ligand-ligand interactions.

on the species distribution in the ternary systems. That such an interaction is intramolecular rather than intermolecular is reasonably deduced from the fact that the NMR spectral patterns and relative CD magnitudes are indifferent to concentrations of the samples.

The side chain interaction should also affect the distribution of geometrical isomers in the ternary systems as estimated from the peak areas of the C^2 proton signals of the imidazole moiety assigned to each isomer. Table 4 shows that, although the fractions of the *cis* isomers $r_{L\text{-His}}$ and $r_{D\text{-His}}$ in Pd(L-Ala)(L-His) and Pd(L-Ala)(D-His), respectively, are almost identical, those in Pd(L-His)(L-AA) and Pd(D-His)(L-AA) (AA= Thr or Gln) slightly differ from each other, the difference

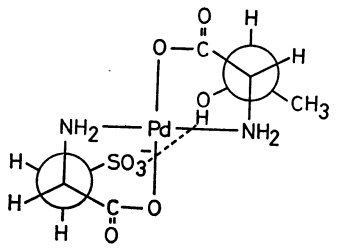


Fig. 6. Conformations of α-amino acids in Pd(L-$CySO_3H$)(L-Thr) with a ligand-ligand interaction.

being more clearly seen from the ratios of *cis* isomer contents in both systems. As shown previously for copper(II) complexes, the intramolecular ligand-ligand interaction requires *cis* arrangements of the NH_2 groups in Pd(L-His)(L-AA) and *trans* arrangements in Pd(D-His)(L-AA) (Fig. 5). In the palladium(II) systems investigated, the *cis* isomer contents in Pd(L-His)(L-AA) are greater than those in Pd(D-His)(L-AA), but the isomers that do not allow the ligand-ligand interaction still predominate, indicating that the stabilization due to the interaction is minimal in aqueous media.

Cysteate-containing Systems: The conformation of a coordinated α-amino acid is represented by the weighted average of three staggered rotational isomers, whose populations can be estimated by using the coupling constants between the protons on the α- and β-carbons and the constants for *trans* and vicinal couplings evaluated for α-amino acids by Pachler[30] and Martin.[31] The ligand-ligand interaction expected between the side chains of L-cysteate, which offers an SO_3^- group instead of the COO^- group of His, and L-Thr in Pd(L-$CySO_3H$)(L-Thr) requires that each amino acid assumes the conformation depicted in Fig. 6. In this connection, we reported in a previous communication[32] that the fractional population of L-$CySO_3H$ assuming the conformation shown in Fig. 6 increases with temperature decrease in 50% CD_3OD, which was taken as evidence for the presence of the hydrogen bond-type ligand-ligand interaction in solution. The abnormal CD magnitude of Pd(L-$CySO_3H$)(L-Thr) in 75% aqueous dioxane as compared with the magnitude of Pd(L-$CySO_3H$)(L-Ala) is also in line with the above conclu-

Table 5. Absorption and CD spectral data for L-$CySO_3H$-containing ternary systems

System	Solvent	pH	Absorption spectrum λ_{max} nm	Absorption spectrum ε	CD spectrum λ_{max} nm	CD spectrum Δε	Relative magnitude[a] $\Delta\varepsilon/\Delta\varepsilon_{calcd}$
Pd(L-$CySO_3H$)(L-Ala)	H_2O	6.6	304	330	344	0.32	0.99
					303	−0.76	0.99
	75% aq dioxane	8.2			347	0.33	0.96
					307	−0.65	0.99
Pd(L-$CySO_3H$)(L-Thr)	H_2O	6.4	319	320	353	0.37	0.94
					311	−1.45	1.00
	75% aq dioxane	7.9			353	0.40	0.87
					309	−1.32	0.96
Pd(L-Ala)(L-Thr)	75% aq dioxane	7.7			353	0.34	1.06
					310	−0.88	1.03

a) $\Delta\varepsilon_{calcd}=1/2(\Delta\varepsilon_{Pd(L\text{-}CySO_3H)_2}+\Delta\varepsilon_{Pd(L\text{-}AA)_2})$. The Δε values were measured at λ_{max} of Pd(L-$CySO_3H$)(L-AA).

sion (Table 5). The system involving L-lysinate (L-Lys) in place of L-Thr exhibits greater deviation from the CD magnitude additivity and greater increase with temperature decrease of the population of the rotamer of L-$CySO_3H$ shown in Fig. 6,[15] demonstrating that the electrostatic interaction between the ε-NH_3^+ group of L-Lys and the SO_3^- group of L-$CySO_3H$ is more effective than the hydrogen bonding. Involvement of the negatively charged group in the interaction is further supported by the ^1H NMR signal pattern of Glu in Pd(L- or D-Glu)(L-Thr).

Comparison with the Copper(II) Systems. On the basis of synthetic and spectroscopic studies, histidinate-containing ternary copper(II) systems with AA have been inferred to involve an intramolecular hydrogen bond around the central copper(II) ion.[16] Since both copper(II) and palladium(II) form essentially planar complexes with α-amino acids except ornithinate in the same mode of coordination, the present conclusion on the ligand-ligand interaction in the palladium(II) complexes, reached from the CD and NMR studies, most probably holds for the corresponding copper(II) systems and substantiates our previous interpretation[16] of the preferential formation of Cu(L-His)(L-AA) (AA= Asn, Gln, and Thr) in human blood plasma.[33,34] The complex species Cu(L-His)(L-AA) should meet the requirement for copper(II) transport across biological membranes, because hydrogen bonding is more effective in such hydrophobic regions and may have a ligand-discriminating ability. The hydrogen bonded cyclic structure has been elucidated by X-ray analysis for the silver(I) and other metal complexes of an antibiotic monensin,[35] whose ring structures are best suited for the transport.

Interestingly, very recent X-ray structural analysis of [Cu(L-Ala)(L-His)(H_2O)]·$3H_2O$ shows that L-His coordinates to copper(II) through the amino and imidazole nitrogens with the carboxylato group axially bound to a neighboring copper(II).[36] This is in contrast with the modes of coordination found in Cu(L-His)(L-Thr)[27] and Cu(L-Asn)(L-His),[18] where the carboxylato group of His occupies an apical position within the same molecule. The difference in coordination has been attributed to slightly higher basicity of the carboxylato group of L-Ala as compared with that of L-Thr and of L-Asn and resulting lower electronegativity of copper(II).[36] Considering that the difference in the acid dissociation constants (<0.3 log unit) does not seem to be large enough to warrant such a structural difference, however, we are inclined to ascribe it to the absence of the intramolecular ligand-ligand interaction in Cu(L-Ala)(L-His).

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