Ternary Metal(II) Complexes with Tyrosine-Containing Dipeptides. Structures of Copper(II) and Palladium(II) Complexes Involving L-Tyrosylglycine and Stabilization of Copper(II) Complexes Due to Intramolecular Aromatic Ring Stacking

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The structures and stabilities of metal(II) complexes of tyrosine- (tyr-) containing dipeptides (L), L-tyr·X [X = glycine (gly), L-/D-alanine, -tyr, -tryptophan, and -phenylalanine] and diamines [DA = ethylenediamine (en), 2,2′-bipyridine (bpy), and 1,10-phenanthroline (phen)] have been studied by crystallographic, spectroscopic, and potentiometric methods. The absorption spectra of the 1:1:1 Cu(DA)(L) systems exhibited a single d–d peak at 610–640 nm (pH 6–7) and at 620–640 nm (pH ~9) with an additional peak at ~850 nm indicating the formation of a five-coordinate complex. The circular dichroism (CD) spectra showed magnitude anomaly resulting from conformational changes. The stability constants β_{pqrs} of the ternary complexes $Cu_p(DA)_q(L)_rH_s$ have been determined by potentiometric titrations at 25 °C and I = 0.1M (KNO_3). The complexes with DA = bpy or phen are stabilized relative to Cu(en)(glycylglycine) by the stacking interaction between the side-chain aromatic ring of L and DA. Two complexes with L = L-tyr·gly, [Pd(bpy)(L-tyr·gly)]·3H_2O (**1**) and [Cu(phen)(L-tyr·gly)]·3H_2O (**2**), were isolated as crystals, and the structures were determined by the X-ray diffraction method. Complex **1** crystallizes in the triclinic space group, $P\bar{1}$, with one molecule in a unit cell of dimensions a = 10.856(2), b = 8.114(1), c = 7.704(1) Å; α = 81.58(1); β = 112.89(1); and γ = 117.48(1)°. The Pd(II) ion is in a four-coordinate square-planar geometry with the two nitrogens of bpy and two nitrogens of L-tyr·gly. The phenol ring of L-tyr·gly is situated above the coordination plane and stacked with bpy with the average spacing of 3.28 Å. Complex **2** crystallizes in the orthorhombic space group, $P2_12_12_1$, with four molecules in a unit cell of dimensions a = 10.765(2), b = 22.074(3), and c = 10.078(2) Å. The Cu(II) ion has a five-coordinate square-pyramidal geometry; the two nitrogens and one oxygen of L-tyr·gly and one of the two nitrogens of phen occupy the equatorial positions in a slightly distorted square plane, and the other nitrogen of phen is coordinated at an axial position. Intramolecular aromatic ring stacking has been detected between the phenol ring of L-tyr·gly and the aromatic ring of phen perpendicular to the Cu(II) coordination plane, the average spacing between the rings being 3.61 Å. The results confirm the stabilization of Cu(DA)(L) (DA = bpy or phen) evaluated from log β_{pqrs} values and suggest that the conformation of side chain aromatic rings and coordination structures can be regulated by intramolecular stacking.

Introduction

Conformation of aromatic side chains of metal-ion-coordinated amino acids and peptides is governed by steric requirements, aromatic ring stacking, and metal–aromatic ring interactions. X-ray structural studies on complexes of aromatic amino acids and peptides containing aromatic amino acids, such as Pd(L-tyrosinate)$_2$,[2] Cu(L-tyrosinate)$_2$,[3] and Cu(glycyl-L-tryptophanate),[4] showed that the side-chain aromatic ring often occupies the space above the coordination plane with the metal–aromatic ring distance of ca. 3.0–3.3 Å, which is less than the van der Waals distance. Intramolecular aromatic ring stacking and hydrophobic interactions have been extensively studied by Sigel and his collaborators for ternary complexes involving aromatic nitrogen ligands and nucleotides[5] or amino acids.[6] Factors which affect ternary Cu(II) complex formation with aromatic nitrogen ligands and aliphatic dipeptides have also been studied.[7] We have been studying the ligand–ligand interactions in ternary metal complexes of amino acids and established the electrostatic or hydrogen bonding between an acidic and a basic amino acid[8] and the stacking between the side-chain aromatic ring and coordinated 2,2′-bipyridine in ternary copper(II) and palladium(II) complexes such as Cu(2,2′-bipyridine)(L-tyrosinate)[8f,9] both in the solid state and in solution.

Among the aromatic amino acids, tyrosine (tyr)[10] is unique in the sense that its phenol group can be involved in both hydrophobic and hydrophilic interactions. The OH group forms a hydrogen

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bond with polar amino acid residues in proteins and serves as metal-binding sites in transferrin[11] and galactose oxidase.[12] Tyr is also important as the N-terminal residue of enkephalin and other endogenous analgesic peptides (opioid peptides),[13] where the phenol group is essential for the analgesic activity, suggesting that the hydrogen bond through the OH group and/or aromatic ring stacking may be necessary for the specific receptor binding. Recent studies on the active site structures of galactose oxidase[12] and ribonucleotide reductase[14] revealed that the radical species of tyr, which plays an essential role in enzyme activity, is located near the metal center. In view of the important biological functions of the tyr residue in proteins and peptides, we previously studied the structures and stabilities of the binary copper(II) complexes of tyr-containing dipeptides.[15] The ^{1}H-NMR spectra of the ternary palladium(II) complexes with bpy and various dipeptides containing an aromatic amino acid indicated that the side-chain aromatic ring of the dipeptides is located above Pd(II) to be involved in stacking with bpy.[16] In order to confirm the stacking interaction and close metal ion–aromatic ring contact and obtain information on factors affecting the side-chain conformations, we extended our previous studies[15,16] and carried out X-ray crystal structure determinations of ternary Pd(II) and Cu(II) complexes involving a bidentate nitrogen ligand (DA) and L-tyr·gly and potentiometric titrations of the solution equilibria of Cu(II)–DA–dipeptide (L) systems, where DA refers to en, bpy, or phen and L to dipeptides with the N-terminal tyr residue. The present paper deals with the findings on the ternary complex formation in 1:1:1 Cu(II)–DA–L systems and intramolecular aromatic ring stacking interactions and discussions of their effects on structures and stabilities of the complexes.

Experimental Section

Materials. L-tyr·gly, L-tyr·L-ala, and L-tyr·L-phe were purchased from Sigma. The other peptides were prepared in our laboratory and checked by elemental analysis and thin-layer chromatography. $PdCl_2$, $Cu(NO_3)_2 \cdot 3H_2O$, bpy, en, and phen were purchased from Nacalai Tesque. All other chemicals used were of analytical grade or the highest grade available. Water was distilled, deionized, and purified by a Milli-Q water purification system.

Synthesis of [Pd(bpy)(L-tyr·gly)]·3H$_2$O (1). To a solution of $PdCl_2$ (88.7 mg, 0.5 mmol) in 0.5 M HCl (2 mL) was added an aqueous solution of L-tyr·gly (119.1 mg, 0.5 mmol), and the pH of the mixture was adjusted to 6–7 with aqueous NaOH. A solution of bpy (78.1 mg, 0.5 mmol) in methanol was added to the mixture after it was stirred overnight. The resulting solution was concentrated in vacuo to a small volume at room temperature. When the solution was kept for 1 week at room temperature, it gave light yellow crystals of **1**, which were isolated and recrystallized from water.

Synthesis of [Cu(phen)(L-tyr·gly)]·3H$_2$O (2). An aqueous methanol solution containing $Cu(NO_3)_2 \cdot 3H_2O$ (120.8 mg, 0.5 mmol), phen (99.1 mg, 0.5 mmol), L-tyr·gly (119.1 mg, 0.5 mmol), and 1 M NaOH (1 mL) was left to evaporate at room temperature. When the solution was kept for 1 month, it gave greenish-blue prismatic crystals of **2**.

Table I. Crystal Data for [Pd(bpy)(L-tyr·gly)]·3H$_2$O (**1**) and [Cu(phen)(L-tyr·gly)]·3H$_2$O (**2**)

	1	**2**
formula	$PdO_7N_4C_{21}H_{24}$	$CuO_7N_4C_{23}H_{24}$
formula weight	550.86	532.01
crystal system	triclinic	orthorhombic
space group	$P1$	$P2_12_12_1$
a/Å	10.856(2)	10.765(2)
b/Å	8.114(1)	22.074(3)
c/Å	7.704(1)	10.078(2)
α/deg	81.58(1)	
β/deg	112.89(1)	
γ/deg	117.48(1)	
V/Å^3	554.2	2394.8
Z	1	4
ρ/g·cm^{-3}	1.65	1.48
μ/cm^{-1}	8.73	9.61
$F(000)$	280	1100
crystal size/mm	0.2 × 0.2 × 0.4	0.3 × 0.3 × 0.3
λ(Mo Kα)/Å	0.71073	0.71073
2θ limit/deg	60	60
no. of reflections used ($\|F_o\| > 3\sigma(\|F_o\|)$)	3244	2153
R	0.025	0.061
R_w	0.031	0.066

Spectroscopic Measurements. Electronic spectra were measured at room temperature on a Hitachi 330 and a Shimadzu UV-3101PC spectrophotometer in quartz cells with a path length of 10 mm. CD spectra were measured with a Jasco J-40CS and a J-500C spectropolarimeter at room temperature. Samples for the measurements were freshly prepared at pH 6–7 or 9–10 in a 1:1:1 ratio of Cu(II), DA, and L, the concentrations of Cu(II) being 1–5 mM.

X-ray Structure Determinations of [Pd(bpy)(L-tyr·gly)]·3H$_2$O (1) and [Cu(phen)(L-tyr·gly)]·3H$_2$O (2). Crystals of **1** and **2** suitable for X-ray analysis were obtained by recrystallization of **1** (ca. 20 mg) and **2** (ca. 50 mg) from water (ca. 5 mL). Crystal data and experimental details for both crystals are summarized in Table I. Diffraction data for **1** and **2** were obtained with an Enraf-Nonius CAD4 and a Rigaku AFC-5R four-circle automated diffractometer, respectively. The crystals were mounted on the glass capillary. The reflection intensities for **1** and **2** were monitored by three standard reflections at every 2 h and 150 measurements, respectively, and the decays of intensities for both crystals were within 2%. Reflection data were corrected for both Lorentz and polarization effects. Absorption correction was not applied in either case, because the absorption coefficients for both crystals were very small.

The structures were solved by the heavy-atom method and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. Each refinement was continued until all shifts were smaller than one-third of the standard deviations of the parameters involved. Atomic scattering factors and anomalous dispersion terms were taken from ref 17. Hydrogen atoms for both structures were located from difference Fourier maps, and their parameters were isotropically refined. The final R and R_w values were 0.025 and 0.031 for **1**, and 0.061 and 0.066 for **2**, respectively. The weighting scheme $w^{-1} = (\sigma^2(F_o)) + (0.015F_o)^2)$ was employed for both crystals. The final difference Fourier map did not show any significant features. The calculations were performed on a Hitachi M-680H computer at the Computer Center of the Institute for Molecular Science by using the program system UNICS III.[18]

The final atomic parameters for non-hydrogen atoms for **1** and **2** are given in Tables II and III, respectively, and the selected bond lengths and angles for **1** and **2** are listed in Tables IV and V, respectively.

pH Titrations. Carbonate-free 0.1 M KOH was prepared under N_2 and standardized against standard potassium hydrogen phthalate. Copper(II) nitrate (0.01 M) was standardized by chelatometry with metallic zinc (JIS primary standard) as standard. pH values were measured with a Beckman pHI71 pH meter equipped with a Beckman 39314 glass electrode and a 39419 double-junction reference electrode.

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(10) The following abbreviations were used throughout the text: tyr, tyrosinate; phe, phenylalaninate; trp, tryptophanate; gly·gly, glycylglycinate; tyr·gly, tyrosylglycinate; tyr·ala, tyrosylalaninate; tyr·phe, tyrosylphenylalaninate; tyr·tyr, tyrosyltyrosinate; tyr·trp, tyrosyltryptophanate; tyram, tyrosineamide; glyam, glycineamide; im, imidazole; en, ethylenediamine; bpy, 2,2′-bipyridine; phen, 1,10-phenanthroline; terpy, 2,2′,6′,2″-terpyridine.

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Table II. Final Positional Parameters (×10⁴) and B_{eq} Values (Å²) for the Non-Hydrogen Atoms of [Pd(bpy)(L-tyr·gly)]·3H₂O (**1**)

atom	X	Y	Z	B_{eq}
Pd	0	0	0	1.8
O(1)	−4498(3)	−3358(4)	−3543(4)	3.5
O(2)	−5589(3)	−1486(4)	−4524(5)	4.1
O(3)	−3992(3)	−2397(4)	609(4)	2.8
O(4)	1600(3)	6122(4)	3816(4)	3.6
N(1)	−2172(3)	−766(4)	−607(3)	2.1
N(2)	−566(3)	−2487(4)	1183(4)	2.4
N(3)	2135(3)	733(4)	313(4)	2.4
N(4)	629(3)	2621(4)	−1036(4)	2.4
C(1)	−4529(3)	−1851(4)	−3507(4)	2.4
C(2)	−3183(3)	−267(4)	−2158(4)	2.3
C(3)	−2728(3)	−1931(4)	597(4)	1.9
C(4)	−1706(3)	−2705(4)	2012(4)	2.2
C(5)	−977(4)	−1750(5)	3993(4)	2.7
C(6)	−257(4)	339(5)	4020(4)	2.5
C(7)	1251(4)	1368(5)	4345(5)	3.0
C(8)	1898(4)	3299(5)	4281(5)	3.1
C(9)	1031(4)	4234(5)	3898(5)	2.8
C(10)	−475(4)	3218(5)	3603(6)	3.4
C(11)	−1106(4)	1300(5)	3665(6)	3.1
C(12)	2848(4)	−390(5)	1042(5)	2.9
C(13)	4222(4)	75(6)	967(6)	3.4
C(14)	4866(4)	1673(6)	81(6)	3.5
C(15)	4139(4)	2799(5)	−658(6)	3.0
C(16)	2794(3)	2294(4)	−498(4)	2.2
C(17)	1989(3)	3419(4)	−1102(4)	2.2
C(18)	2607(4)	5234(5)	−1629(5)	2.7
C(19)	1809(4)	6259(5)	−2043(5)	3.0
C(20)	439(4)	5470(5)	−1864(6)	2.9
C(21)	−113(4)	3645(4)	−1313(5)	2.5
O(1W)	−2703(4)	−5037(5)	−1853(5)	4.0
O(2W)	−4049(9)	−7475(8)	−4937(9)	11.3
O(3W)	−5016(5)	−4957(5)	3093(5)	4.4

Table III. Final Positional Parameters (×10⁴) and B_{eq} Values (Å²) for the Non-Hydrogen Atoms of [Cu(phen)(L-tyr·gly)]·3H₂O (**2**)

atom	X	Y	Z	B_{eq}
Cu	−2760(1)	4541(1)	−781(1)	2.8
O(1)	−3770(5)	5091(2)	417(5)	3.3
O(2)	−5692(5)	5212(3)	−1171(6)	4.7
O(3)	−5484(5)	3584(2)	−2497(5)	3.6
O(4)	−2506(5)	1566(2)	1178(5)	4.5
N(1)	−4335(5)	4203(3)	−1163(6)	2.9
N(2)	−2265(6)	4108(2)	−2467(6)	3.0
N(3)	−1101(6)	4925(3)	−426(6)	3.2
N(4)	−2080(5)	3988(3)	915(6)	3.5
C(1)	−4913(7)	4954(3)	512(7)	3.3
C(2)	−5330(7)	4398(3)	−305(8)	3.4
C(3)	−4481(7)	3844(3)	−2172(7)	2.8
C(4)	−3321(7)	3767(3)	−3029(7)	3.0
C(5)	−3021(8)	3098(3)	−3335(7)	3.8
C(6)	−2845(8)	2713(3)	−2112(7)	3.3
C(7)	−1708(8)	2588(4)	−1559(10)	5.0
C(8)	−1545(7)	2205(4)	−440(9)	5.0
C(9)	−2575(7)	1945(3)	119(8)	3.4
C(10)	−3724(8)	2059(4)	−465(10)	4.8
C(11)	−3851(8)	2427(4)	−1560(9)	4.6
C(12)	−597(7)	5360(4)	−1141(8)	4.2
C(13)	581(8)	5607(4)	−862(10)	5.0
C(14)	1209(8)	5378(5)	177(9)	5.6
C(15)	742(7)	4903(4)	956(9)	4.3
C(16)	−451(7)	4697(3)	594(8)	3.3
C(17)	−988(7)	4207(4)	1354(8)	3.6
C(18)	−371(8)	3977(4)	2492(9)	4.7
C(19)	−931(10)	3496(5)	3182(10)	6.1
C(20)	−2056(10)	3273(4)	2796(9)	5.9
C(21)	−2563(8)	3527(4)	1611(9)	5.0
C(22)	1340(8)	4634(5)	2063(10)	6.3
C(23)	831(9)	4213(5)	2810(10)	6.2
O(W1)	−367(5)	−1228(2)	−2481(7)	5.3
O(W2)	−4171(7)	2161(3)	−5641(8)	8.9
O(W3)	−1361(9)	2014(3)	−5219(7)	9.4

Calibration of the meter was made with NBS standard buffer solutions (pH 4.008, 7.413, and 9.180 at 25 °C). The difference between the pH meter reading, pH_M, and −log [H], where [H] denotes the hydrogen ion concentration, was determined as reported previously[19] to be 0.068 at ionic strength (I) = 0.1 (KNO_3).[20] The apparent ion product of water $pK_w = pH_M - \log [OH]$, where [OH] is the hydroxide ion concentration, was 13.96 at I = 0.1.[20] pH titrations were carried out at 25 ± 0.05 °C under N_2 for solutions containing Cu(II), DA, and L in the molar ratio of 0:0:1, 1:0:1, and 1:1:1, the concentration of Cu(II) being ca. 2 mM.

Table IV. Selected Bond Lengths (Å) and Valence Angles (deg) in [Pd(bpy)(L-tyr·gly)]·3H₂O (**1**)

bond	length	bond	length
Pd–N(1)	2.010(3)	Pd–N(2)	2.008(3)
Pd–N(3)	2.030(3)	Pd–N(4)	2.052(3)
bond	**angle**	**bond**	**angle**
N(1)–Pd–N(2)	80.2(1)	N(1)–Pd–N(3)	173.9(1)
N(1)–Pd–N(4)	100.2(1)	N(2)–Pd–N(3)	101.8(1)
N(2)–Pd–N(4)	176.2(1)	N(3)–Pd–N(4)	78.2(1)
Pd–N(1)–C(2)	129.0(2)	Pd–N(1)–C(3)	114.2(2)
Pd–N(2)–C(4)	106.5(2)	Pd–N(3)–C(12)	124.5(2)
Pd–N(3)–C(16)	116.2(3)	Pd–N(4)–C(17)	115.0(3)
Pd–N(4)–C(21)	124.3(3)		

Table V. Selected Bond Length (Å) and Valence Angles (deg) in [Cu(phen)(L-tyr·gly)]·3H₂O (**2**)

bond	length	bond	length
Cu–O(1)	2.028(5)	Cu–N(1)	1.892(6)
Cu–N(2)	2.020(6)	Cu–N(3)	2.009(6)
Cu–N(4)	2.224(6)		
bond	**angle**	**bond**	**angle**
O(1)–Cu–N(1)	82.9(2)	O(1)–Cu–N(2)	157.6(2)
O(1)–Cu–N(3)	96.8(2)	O(1)–Cu–N(4)	92.7(2)
N(1)–Cu–N(2)	83.1(3)	N(3)–Cu–N(1)	177.8(3)
N(3)–Cu–N(2)	96.6(3)	N(4)–Cu–N(1)	103.6(2)
N(4)–Cu–N(2)	107.5(2)	N(4)–Cu–N(3)	78.6(2)
Cu–O(1)–C(1)	115.0(4)	Cu–N(1)–C(2)	115.2(5)
Cu–N(1)–C(3)	120.5(5)	Cu–N(2)–C(4)	111.1(4)
Cu–N(3)–C(12)	125.2(5)	Cu–N(3)–C(16)	116.2(5)
Cu–N(4)–C(17)	110.1(5)	Cu–N(4)–C(21)	133.7(5)

Calculation of Stability Constants. The stability constants, β_{pqrs}, defined by eq 1 were calculated by the method of nonlinear least-squares using a computer program SUPERQUAD[21] with the aid of a Facom M-170F computer at the Kanazawa University Computation Center (charges are omitted for simplicity):

$$p\mathrm{Cu} + q(\mathrm{DA}) + r(\mathrm{L}) + s\mathrm{H} \overset{\beta_{pqrs}}{\rightleftarrows} \mathrm{Cu}_p(\mathrm{DA})_q(\mathrm{L})_r\mathrm{H}_s$$

$$\beta_{pqrs} = \frac{[\mathrm{Cu}_p(\mathrm{DA})_q(\mathrm{L})_r\mathrm{H}_s]}{[\mathrm{Cu}]^p[\mathrm{DA}]^q[\mathrm{L}]^r[\mathrm{H}]^s} \quad (1)$$

where p, q, r, and s are the numbers of Cu(II), DA, L, and proton (H), respectively, in $\mathrm{Cu}_p(\mathrm{DA})_q(\mathrm{L})_r\mathrm{H}_s$. The pK_a values and stability constants of the binary complexes except L = L-tyr·gly and L-tyr·D-phe were taken from the literature.[6a,15,22-25]

Results

Molecular Structure of [Pd(bpy)(L-tyr·gly)]·3H₂O (1). The molecular structure of complex **1** is shown in Figure 1with the atomic labeling scheme in the asymmetric unit. The Pd(II) complex has a square-planar structure, with the two nitrogen atoms of bpy and the amino and deprotonated amide nitrogen atoms of L-tyr·gly coordinated. The Pd–N bond lengths (Pd–

(19) Yamauchi, O.; Seki, H.; Shoda, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3258–3267.
(20) The difference between pH_M and −log[H] and the pK_w value are close to those reported previously: Sigel, H.; Zuberbühler, A. D.; Yamauchi, O. *Anal. Chim. Acta* **1991**, *255*, 63–72.
(21) Gans, P.; Sabatini, A.; Vacca, A. *J. Chem. Soc., Dalton Trans.* **1985**, 1195–1200.
(22) Sigel, H.; Griesser, R.; Prijs, B. *Z. Naturforsch.* **1972**, *27B*, 353–364.
(23) Brooks, G.; Pettit, L. D. *J. Chem. Soc., Dalton Trans.* **1977**, 1918–1924.
(24) Koltun, W. L.; Dexter, R. N.; Clark, R. E.; Gurd, F. R. N. *J. Am. Chem. Soc.* **1958**, *80*, 4188–4194.
(25) Odani, A.; Masuda, H.; Inukai, K.; Yamauchi, O. *J. Am. Chem. Soc.* **1992**, *114*, 6294–6300.

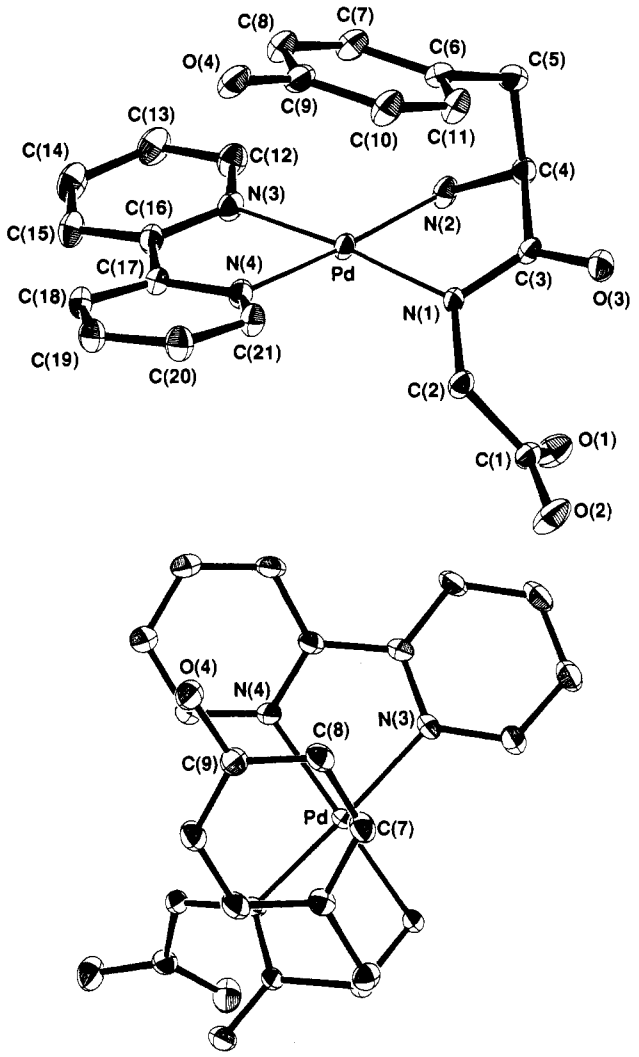


Figure 1. Molecular structure of [Pd(bpy)(L-tyr·gly)]·$3H_2O$ (**1**) showing the atomic numbering scheme: (a, top) side view; (b, bottom) top view. Thermal ellipsoids are drawn at the 50% probability level.

N(1) = 2.010(3), Pd–N(2) = 2.008(3), Pd–N(3) = 2.030(3), and Pd–N(4) = 2.052(3) Å) agree well with those reported for square-planar Pd(II) complexes.[2,26] The deprotonated carboxylate group of L-tyr·gly does not participate in coordination to Pd(II) but forms a hydrogen bond with the phenolic OH group of a neighboring molecule with the O(2)···O(4′) distance of 2.635(4) Å. The side-chain aromatic ring of L-tyr·gly located above the coordination plane is involved in the intramolecular stacking with the coordinated bpy rings, being approximately parallel to the bpy plane with an average spacing of 3.28 Å. There are two close contacts between the Pd(II) ion and the carbon atoms of the phenol ring [Pd···C(6) = 3.28 Å and Pd···C(7) = 3.23 Å], which is indicative of the metal ion–aromatic ring interaction. The tyr phenol ring is located above the coordination plane with one of the carbon atom [C(9)] close to the bpy nitrogen [N(4)]. This orientation is the same as that concluded for Pd(bpy)(L-tyr·gly) in aqueous solution from the ^{1}H-NMR spectra.[16]

Molecular Structure of [Cu(phen)(L-tyr·gly)]·$3H_2O$ (2). The molecular structure of complex **2**, also showing the atomic numbering scheme, is given in Figure 2. The copper atom in complex **2** coordinates phen through one of the nitrogen atoms and L-tyr·gly through the amino and deprotonated amide nitrogen atoms and the carboxylate oxygen atom at the equatorial positions, and the other nitrogen atom of phen is bound at an apical position,

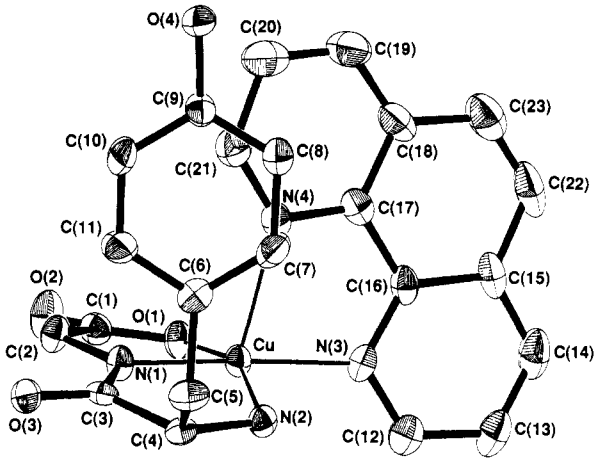
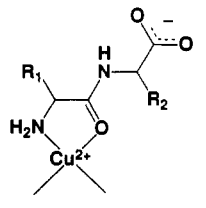


Figure 2. Molecular structure of [Cu(phen)(L-tyr·gly)]·$3H_2O$ (**2**) showing the atomic numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

completing a square-pyramidal structure. The coordination structure is the same as that revealed for Cu(phen)(gly·gly)[27] and Cu(2,9-dimethyl-1,10-phenanthroline)(gly·gly).[28] The equatorial bond lengths [Cu–N(1) = 1.892(6), Cu–N(2) = 2.020(6), Cu–N(3) = 2.009(6), and Cu–O(1) = 2.028(5) Å] and the apical bond length [Cu–N(4) = 2.224(6) Å] agree well with those found in these complexes, although the angle N(2)–Cu–N(4) (107.5°) is significantly larger and O(1)–Cu–N(4) (92.7°) is smaller than the corresponding values of 98.7° and 96.2° in Cu(phen)(gly·gly)·$3H_2O$.[27] The coordination plane is planar to within 0.16 Å and is approximately orthogonal to phen with an angle of 79.2°. The copper atom deviates from the coordination plane by 0.17 Å toward the apical N(4) atom. The side-chain phenol ring of L-tyr·gly is located approximately perpendicular to the coordination plane to be involved in the stacking with coordinated phen, with an average spacing of 3.60 Å and a tilting angle of 22.3° between the two planes. The shortest intramolecular distance between the two rings [C(8)···C(21)] is 3.74 Å.

Stability Constants of Copper(II) Complexes and Evaluation of Complex Stabilization Due to Stacking Interactions. The stability constants for the binary and ternary Cu(II) complexes determined at 25 °C and I = 0.1 M (KNO_3) are listed in Tables VI and VII, respectively, together with the values for the binary complexes taken from the previous studies.[15] The stabilities of the binary complexes have been discussed previously in connection with the dimer formation through the N-terminal tyr phenolate group.[15] Species distribution curves calculated from the stability constants are shown in Figure 3 for Cu(bpy)(L-tyr·L-phe) as an example, where the ternary species Cu(DA)(L) (**3**) and the deprotonated species Cu(DA)(LH_{-1}) (**4**) (LH_{-1} = L with the deprotonated peptide group) with the following Cu(II)–dipeptide-bonding modes predominate at pH 5–8 and 8–10, respectively.



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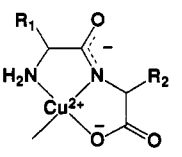

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Although the stability constants of the ternary complexes depend on those of the parent binary complexes, extra stabilization of the ternary complexes Cu(DA)(L) due to aromatic ring stacking

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Table VI. Stability Constants log β_{pqrs} for Proton–Ligand and Cu(II)–Ligand Complexes at 25 °C and I = 0.1 M (KNO_3)[a]

						L									DA				
species *pqrs*	gly-gly[d]	L-tyr-gly	L-tyr-L-ala[e]	L-tyr-D-ala[e]	L-tyr-L-phe[e]	L-tyr-D-phe	L-tyr-L-tyr[e]	L-tyr-D-tyr[e]	L-tyr-L-trp[e]	L-tyr-D-trp[e]	L-tyram	glyam	species *pqrs*	im[f]	en[g]	bpy[g]	phen[h]	terpy[g]
0011	8.13	9.967(2)	9.975(1)	9.790(3)	10.154(2)	9.989(1)	10.424(2)	10.538(2)	9.910(4)	10.046(3)	9.922(4)	8.040(4)	0101	7.08	9.976	4.503	4.95	
0012	11.34	17.587(3)	17.587(3)	17.44(5)	17.526(5)	17.649(2)	20.120(1)	20.269(1)	17.277(5)	17.960(5)	17.353(6)		0102		17.148			
0013		20.736(5)	20.859(3)	20.501(8)	20.661(7)	20.506(3)	27.432(3)	28.012(3)	20.787(8)	21.237(9)			1100	4.20	10.523	8.10	9.25	9.068
0014							30.665(4)	30.942(4)					110-1					0.879
1012							25.09(3)	25.37(2)					1200	7.62	19.505	13.44	16.00	
1011		14.75(6)	15.04(3)	14.70(3)	15.18(1)	15.13(2)	21.907(1)	21.715(1)	15.570(9)	15.505(9)	14.50(2)		1300	10.50				
1010	5.71	11.374(3)	11.623(2)	11.217(1)	11.984(1)	11.420(1)	13.113(8)	12.898(4)	11.724(1)	11.656(1)		5.353(7)	1400	12.55				
101-1	1.56	2.44(2)	2.67(2)	2.11(1)	3.118(4)	2.55(1)	3.205(5)	2.914(3)	2.793(7)	2.823(5)		-1.482(7)	220-1					11.54
101-2	-7.96	-7.808(7)	-7.617(5)	-8.044(6)	-7.495(3)	-7.631(4)	-7.360(5)	-7.683(2)	-7.319(2)	-7.325(1)								
101-3					-19.30(4)	-19.39(8)			-19.44(3)	-19.06(1)								
1022											28.38(3)							
1021											22.31(1)							
1020											14.49(1)	9.30(3)						
102-1											4.75(1)	2.601(9)						
102-2											-5.87(1)	-5.500(7)						
2020							28.94(3)	27.83(5)										
202-1							19.57(2)	18.41(2)										
202-2		7.32(7)	7.66(6)	6.78(6)	8.36(3)	7.47(7)			9.277(8)	8.08(4)								

[a] Values in parentheses denote estimated standard deviations. [b] Reference 6a. [c] Reference 15. [d] Reference 22. [e] Reference 23. [f] Reference 24. [g] Reference 25.

between DA (= bpy, phen) and the aromatic ring of L may be evaluated by considering the following hypothetical equilibrium:[9a,c,d]

$$\mathrm{Cu(DA)(gly{\cdot}gly) + Cu(en)(L) \overset{K}{\rightleftarrows} Cu(DA)(L) + Cu(en)(gly{\cdot}gly)} \quad (2)$$

where the species on both sides of the equilibrium have the same sets of coordinating atoms and aromatic ring stacking is possible only in Cu(DA)(L). The equilibrium constant log K is given by the stability constants of relevant ternary species according to eq 3, where the values $\beta_{Cu(DA)(L)}$, etc., correspond to the stability

$$\log K = \log \beta_{Cu(DA)(L)} + \log \beta_{Cu(en)(gly{\cdot}gly)} - \log \beta_{Cu(DA)(gly{\cdot}gly)} - \log \beta_{Cu(en)(L)} \quad (3)$$

constants β_{1110} or β_{1111} (Table VII) for complexes with structure **3**. The log K value, which is defined to be 0 in the absence of interactions between DA and L, serves as a parameter giving stabilization of the ternary complex due to specific combination of DA and L. With Cu(en)(gly-gly) as standard, we calculated the log K values for various Cu(DA)(L) complexes from their stability constants in Table VII according to eq 3 (Table VIII).

We see from Table VIII that the ternary complexes Cu(DA)(L-tyr-L-/D-X) with structure **3** have a large positive log K value, indicating stabilization due to stacking. The log K values for Cu(DA)(L-tyr-D-X) increase with the size of the aromatic rings of X and DA in the orders of X and DA, trp > tyr > phe > (gly) > ala and phen > bpy, respectively. The complexes Cu(DA)(L-tyr-L-X) have lower values than those for L-tyr-D-X, the order expressed by X being (gly) ≥ ala > trp > phe ≥ tyr. The complexes with L-tyr-D-trp have especially large log K values (2.11 and 2.35 for DA = bpy and phen, respectively), which suggests that the indole residue of D-trp plays an important role in ternary complex stabilization.

With the increase of pH above 8, deprotonation from the coordinated peptide NH group occurs to give the deprotonated complex Cu(DA)(LH_{-1}) (**4**). Stabilization of Cu(DA)(LH_{-1}) due to intramolecular interactions may also be evaluated by the log K' values for the following hypothetical equilibrium:

$$\mathrm{Cu(DA)(gly{\cdot}glyH_{-1}) + Cu(en)(LH_{-1}) \overset{K'}{\rightleftarrows} Cu(DA)(LH_{-1}) + Cu(en)(gly{\cdot}glyH_{-1})} \quad (4)$$

where the species containing en have a planar structure with four nitrogens in the coordination plane and the other species with an aromatic DA mainly assume a square-pyramidal structure as indicated by the absorption spectra (*vide infra*). The equilibrium constant log K' is given by eq 5, which is similar to eq 3:

$$\log K' = \log \beta_{Cu(DA)(LH_{-1})} + \log \beta_{Cu(en)(gly{\cdot}glyH_{-1})} - \log \beta_{Cu(DA)(gly{\cdot}glyH_{-1})} - \log \beta_{Cu(en)(LH_{-1})} \quad (5)$$

where $\beta_{Cu(DA)(LH_{-1})}$, etc., refer to the stability constants β_{1110} or $\beta_{111\text{-}1}$ depending on whether L has a tyrosyl residue or not (Table VII). Again, the log K' values serve as a measure of extra stabilization of the deprotonated ternary complexes. Although straightforward comparison of K and K' values may be inappropriate because of the difference in the coordination structures of Cu(en)(LH_{-1}) and Cu(bpy or phen)(LH_{-1}), the log K' values are smaller than the log K values for the same systems, and there is no significant difference in log K' between the bpy and phen complexes (Table IX). In contrast with the observations with the log K values, the log K' values for L-tyr-L-X are definitely larger than those for L-tyr-D-X, suggesting that the factors affecting the ternary complex stabilization are different in the square-planar four-coordinate and square-pyramidal five-coordinate complexes.

Table VII. Stability Constants log β_{pqrs} for Ternary Cu(II) Complexes Cu(DA)(L) at 25 °C and I = 0.1 M (KNO_3)[a]

		DA				
L	species *pqrs*	phen	bpy	en	im	terpy
L-tyr·L-ala	1111	25.509(4)	24.363(3)	26.13(3)		
	1110	17.704(5)	16.129(5)	17.86(5)		
	111-1	7.899(5)	5.99(1)	8.09(3)		
L-tyr·D-ala	1111	25.090(4)	23.935(1)	25.84(2)		
	1110	16.938(5)	15.448(2)	17.62(4)		
	111-1	7.340(5)	5.759(3)	7.51(4)		
L-tyr·L-phe	1111	25.412(3)	24.302(3)	26.29(2)		
	1110	17.961(3)	16.390(4)	18.01(5)		
	111-1	8.247(3)	6.433(7)	8.37(2)		
L-tyr·D-phe	111	25.626(3)	24.484(1)	25.99(2)		
	1110	17.136(5)	15.468(3)	17.50(5)		
	111-1	7.418(4)		7.57(4)		
L-tyr·L-tyr	1112	35.254(8)	34.182(4)	36.21(2)		
	1111	27.810(9)	26.359(5)	27.55(4)		
	1110	18.17(1)	16.45(2)			
L-tyr·D-tyr	1112	36.160(2)	35.025(2)	36.36(2)		
	1111	27.632(3)	26.095(4)	28.41(2)		
	1110	18.107(3)	16.356(4)	18.70(2)		
L-tyr·L-trp	1111	25.331(7)	24.194(6)	26.07(2)		
	1110	18.05(1)	16.492(7)	18.16(3)		
	111-1		6.76(1)	8.09(3)		
L-tyr·D-trp	1111	26.590(8)	25.507(6)	26.34(3)		
	1110	17.81(1)	16.46(1)	18.17(3)		
	111-1	8.17(1)	6.54(2)	8.17(3)		
L-tyr·gly	1112					28.93(3)
	1111	25.133(3)	24.157(2)	25.75(1)	20.536(8)	23.7(1)
	1110	17.264(4)	15.912(2)	17.51(3)	15.520(3)	15.1(2)
	111-1	7.496(5)	5.736(4)	8.08(1)	5.619(5)	
	1211				24.90(2)	
	1210				17.72(5)	
gly·gly	1110	14.15(3)	13.292(9)	16.23(3)	12.96(1)	12.961(2)
	111-1	6.986(7)	5.458(6)	7.98(3)	7.710(9)	4.307(6)
	1210				19.45(4)	
	121-1				13.344(8)	
L-tyram	1111	24.671(8)	23.526(8)	24.61(2)		
	1110	17.375(8)	16.088(8)	17.38(1)		
	111-1	6.91(1)	5.51(2)	7.80(2)		
glyam	1110	14.24(1)	13.17(1)	15.212(7)		
	111-1	6.70(9)	5.46(1)	7.618(6)		

[a] Values in parentheses denote estimated standard deviations.

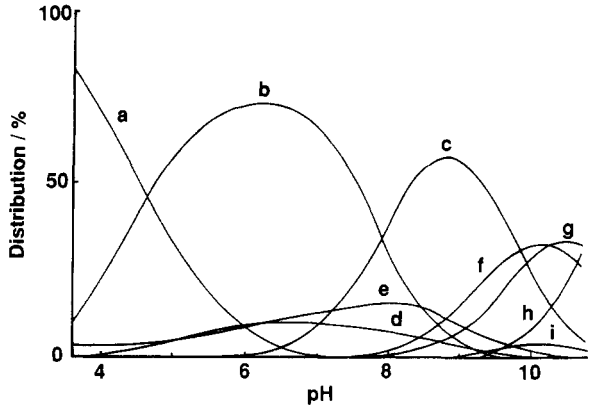


Figure 3. Species distributions as a function of pH in the 1:1:1 Cu(II)-bpy-L-tyr-L-phe system (1 mM). Species: a, Cu(bpy); b, Cu(bpy)(L); c, Cu(bpy)(LH_{-1}); d, $Cu(bpy)_2$; e, Cu(bpy); f, Cu(bpy)(OH); g, Cu(bpy)-(LH_{-1})(OH); h, Cu(bpy)$(OH)_2$; i, $Cu_2(bpy)_2(OH)_2$.

Absorption and CD Spectral Properties of Cu(II) Complexes. The ternary Cu(DA)(L-tyr-X) systems (DA = bpy or phen) in aqueous solution exhibited a d–d absorption peak at 615–633 nm at pH 6–7 (Figure 4 and Table X), which corresponds to a planar complex with NO coordination of L (**3**). In the pH range 8.3–9.4 where species **4** (N_2O coordination) is predominant, a shoulder peak appeared at ~850 nm, indicating that Cu(DA)(LH_{-1}) having a five-coordinate structure with an apical coordination as revealed for **2** is formed. On the other hand, Cu(en)(LH_{-1}) exhibited a peak at ~600 nm (pH ~9) which was rather pH insensitive, and no shoulder peak was observed. This spectral behavior is consistent with a planar N_4 chromophore. At pH 6–7 the 1:1:1 Cu(II)–DA–L-tyr-L-/D-X systems (DA = bpy or phen) showed a single negative CD peak in the region 596–618 nm (Table XI). At pH ~9 they exhibited a negative peak at 540–600 nm with an additional peak at >600 nm for L = L-tyr-D-X (X = phe, tyr), which reflects the structural changes occurring upon pH increase.

Table VIII. log K and P_{st} Values for Cu(DA)(L) Systems

	DA			
L	phen	P_{st}	bpy	P_{st}
L-tyr·L-ala	1.52	0.97	1.16	0.93
L-tyr·D-ala	1.34	0.95	1.03	0.91
L-tyr·L-phe	1.17	0.93	0.95	0.89
L-tyr·D-phe	1.69	0.98	1.43	0.96
L-tyr·L-tyr	1.07	0.91	0.91	0.88
L-tyr·D-tyr	1.81	0.98	1.60	0.97
L-tyr·L-trp	1.36	0.96	1.06	0.91
L-tyr·D-trp	2.35	1.00	2.11	0.99
L-tyr·gly	1.46	0.97	1.35	0.96
L-tyram[a]	1.03	0.91	0.96	0.89

[a] The values are calculated relative to log β_{1110} for Cu(en)(glyam).

Discussion

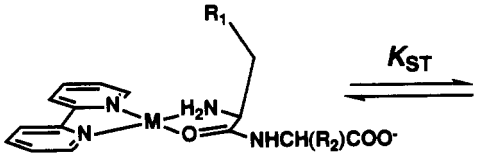
Stacking Conformation in Cu(DA)(L). The species distribution curves (Figure 3) and the electronic absorption spectra at pH 6–7 (Figure 4 and Table X) indicate that L in Cu(DA)(L) coordinates to Cu(II) through the amino nitrogen and the peptide carbonyl oxygen in an essentially planar structure with two

Table IX. log K' Values for Cu(DA)(LH_{-1}) Systems

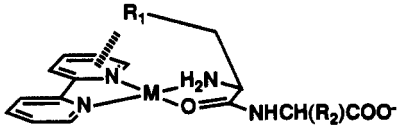
L	DA: phen	DA: bpy
L-tyr·L-ala	0.83	0.77
L-tyr·D-ala	0.37	0.35
L-tyr·L-phe	0.89	0.90
L-tyr·D-phe	0.58	0.49
L-tyr·L-tyr	1.17	1.33
L-tyr·D-tyr	0.18	0.21
L-tyr·L-trp	0.89	0.85
L-tyr·D-trp	0.67	0.81
L-tyr·gly	0.74	0.92
L-tyram[a]	0.91	0.87

[a] The values are calculated relative to log β_{111-1} for Cu(en)(glyamH$_{-1}$).

additional nitrogen atoms from DA. This coordination mode is similar to that of the ternary complexes involving an amino acid (AA) in place of L, Cu(DA)(AA), whose structure and aromatic ring stacking have been revealed for Cu(bpy)(L-tyr), Cu(phen)(L-trp), etc., by various methods.[8f,9] Since the log K and log K' values for Cu(DA)(L-tyr),[9a] Cu(DA)(L-tyram), and Cu(DA)(L-tyramH$_{-1}$) which are based on Cu(en)(glyam) and Cu(en)(glyamH$_{-1}$) are similar to each other (0.87–1.03 for DA = bpy or phen), the difference in the effect of the carboxylate O$^-$ and amide N$^-$ coordinations may be negligible. The log K values for Cu(DA)(L-tyr·gly) (DA = bpy or phen) are larger than those for Cu(DA)(L-tyram) by ca. 0.5, which may be due to solvation of the free carboxylate group in the peptide complex. The magnitudes of the negative CD peak at 597–606 nm (Table XI) are roughly proportional to the log K values or the populations of the stacked species (P_{st})[8e,9c] calculated according to eq 6 (R_1 = 4-hydroxyphenyl; R_2 = H, CH_3, phenyl, 3-indolyl):[6a,9c,29]



unstacked form
Cu(DA)(L)u



stacked form
Cu(DA)(L)s

$$P_{st} = \frac{[Cu(DA)(L)_s]}{[Cu(DA)(L)_u] + [Cu(DA)(L)_s]} = 1 + \frac{1}{K_{st} + 1} \qquad (6)$$

Since $K = 1$ when $[Cu(DA)(L)_s] = 0$, we have $K = K_{st} + 1$ and hence $P_{st} = 1 - 10^{-\log K}$.[8e,9c] The P_{st} values thus calculated are in good agreement with the CD magnitudes $\Delta\epsilon$, which are indicative of restricted side-chain conformation. This shows that stacking affects the asymmetry of the α-carbon bearing the side chain. In this regard, CD magnitude anomaly was observed for ternary Cu(II) complexes involving an aromatic amino acid and glycine, and this was taken to suggest possible attractive interactions between Cu(II) and the aromatic ring.[7d,30,31] Kim and Martin[32] studied the ternary complex formation in various Pd(dipeptide)–amine systems and evaluated the stability enhancement in $-\Delta G°$ due to the Pd(II)–aromatic ring and ligand–ligand interactions on the basis of the stability constants and K_{st} values being 0.3–1.5 and 2.6–3.8 kJ mol^{-1} for Pd(II)–aromatic and phenyl–aromatic interactions, respectively.

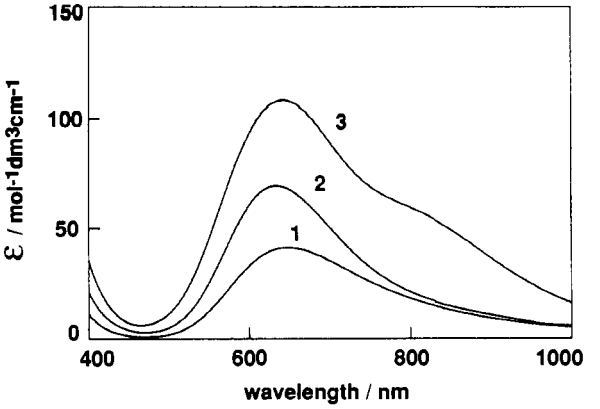


Figure 4. pH dependence of absorption spectra of [Cu(phen)(L-tyr·gly)] in the d–d region. Curves: 1, pH 4.2; 2, pH 6.4; 3, pH 8.7.

The log K values for Cu(DA)(L-tyr·D-X) are larger than those for Cu(DA)(L-tyr·gly) and Cu(DA)(L-tyr·L-X), the difference between Cu(DA)(L-tyr·D-trp) and Cu(DA)(L-tyr·L-trp) being as large as a 1.0 log unit. This stability difference is in line with the extent of deviation of the CD magnitude from the calculated value $\Delta\epsilon_{calcd}$ based on magnitude additivity:[7d,15,30,31,33]

$$\Delta\epsilon_{Cu(DA)(L\text{-}tyr\text{-}L\text{-}/D\text{-}X)calcd} = \Delta\epsilon_{Cu(DA)(L\text{-}tyr\text{-}gly)} + \Delta\epsilon_{Cu(DA)(gly\text{-}L\text{-}/D\text{-}X)} \qquad (7)$$

The reason for stereoselectivity arising from the C-terminal amino acid chirality is not clear from the present experimental data and may require further investigations.

Stacking in the Axial Position in Cu(DA)(LH$_{-1}$). Square-pyramidal coordination mode for Cu(DA)(LH$_{-1}$) (DA = bpy or phen) is evidenced by both spectral and structural studies, and the stacking interaction has been confirmed in the solid state for Cu(bpy)(L-tyr·gly) as shown in Figure 2. In solution, however, both square-pyramidal (**2**) and planar (**1**) structures are possible. In order to assign the stability enhancement expressed in terms of log K' mainly to the stacking in the axial position (**2**), we estimated the population of the square-pyramidal species from the constant (K_c) for deprotonation from the coordinated peptide group, which is defined by

$$Cu(DA)(L) \overset{K_c}{\rightleftarrows} Cu(DA)(LH_{-1}) + H \qquad (8)$$

and the $-\log K_c$ (pK_c) values are calculated as follows: For Cu(bpy)(L-tyr·gly) $pK_c = \log \beta_{1111} - \log \beta_{1110} = 8.25$ and for Cu(bpy)(gly·gly) $pK_c = \log \beta_{1110} - \log \beta_{111-1} = 7.83$. These values are between those for planar four-coordinate Cu(im)$_2$(L-tyr·gly) (7.18) and Cu(im)$_2$(gly·gly) (6.16) and the values for square-pyramidal Cu(terpy)(L-tyr·gly) (8.58) and Cu(terpy)(gly·gly) (8.65). On the assumption that the population of the five-coordinate species is proportional to 10^{pK_c} in these ranges, we calculated the population of Cu(bpy)(L-tyr·gly) and Cu(bpy)(gly·gly) to be 85 and 89%, respectively. Because the ϵ values at ~850 nm for the ternary systems are nearly the same, the population for the other complexes may be taken to be the same and inferred to be mostly in the five-coordinate structure. From these considerations, we conclude that the positive log K' values (Table IX) represent stabilization of the complexes due to stacking in the five-coordinate structure. Interestingly, Cu(DA)-

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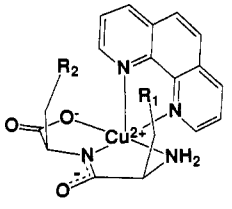
Table X. Absorption Spactral Data for 1:1:1 Cu(II)–DA–L Systems

	DA							
	en		bpy			phen		
L	pH	λ_{max}/nm (ϵ/$M^{-1}\cdot cm^{-1}$)	pH	λ_{max}/nm	(ϵ/$M^{-1}\cdot cm^{-1}$)	pH	λ_{max}/nm	(ϵ/$M^{-1}\cdot cm^{-1}$)
L-tyr·L-ala			6.5	620 (70)		6.2	628 (74)	
	9.2	600 (69)	8.8	625 (102)	850sh (41)	9.3	628 (119)	850sh (50)
L-tyr·D-ala			6.2	618 (73)		6.6	632 (73)	
	9.3	598 (64)	8.9	625 (94)	850sh (35)	9.4	625 (107)	850sh (40)
L-tyr·L-phe			6.0	618 (73)		6.0	633 (71)	
	9.1	602 (70)	8.6	625 (113)	850sh (45)			
L-tyr·D-phe			6.1	618 (73)		6.6	633 (75)	
	9.2	600 (67)	9.1	618 (92)	850sh (29)	8.9	625 (99)	850sh (28)
L-tyr·L-tyr			6.7	621 (78)		6.2	625 (77)	
	9.0	602 (73)	8.6	622 (110)	850sh (44)			
L-tyr·D-tyr			6.3	618 (77)		6.4	628 (74)	
	9.0	595 (68)	9.0	619 (97)	850sh (30)	8.7	623 (96)	850sh (26)
L-tyr·L-trp			6.5	617 (76)		6.2	623 (81)	
	8.8	598 (74)	8.5	622 (115)	850sh (48)			
L-tyr·D-trp			6.1	615 (76)		6.0	621 (80)	
	9.1	595 (67)	9.1	618 (98)	850sh (30)	9.1	626 (107)	850sh
L-tyr·gly			6.1	625 (67)		6.4	631 (69)	
	9.1	593 (65)	8.7	642 (108)	850sh (50)	8.7	642 (109)	850sh (49)
gly·gly			6.9	640 (58)		7.0	643 (59)	
	9.8	595 (58)	9.2	638 (90)	850sh (40)	9.0	636 (91)	850sh (36)

Table XI. CD Spectral Data for 1:1:1 Cu(II)–DA–L Systems

	DA					
	bpy			phen		
L	pH	λ_{max}/nm	$\Delta\epsilon$/$M^{-1}\cdot cm^{-1}$	pH	λ_{max}/nm	$\Delta\epsilon$/$M^{-1}\cdot cm^{-1}$
L-tyr·L-ala	6.5	602	−1.17	6.2	611	−1.00
	8.8	576	−0.53	8.6	594	−0.22
L-tyr·D-ala	6.2	597	−1.01	6.6	610	−0.79
	8.9	600	−0.39	8.9	560	−0.27
L-tyr·L-phe	6.0	596	−1.05	6.0	618	−0.90
	8.6	595	−0.56			
L-tyr·D-phe	6.1	597	−1.04	6.6	615	−0.94
	9.1	656	0.28	9.0	645	0.37
		550	−0.14		540	−0.06
L-tyr·L-tyr	6.7	598	−1.07	6.2	612	−0.87
	8.6	595	−0.60			
L-tyr·D-tyr	6.3	597	−1.12	6.4	615	−1.01
	9.0	578	−0.36	8.9	660	0.09
					560	−0.13
L-tyr·L-trp	6.5	597	−1.09	6.2	605	−0.65
	8.5	577	−0.52			
L-trp·D-trp	6.1	597	−1.22	6.0	608	−0.78
	9.1	567	−0.26	9.1	560	−0.17
L-tyr·gly	6.5	597	−1.07	6.6	610	−0.74
				8.9	675	−0.27
					563	−0.32
L-tyram	6.6	597	−0.81	6.6	606	−0.69

(L-tyr·L-XH_{-1}) is more stabilized than Cu(DA)(L-tyr·D-XH_{-1}), showing that the conformation of the C-terminal side-chain group affects the stabilization. The extent of stabilization appears to be dependent on the chirality only and independent of the nature and size of the side group. Cu(DA)(LH_{-1}) has LH_{-1} coordinated equatorially as a terdentate ligand, the side groups of L-tyr·L-X being located on the same side of the coordination plane. This conformation allows the side groups to interact with apically bound DA (= phen or bpy) as shown by **5**.



5

Space-filling models suggest that for complexes with X = phe, tyr, or trp, DA can be sandwiched by two aromatic rings, whereas with L-tyr·D-X, the side chains are located on different sides of the coordination plane and only one of them is involved in stacking. This reasonably explains the observed stability difference between L-tyr·L-X and L-tyr·D-X. For X = Ala, the CH_3 group may contribute to sandwiching the DA molecule.

Factors Affecting the Complex Structure. The structures of **1** and **2** contrast well with each other and illustrate the difference in the affinity for nitrogen donors and the availability of the axial positions. The side-chain phenol group of L-tyr·gly in **1** is tilted over the Pd(II) coordination plane with a tilting angle of 21.9° to the bpy ring, the average spacing between the rings being 3.28 Å. In order to accommodate the strain due to stacking, the C(4) atom of the peptide chelate ring is displaced from the coordination plane, affecting the bond direction around the N(2) atom. The dangling carboxylate group forms a hydrogen bond network with the phenolic OH group of neighboring molecules and stabilizes the crystal structure. ^{1}H-NMR studies on the same complex indicated that the phenol moiety is bent over the coordination plane; from the upfield shifts due to the ring current effect, the C(7) atom is close above one of the bpy nitrogens.[16] Since the structure in solution is very similar to that in the solid state (**1**), aromatic ring stacking and possibly the metal ion–aromatic ring interaction may be important factors for the conformation of aromatic side chains in complexes.

On the other hand, the unique stacking in **2** can be a structure-determining factor. It has the same coordination structure as that of Cu(phen)(gly·gly)[27] and its analog[28] and involves in addition a perpendicularly oriented phenol group, which is stacked with coordinated phen with an average spacing of 3.60 Å. The overlap is limited as compared with that observed for Cu(bpy)(L-tyr)ClO_4[8f] with a spacing of 3.35 Å, and this may explain the rather small stability enhancement of Cu(DA)(LH_{-1}). Axial coordination by phen from the back side would be favored for steric reasons, because there would be little or no hindrance due to a bulky group in Cu(DA)(L-tyr·gly) and Cu(DA)(L-tyr·L-X). Actually, however, one of the phen nitrogen atoms prefers the axial site, which is closer to the side chain of L-tyr·glyH_{-1}, to enable the stacking to take place. The stacking is thus concluded to be a decisive factor for orientation of **2**, and this is supported by the stability enhancement.

The present findings may serve as a basis for understanding specific interactions involving aromatic amino acids. In this connection, the stacking between a trp indole ring and the coordinated tyr phenolate group is inferred to stabilize the tyr

radical species formed in galactose oxidase,[12] and the indole ring of trp (trp 191) of cytchrome *c* peroxidase is within the van der Waals contact with the heme group perpendicular to it, indicating a possible electron-transfer pathway.[34]

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Supplementary Material Available: Tables of fractional coordinates and isotropic thermal parameters for hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond lengths and bond angles, and torsion angles for **1** and **2** (6 pages). Ordering information is given on any current masthead page. Observed and calculated structure factors are available for **1** and **2** from the authors upon request.