Structural Dependence of Aromatic Ring Stacking and Related Weak Interactions in Ternary Amino Acid−Copper(II) Complexes and Its Biological Implication

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Received July 18, 1996[⊗]

Structures and stabilization due to stacking of ternary copper(II) complexes containing an aromatic amino acid (AA) and an aromatic diamine (DA), Cu(AA)(DA), have been investigated by potentiometric, spectroscopic, and X-ray diffraction methods. For the systems with AA = *para*-X-substituted L-phenylalanine (L-XPhe; X = H, NO_2, OH, NH_2) and DA = 2,2′-bipyridine (bpy) or 1,10-phenanthroline (phen), the difference absorption spectra in the region 320−400 nm exhibited a peak assignable to the charge transfer interaction between the aromatic rings of DA and L-XPhe, the intensity being in the order NH_2 > OH > H ≫ NO_2 with respect to X. The stability constants of Cu(AA)(DA) determined for AA = DL-XPhe (X = F, Cl, Br) and L-XPhe (X = NH_2, NO_2, I) at 25 °C and I = 0.1 M (KNO_3) indicated that stabilization of Cu(L-XPhe)(DA) relative to Cu(L-Ala)(en) (Ala = alanine; en = ethylenediamine) is in the order Br > OH > Cl ≈ NH_2 > NO_2 ≥ H ≥ F. The structures of [Cu(L-NH_2-Phe)(bpy)]NO_3·H_2O (**1**), [Cu(L-Tyr)(phen)]ClO_4·2.5H_2O (**2**), [Cu(L-Phe)(phen)]Cl·3H_2O (**3**), and [Cu(L-Phe)-(bpy)]ClO_4·H_2O (**4**), isolated as crystals, were determined by the X-ray diffraction method: **1**, orthorhombic, $P2_12_12_1$, a = 10.292(1) Å, b = 13.576(4) Å, c = 14.407(1) Å, V = 2012.9 Å^3, Z = 4, R = 0.037, R_w = 0.038; **2**, orthorhombic, $P2_12_12_1$, a = 18.20(2) Å, b = 32.63(1) Å, c = 8.14(1) Å, V = 4833 Å^3, Z = 4, R = 0.111, R_w = 0.087; **3**, monoclinic, $P2_1$, a = 11.738(2) Å, b = 16.301(1) Å, c = 11.795(1) Å, β = 102.01(1)°, V = 2207.4 Å^3, Z = 2, R = 0.045, R_w = 0.035; **4**, monoclinic, $P2_1$, a = 9.954(2) Å, b = 24.179(3) Å, c = 9.780(2) Å, β = 107.32(1)°, V = 2257.1 Å^3, Z = 4, R = 0.065, R_w = 0.060. All of the complexes have a similar distorted square-pyramidal structure around the central Cu(II) ion. While **1** and **2** have a structure involving aromatic ring stacking in the solid state, **4** has a structure without it and **3** has both types of structures in the unit cell.

Introduction

Weak interactions play vital roles in highly efficient and specific biological reactions[2] and are essential for molecular recognition and self-organization of molecules in supramolecular chemistry that is inspired by biology.[3] Interactions between aromatic rings are very important in proteins and protein−DNA systems for protein stabilization and various regulatory processes,[4] but little is known about the details of their mode and strength. Specific binding between molecules is achieved by a combination of weak interactions, such as hydrogen bonding, electrostatic bonding, and aromatic ring stacking, which have been established for such processes as enzyme−substrate and antigen−antibody binding.[5] Recent findings about zinc finger−DNA interactions involving the side chains of the amino acid residues of transcription factors and nucleic bases of DNA have greatly added to the information on the roles played by weak interactions in the initial process of DNA transcription.[4,6]

Of the four amino acids with a side chain aromatic ring, phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp), and histidine (His), His and Tyr have been established to be effective metal binding sites, whereas Phe contributes mainly to the stabilization of proteins through hydrophobic interactions and the formation of hydrophobic environments.[7] Trp has the electron-rich indole ring whose role in electron transfer, such as in the cytochrome *c*-cytochrome *c* peroxidase complex,[8] and in stabilization of the tyrosine radicals at the active site of galactose oxidase[9] is attracting much attention. In many of the instances, aromatic rings are involved in stacking interactions and thus contribute to structural stabilization and molecular recognition. Stacking is an entropically unfavorable process

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⊗ Abstract published in *Advance ACS Abstracts,* January 1, 1997.

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S0020-1669(96)00855-5 CCC: $14.00

and may be regarded as a step toward self-organization of molecules.[3,10] Metal ions enable orientation of molecules through coordination, affect their electron density by through-metal interactions, and thus favor intramolecular interactions between selected groups in selected directions, and this may be regarded as a basic aspect of discrimination of molecules and catalytic functions. Mixed ligand metal complexes with interacting biomolecules may, therefore, serve as models for metalloenzyme active sites and the sites of molecular recognition.[11] With these points in mind, we have been studying ligand−ligand interactions in ternary metal complexes involving stacking interactions in and around the metal coordination sphere as biological models and as cases of self-assembly. On the basis of electronic and NMR spectra and stability constants, we concluded the existence of stacking interactions in ternary metal (M) complexes containing an aromatic amino acid (AA = Phe, Tyr, Trp, etc.) and an aromatic diamine (DA = 2,2′-bipyridine (bpy), 1,10-phenanthroline (phen), etc.), M(AA)(DA) (M = Cu(II), Pd(II)), in solution.[12] X-ray crystal structure analyses of some ternary complexes containing aromatic amino acids substantiated the conclusion from the solution studies and further revealed the precise modes of aromatic−aromatic interactions.[13] Intermolecular stacking interactions have been established for nucleotides and Pt(II) complexes with aromatic ligands in solution and in the solid state.[14] As expected, the interactions are dependent on the structures of the aromatic rings and may be interpreted as due to the interaction between the molecular orbitals.[13b] Ring substituents also have influences on the stability of stacked structures; stacking of Tyr is more effective than that of Phe in Cu(AA)(DA), and conversion of the Tyr phenol OH group to the phosphoester group by phosphorylation drastically decreases the stability due to the hydrophilic nature of the negatively charged phosphoester moiety.[12a] Certain biological processes are regulated by modification of the Tyr side group by phosphorylation, whose observed effect on intermolecular stacking interactions has been proposed as a basis for understanding molecular recognition and biological regulation of reactions.[12a,b,e,15]

In order to get detailed information on the structure dependence of stacking interactions in metal complexes, we studied the ternary copper(II) complexes, Cu(AA)(DA) (AA = L-XPhe (Phe with a substituent X = NH_2, NO_2, OH and halogens in the *para*-position of the benzene ring); DA = bpy, phen), by potentiometric, spectroscopic, and X-ray diffraction methods. This paper deals with the modes of aromatic−aromatic interactions, the effects of substitutents X on the structure and stability of the ternary complexes, and their relevance to biological processes.

Experimental Section

Materials. $Cu(NO_3)_2 \cdot 3H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, bpy, phen, L-Phe, and L-Tyr were purchased from Nacalai Tesque, and L-NH_2Phe and L-NO_2Phe were purchased from Sigma. All reagents used were of the highest grade available.

Preparations of Ternary Complexes. The $[Cu(AA)(DA)]^+$ complexes were prepared according to the following procedures. (a) $Cu(NO_3)_2 \cdot 3H_2O$ (1.21 g, 5 mmol) and bpy (0.78 g, 5 mmol), each dissolved in aqueous methanol, were mixed with L-NH_2Phe (0.90 g, 5 mmol) and NaOH (0.20 g, 5 mmol) in water, and the mixture was heated to complete dissolution. The crystals which separated on standing at room temperature were collected and recrystallized from aqueous methanol to give the analytically pure complex [Cu(L-NH_2-Phe)(bpy)]$NO_3 \cdot H_2O$ (**1**). (b) For isolation of the ternary complexes containing L-Tyr or L-Phe, $Cu(ClO_4)_2 \cdot 6H_2O$, L-Tyr·HCl or L-Phe, and DA (DA = phen or bpy, 5 mmol each) were dissolved in aqueous methanol, and an aqueous solution of NaOH (0.40 g, 10 mmol) was added to the mixture. The crystals of [Cu(L-Tyr)(phen)]$ClO_4 \cdot 2.5H_2O$ (**2**) and [Cu(L-Phe)(bpy)(H_2O)]$ClO_4 \cdot H_2O$ (**4**) were obtained according to procedure a. (c) The ternary complex with AA = L-Phe, [Cu(L-Phe)(phen)]$Cl \cdot 3H_2O$ (**3**), was obtained from an aqueous solution of [Cu(L-Phe)(phen)(H_2O)]$NO_3 \cdot H_2O$ (**5**) (2.53 g, 5 mmol) in the presence of acetylcholine chloride (1.82 g, 10 mmol) and crystallized according to procedure a.

Spectral Measurements. Absorption spectra were measured in the range 250−800 nm with a Shimadzu 3101PC recording spectrophotometer in a 1-, 10-, or 50-mm path length quartz cell. Samples were prepared by dissolving the isolated ternary Cu(II) complexes, the concentrations being adjusted at 2 or 0.2 mM (1 M = 1 mol dm^{-3}) with respect to Cu(II). Circular dichroism (CD) spectra of the complexes were measured with a JASCO J-40CS spectropolarimeter in a 10-mm path length quartz cell for 1 mM aqueous solutions.

pH Titrations. pH titrations were carried out according to the procedure previously reported.[16] Aqueous solutions of AA = L-XPhe (X = NH_2, NO_2, I) and DL-XPhe (X = F, Cl, Br) and binary and ternary Cu(II) systems containing AA and/or DA were titrated with 0.1 M carbonate-free KOH at 25 °C and I = 0.1 M (KNO_3). $Cu(NO_3)_2$ (0.02 M) was standardized by chelatometric titration with 0.02 M EDTA standardized against standard zinc (JIS primary standard). Measurements of pH values were made with an Orion EA920 pH meter equipped with a Beckman 39321 glass electrode and a 39419 double-junction reference electrode. The pH meter was calibrated with NBS standard buffer solutions (pH 4.008, 7.413, and 9.180 at 25 °C). Conversion of the pH meter reading pH_M to the hydrogen ion concentration $[H^+]$ was made in a manner reported previously,[16] the conversion factor $10^{-pH_M}/[H^+]$ being 0.885 under the present conditions. The apparent ion product of water, $pK_w' = pH_M - \log[OH^-]$, was determined to be 13.88. Because of the low solubility of L-IPhe in water, titrations of the L-IPhe-containing systems were made at concentrations <0.2 mM. All other titrations were made for 1−2 mM solutions.

Calculation of Stability Constants. The stability constant for the species $Cu_p(AA)_q(DA)_r(H)_s$, β_{pqrs}, is defined by the following equation (eq 1, charges are omitted for clarity):

$$p\mathrm{Cu} + q\mathrm{AA} + r\mathrm{DA} + s\mathrm{H} \overset{\beta_{pqrs}}{\rightleftharpoons} \mathrm{Cu}_p(\mathrm{AA})_q(\mathrm{DA})_r(\mathrm{H})_s \qquad (1)$$

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

where p, q, r, and s are the moles of Cu, AA, DA, and H in $Cu_p(AA)_q(DA)_r(H)_s$, respectively. The data points collected in the pH range 3−10

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Table 1. Crystal Data for [Cu(L-NH_2Phe)(bpy)]NO_3·H_2O (**1**), [Cu(L-Tyr)(phen)]ClO_4·2.5H_2O (**2**), [Cu(L-Phe)(phen)Cl]·3H_2O (**3**), and [Cu(L-Phe)(bpy)(H_2O)]ClO_4·H_2O (**4**)

	[Cu(L-NH_2Phe)(bpy)]NO_3·H_2O (**1**)	[Cu(L-Tyr)(phen)ClO_4]·2.5H_2O (**2**)	[Cu(L-Phe)(phen-Cl]·3H_2O (**3**)	[Cu(L-Phe)(bpy)(H_2O)]ClO_4·H_2O (**4**)
formula	$CuO_6N_5C_{19}H_{21}$	$CuN_3O_{9.5}C_{21}H_{22}Cl$	$CuN_3O_5C_{21}H_{24}Cl$	$CuClO_7N_3C_{19}H_{18}$
formula weight	478.95	567.42	497.44	483.37
color	greenish blue	blue	blue	blue
crystal size/mm	0.2 × 0.2 × 0.3	0.15 × 0.05 × 0.05	0.2 × 0.1 × 0.1	0.5 × 0.5 × 0.5
crystal system	orthorhombic	orthorhombic	monoclinic	monoclinic
space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_1$
a/Å	10.292(1)	18.20(2)	11.738(2)	9.954(2)
b/Å	13.576(4)	32.63(1)	16.301(1)	24.179(3)
c/Å	14.407(1)	8.14(1)	11.795(1)	9.780(2)
α/deg				
β/deg			102.01(1)	107.32(1)
γ/deg				
V/Å^3	2012.9	4833(6)	2207.4(4)	2247.1
Z	4	8	4	4
D_c/g cm^{-3}	1.581	1.559	1.497	1.429
λ/Å	0.710 73 (Mo Kα)	1.541 78 (Cu Kα)	1.541 78 (Cu Kα)	1.541 78 (Cu Kα)
μ/cm^{-1}	11.32	28.19	28.60	28.01
F(000)	988	2328	1028	988
scan method	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$
$2\theta_{max}$/deg	60	119.8	120.2	120.2
no. of reflctns used	2529	2850	2400	3147
R	0.037	0.111	0.045	0.065
R_w	0.038	0.087	0.035	0.060

were used for the calculations. The log β_{pqrs} values were calculated by using a computer program SUPERQUAD[17] with the aid of a FACOM M-170F computer at the Nagoya University Computation Center. The stability constants for some binary complexes and the hydrolysis constants for Cu(II) were taken from the literature.[18]

X-ray Structure Determinations. Crystallographic data for complexes **1**, **2**, **3**, and **4** are listed in Table 1. X-ray diffraction measurements were made at room temperature with the use of a Rigaku AFC-5R diffractometer for complexes **2**, **3**, and **4** and an Enraf-Nonius CAD4 diffractometer for complex **1**. Cell dimensions for each analysis were determined from the setting angle values of 25 centered reflections. Intensity data were collected by $\omega-2\theta$ scans for unique portions of reciprocal space and corrected for Lorentz, polarization, and absorption effects. The structures were solved by heavy-atom methods and refined by full-matrix least-squares methods. All non-hydrogen atoms were assigned anisotropic displacement parameters. All hydrogen atoms were assigned isotropic displacement parameters and were constrained to ideal geometries with C−H = 0.95 Å. Final difference Fourier syntheses showed no chemically significant features, the largest being close to the metal or heavy atoms. Scattering factors and anomalous dispersion terms were taken from ref 19. Data reduction and structure solution and refinement were carried out on a Micro VAX II computer by using the SDP program system[20] for **1** and on an IRIS Indigo computer by using the teXsan program system[21] for **2**, **3**, and **4**.

The selected bond lengths and angles for complexes **1**, **2**, **3**, and **4** are listed in Tables 2, 3, 4, and 5, respectively.

Results and Discussion

Absorption and CD Spectral Properties. The ternary complexes Cu(L-XPhe)(DA)NO_3 in aqueous solution showed several peaks in the UV region and a d−d absorption peak at 605−613 nm at neutral pH. The difference spectra that were obtained by subtracting the spectra for 1:1:1 Cu(II)−DA−L-alaninate and L-XPhe from the spectrum for Cu(L-XPhe)(phen)-NO_3 gave a weak broad peak at 320−400 nm, which is ascribable to the charge transfer (CT) between stacked aromatic rings in the complexes.[22] As shown in Figure 1, the absorption intensity around 350 nm increased with the increase of the electron donating ability of the *para*-substituent groups (the difference spectrum for Cu(L-NO_2Phe)(phen) exhibited a negative peak), the order being $NO_2 \ll H < OH < NH_2$. The

Table 2. Selected Bond Lengths (Å) and Angles (deg) of [Cu(L-NH_2Phe)(bpy)]NO_3·H_2O (**1**)

Bond Lengths			
Cu−O(1)	1.956(3)	Cu−N(1)	2.003(4)
Cu−N(2)	1.997(4)	Cu−N(3)	2.005(4)
Cu−N(5)	2.334(3)		
Bond Angles			
O(1)−Cu−N(1)	171.5(1)	O(1)−Cu−N(2)	92.0(1)
O(1)−Cu−N(3)	83.7(1)	N(1)−Cu−N(2)	80.8(1)
N(1)−Cu−N(3)	100.9(2)	N(2)−Cu−N(3)	153.3(1)
Cu−O(1)−C(11)	114.8(3)	Cu−N(1)−C(1)	125.3(3)
Cu−N(1)−C(5)	114.7(3)	Cu−N(2)−C(6)	115.0(3)
Cu−N(2)−C(10)	125.1(3)	Cu−N(3)−C(12)	106.8(3)

Table 3. Selected Bond Lengths (Å) and Angles (deg) of [Cu(L-Tyr)(phen)(H_2O)]ClO_4·2.5H_2O (**2**)

Bond Lengths			
Cu(A)−O(1A)	1.94(2)	Cu(B)−O(1B)	1.95(2)
Cu(A)−N(1A)	1.99(2)	Cu(B)−N(1B)	2.01(2)
Cu(A)−N(2A)	1.88(2)	Cu(B)−N(2B)	2.03(2)
Cu(A)−N(3A)	1.98(2)	Cu(B)−N(3B)	2.00(2)
Bond Angles			
O(1A)−Cu(A)−N(1A)	173.6(9)	O(1B)−Cu(B)−N(1B)	170.7(8)
O(1A)−Cu(A)−N(2A)	92.0(8)	O(1B)−Cu(B)−N(2B)	89.1(9)
O(1A)−Cu(A)−N(3A)	83.5(7)	O(1B)−Cu(B)−N(3B)	82.2(8)
N(1A)−Cu(A)−N(2A)	84(1)	N(1B)−Cu(B)−N(2B)	84.8(9)
N(1A)−Cu(A)−N(3A)	98(1)	N(1B)−Cu(B)−N(3B)	101.4(9)
N(2A)−Cu(A)−N(3A)	161.8(4)	N(2B)−Cu(B)−N(3B)	160.2(8)
Cu(A)−N(1A)−C(1A)	133(3)	Cu(B)−N(1B)−C(1B)	134(2)
Cu(A)−N(1A)−C(5A)	115(2)	Cu(B)−N(1B)−C(5B)	113(2)
Cu(A)−N(2A)−C(6A)	112(2)	Cu(B)−N(2B)−C(6B)	109(2)
Cu(A)−N(2A)−C(10A)	131(2)	Cu(B)−N(2B)−C(10B)	129(2)
Cu(A)−N(3A)−C(13A)	103(2)	Cu(B)−N(3B)−C(13B)	106(2)

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Table 4. Selected Bond Lengths (Å) and Angles (deg) of [Cu(L-Phe)(phen)(H_2O)]ClO_4·3H_2O (**3**)

Bond Lengths			
Cu(A)−O(1A)	1.968(8)	Cu(B)−O(1B)	1.953(9)
Cu(A)−N(1A)	2.02(1)	Cu(B)−N(1B)	2.04(1)
Cu(A)−N(2A)	1.988(9)	Cu(B)−N(2B)	2.02(1)
Cu(A)−N(3A)	2.046(8)	Cu(B)−N(3B)	1.986(9)
Bond Angles			
O(1A)−Cu(A)−N(1A)	163.2(3)	O(1B)−Cu(B)−N(1B)	161.8(4)
O(1A)−Cu(A)−N(2A)	90.6(4)	O(1B)−Cu(B)−N(2B)	91.7(4)
O(1A)−Cu(A)−N(3A)	82.6(3)	O(1B)−Cu(B)−N(3B)	81.9(4)
N(1A)−Cu(A)−N(2A)	83.1(4)	N(1B)−Cu(B)−N(2B)	82.0(4)
N(1A)−Cu(A)−N(3A)	98.7(4)	N(1B)−Cu(B)−N(3B)	101.6(4)
N(2A)−Cu(A)−N(3A)	161.8(4)	N(2B)−Cu(B)−N(3B)	169.7(4)
Cu(A)−N(1A)−C(1A)	130.1(9)	Cu(B)−N(1B)−C(1B)	131.1(9)
Cu(A)−N(1A)−C(5A)	112.1(9)	Cu(B)−N(1B)−C(5B)	109.0(8)
Cu(A)−N(2A)−C(6A)	111.8(8)	Cu(B)−N(2B)−C(6B)	114.0(8)
Cu(A)−N(2A)−C(10A)	118(1)	Cu(B)−N(2B)−C(10B)	128(1)
Cu(A)−N(3A)−C(13A)	105.9(6)	Cu(B)−N(3B)−C(13B)	109.4(8)

Table 5. Selected Bond Lengths (Å) and Angles (deg) of [Cu(L-Phe)(bpy)(H_2O)]ClO_4·H_2O (**4**)

Bond Lengths			
Cu(A)−O(1A)	1.94(1)	Cu(B)−O(1B)	1.92(1)
Cu(A)−N(1A)	1.96(1)	Cu(B)−N(1B)	2.06(1)
Cu(A)−N(2A)	2.01(1)	Cu(B)−N(2B)	2.00(1)
Cu(A)−N(3A)	2.00(1)	Cu(B)−N(3B)	1.99(1)
Cu(A)−O(1W)	2.50(1)	Cu(B)−O(2W)	2.27(1)
Bond Angles			
O(1A)−Cu(A)−O(1W)	88.5(5)	O(1B)−Cu(B)−O(2W)	90.0(5)
O(1A)−Cu(A)−N(1A)	173.9(5)	O(1B)−Cu(B)−N(1B)	172.0(5)
O(1A)−Cu(A)−N(2A)	94.9(5)	O(1B)−Cu(B)−N(2B)	92.6(5)
O(1A)−Cu(A)−N(3A)	82.2(5)	O(1B)−Cu(B)−N(3B)	86.9(5)
O(W1)−Cu(A)−N(1A)	97.4(5)	O(W2)−Cu(B)−N(1B)	93.5(5)
O(W1)−Cu(A)−N(2A)	90.7(5)	O(W2)−Cu(B)−N(2B)	92.6(5)
O(W1)−Cu(A)−N(3A)	98.2(5)	O(W2)−Cu(B)−N(3B)	92.2(5)
N(1A)−Cu(A)−N(2A)	83.6(6)	N(1B)−Cu(B)−N(2B)	80.1(6)
N(1A)−Cu(A)−N(3A)	98.3(6)	N(1B)−Cu(B)−N(3B)	100.1(5)
N(2A)−Cu(A)−N(3A)	170.6(6)	N(2B)−Cu(B)−N(3B)	175.2(6)
Cu(A)−O(1A)−C(11A)	117(1)	Cu(B)−O(1B)−C(11B)	114(1)
Cu(A)−N(1A)−C(1A)	130(1)	Cu(B)−N(1B)−C(1B)	124(1)
Cu(A)−N(1A)−C(5A)	115(1)	Cu(B)−N(1B)−C(5B)	112(1)
Cu(A)−N(2A)−C(6A)	112(1)	Cu(B)−N(2B)−C(6B)	116(1)
Cu(A)−N(2A)−C(10A)	130(1)	Cu(B)−N(2B)−C(10B)	123(1)
Cu(A)−N(3A)−C(12A)	108.5(9)	Cu(B)−N(3B)−C(12B)	112(1)

enhanced intensities for the Cu(AA)(bpy) systems in water are reduced in less polar solvents, indicating that the population of the intramolecularly stacked species decreases with decreasing solvent polarity. Cu(L-XPhe)(DA)NO_3 in aqueous solution exhibited a negative CD maximum near 590 nm at neutral pH due to the d−d transition (Table 6). For ternary complexes of oligopeptides and amino acids, the CD magnitude has been known to be an additive function of the magnitudes of the component binary complexes in the absence of ligand−ligand interactions, but it deviates from the additivity when through-space or through-metal ligand−ligand interactions exist.[12e,23,24] The deviation from additivity is interpreted as being due to increased asymmetry arising from limited side chain motion. The magnitudes in water, $\Delta\epsilon$ (H_2O), of the negative peak of Cu(L-XPhe)(DA)NO_3 are reduced in less polar solvents, such as 60 v/v % acetonitrile−water (AN_{60}), which is in accordance with the decrease of the CT band intensity mentioned above. The extent of the CD magnitude decrease at the maximum wavelength, $\Delta\epsilon_r$ defined as [$\Delta\epsilon$ (H_2O) − $\Delta\epsilon$ (AN_{60})]·100/$\Delta\epsilon$ (H_2O), approximately corresponds with the electron-withdrawing properties of the *para*-substituents, X = OH ≤ NH_2 < H < NO_2 (Table 6).

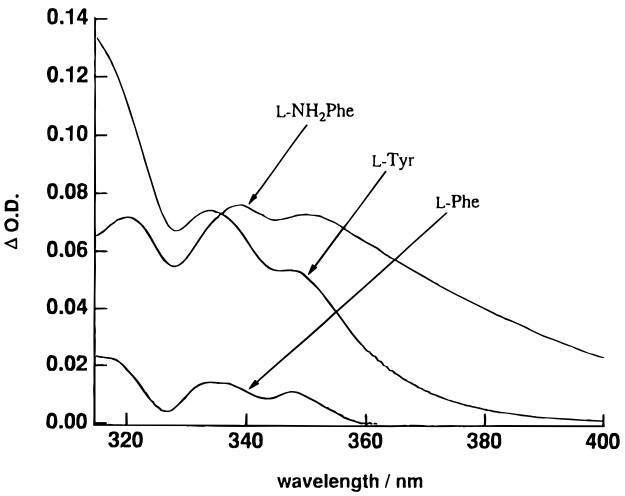

Figure 1. Difference absorption spectra indicating charge transfer between the aromatic diamine and phenyl rings in 1:1:1 Cu(II)/phen/XPhe systems. Total concentration [Cu] = 2 mM.

Table 6. Solvent Effects on CD Spectral Magnitudes of [Cu(AA)(DA)](NO_3)

		DA					
		bpy			phen		
AA	solvent[b]	λ_{max}/nm	$\Delta\epsilon_{max}$	$\Delta\epsilon_r$[a]/%	λ_{max}/nm	$\Delta\epsilon_{max}$	$\Delta\epsilon_r$[a]/%
L-NH_2Phe	H_2O	585	−1.18	13.6	597	−1.07	13.1
	AN_{60}	583	−1.02		590	−0.93	
L-Tyr	H_2O	590	−1.21	16.5	598	−1.05	11.4
	AN_{60}	583	−1.01		590	−0.93	
L-Phe	H_2O	587	−1.04	20.2	596	−0.91	15.4
	AN_{60}	582	−0.83		591	−0.77	
L-NO_2Phe	H_2O	597	−1.02	31.4	602	−0.88	27.3
	AN_{60}	588	−0.70		596	−0.64	

[a] $\Delta\epsilon_r = (\Delta\epsilon_{max}(H_2O) - \Delta\epsilon_{max}(AN_{60})) \times 100/\Delta\epsilon_{max}(H_2O)$ [b] AN_{60} = 60 v/v % acetonitrile−water.

Stability Constants for the Ternary Complexes. The stability constants log β_{pqrs} for the binary and ternary complexes, $Cu_p(AA)_q(DA)_r(H)_s$, determined at 25 °C and I = 0.1 M (KNO_3) are summarized in Tables 7 and 8, respectively. Species distribution curves calculated from the stability constants indicate that the ternary species Cu(AA)(DA) predominates at pH > 5 (>90% at pH > 6 for 1:1:1 Cu(II)/L-NH_2Phe/bpy (1 mM)). Preference of ternary complex formation may be evaluated by the stability constants according to the following relationships:

$$\text{Cu(XPhe)} + \text{Cu(DA)} \overset{10^{\Delta\log K}}{\rightleftharpoons} \text{Cu(XPhe)(DA)} + \text{Cu} \quad (2)$$

$$\text{Cu(XPhe)(en)} + \text{Cu(Ala)(DA)} \overset{K}{\rightleftharpoons} \text{Cu(XPhe)(DA)} + \text{Cu(Ala)(en)} \quad (3)$$

where Δ log K refers to the stabilization of the ternary species relative to the original complexes Cu(XPhe) and Cu(DA) (DA = bpy or phen), whereas log K denotes the stabilization of Cu(XPhe)(DA) relative to Cu(XPhe)(en) or Cu(Ala)(DA). Table 9 summarizes the Δ log K and log K values calculated

(22) (a) Yoshino, H.; Morita, F.; Yagi, K. *J. Biochem.* **1972**, *71*, 351−353. (b) Yoshino, H.; Morita, F.; Yagi, K. *J. Biochem.* **1972**, *72*, 1227−1235. (c) Naumann, C. F.; Sigel, H. *J. Am. Chem. Soc.* **1974**, *96*, 2750−2756.
(23) (a) Tsangaris, J. M.; Martin, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4255−4260. (b) Martin, R. B. *Met. Ions. Biol. Syst.* **1974**, *1*, 129−156.
(24) (a) Yamauchi, O. *J. Mol. Catal.* **1984**, *23*, 255−261. (b) Yamauchi, O.; Nakao, Y.; Nakahara, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2572−2578. (c) Yamauchi, O.; Odani, A. *J. Am. Chem. Soc.* **1981**, *103*, 391−398. (d) Yamauchi, O.; Odani, A. *Inorg. Chim. Acta* **1985**, *100*, 165−172.

Table 7. Stability Constants log β_{pqrs} for Proton−Ligand and Cu(II)−Ligand Complexes at 25 °C and $I = 0.1$ M (KNO_3)

species	AA									species	DA		
pqrs	L-NH_2Phe	DL-FPhe	DL-ClPhe	DL-BrPhe	L-IPhe	L-NO_2Phe[a]	L-Phe[b]	L-Tyr[c]	L-Ala[d]	*pqrs*	en[b]	bpy[b]	phen[e]
0101	9.158(2)	8.918(2)	8.894(1)	8.869(2)	9.020(1)	8.523	9.194	10.142	9.82	0011	9.976	4.503	4.95
0102	13.620(1)	10.956(4)	10.978(6)	11.062(6)	11.291(4)		11.452	19.170	12.16	0012	17.148		
0103	15.522(6)							21.051		1010	10.523	8.10	9.25
1101								17.99		1020	19.505	13.44	16.00
1100	7.874(5)	7.403(3)	7.314(7)	7.340(6)	7.623(4)	7.421	7.931	10.64	8.33				
1202								34.90					
1201								25.47					
1200	14.470(5)	13.825(3)	13.818(6)	13.898(5)	14.987(6)	13.712	14.834	15.36	15.27				

[a] Reference 18a. [b] Reference 18b. [c] Reference 18c. [d] Reference 18d. [e] Reference 18b.

Table 8. Stability Constants log β_{pqrs} for Ternary Cu(II) Complexes Cu(AA)(DA) at 25 °C and $I = 0.1$ M (KNO_3)

AA	species *pqrs*	DA		
		en	bpy	phen
L-NH_2Phe	1110	17.689(1)	16.560(3)	17.791(3)
DL-FPhe	1110	17.373(2)	16.065(2)	17.181(1)
DL-ClPhe	1110	17.303(3)	16.292(1)	17.381(2)
DL-BrPhe	1110	17.191(2)	16.424(2)	17.502(2)
L-IPhe	1110	18.32(1)	16.716(2)	17.892(2)
L-NO_2Phe[a]	1110	17.170	16.015	17.004
L-Phe	1110	17.746[c]	16.513[b]	17.570[b]
L-Tyr	1111	27.772[c]	26.838[b]	28.001[b]
L-Ala	1110	17.949[c]	16.116[b]	17.131[b]

[a] Reference 18a. [b] Reference 12a. [c] Reference 18g.

Table 9. $\Delta \log K$ and $\log K$ Values for $Cu_p(AA)_q(DA)_rH_s$ Systems at 25 °C and $I = 0.1$ M (KNO_3)

AA	species *pqrs*	$\Delta \log K$			$\log K$	
		en	bpy	phen	bpy	phen
L-NH_2Phe	1110	−0.708	0.586	0.667	0.704	0.920
DL-FPhe	1110	−0.553	0.562	0.528	0.525	0.626
DL-ClPhe	1110	−0.534	0.878	0.817	0.822	0.896
DL-BrPhe	1110	−0.672	0.984	0.912	1.066	1.129
L-IPhe	1110	0.18	1.00	1.02	0.23	0.39
L-NO_2Phe	1110	−0.774	0.494	0.333	0.678	0.652
L-Phe	1110	−0.708	0.482	0.389	0.600	0.642
L-Tyr	1111	−0.741	0.748	0.761	0.899	1.047
L-Ala	1110	−0.904	−0.314	−0.449	0.000	0.000

from the stability constants listed in Table 8. The $\Delta \log K$ values are 0.33−1.02 for DA = bpy and phen and −0.77 to 0.18 for DA = en and exhibit a stability sequence depending on the substituent X of AA, the order being I > Br > Cl > OH > NH_2 > F > H ≈ NO_2, where the anomalous values for X = I may be due to the unusually high stability constant for Cu(L-IPhe)$_2$ as compared with the other racemic *p*-halo derivatives. The $\log K$ values (0.23−1.13) gave the stability sequence Br > OH > Cl ≈ NH_2 > NO_2 > H > F > I. Both $\Delta \log K$ and $\log K$ values show that the ternary complexes are stabilized by stacking interactions and that the intensity of the difference spectral peak that is observed in the near-UV region reflects the strength of stacking as a complex stabilizing factor.

Molecular Structures of Isolated Complexes. Figures 2 and 3 show perspective views of complexes **1** and **2**. The central Cu(II) ion in complex **1** has a tetrahedrally distorted square-pyramidal geometry, with the two nitrogen atoms of bpy and the α-amino nitrogen and carboxylate oxygen atoms of L-NH_2-Phe at the equatorial positions and the nitrogen atom of the *p*-amino group of a neighboring L-NH_2Phe molecule at an axial position. The bond lengths in the Cu(II) coordination plane (Cu−O(1) = 1.956(3) Å, Cu−N(1) = 2.003(4) Å, Cu−N(2) = 1.997(4) Å, and Cu−N(3) = 2.005(4) Å) agree well with those reported for five-coordinate Cu(II) complexes, and the axial Cu−N bond length (Cu−N(5′) = 2.334(3) Å) is also within the reported values.[13,25] The crystal **2** contains two independent

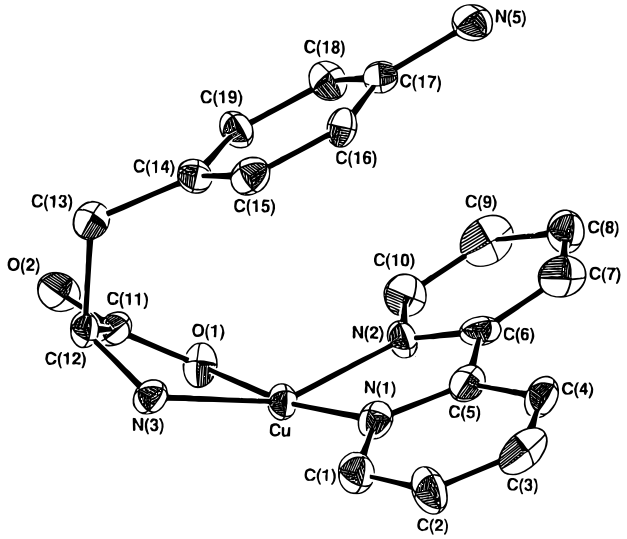

Figure 2. Structure of [Cu(L-NH_2Phe)(bpy)]$^+$ (**1**). The nitrate ion, water molecule, and hydrogen atoms were omitted for clarity.

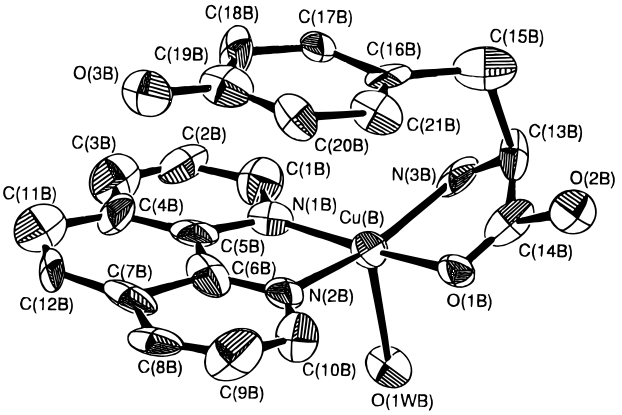

Figure 3. Structure of one of two crystallographically independent molecules of [Cu(L-Tyr)(phen)(H_2O)]$^+$ (**2**). The perchlorate ion, water molecules, and hydrogen atoms were omitted for clarity.

[Cu(L-Tyr)(phen)(H_2O)]$^+$ complexes, **2A** and **2B**, having essentially the same structure. Each Cu(II) ion coordinates the two nitrogen atoms of phen and the amino nitrogen and carboxylate oxygen atoms of L-Tyr in the equatorial positions (Cu(A)−O(1A) = 1.94(2) Å, Cu(A)−N(1A) = 1.99(2) Å, Cu(A)−N(2A) = 1.88(2) Å, and Cu(A)−N(3A) = 1.98(2) Å for complex **2A** and Cu(B)−O(1B) = 1.95(2) Å, Cu(B)−N(1B) = 2.01(2) Å, Cu(B)−N(2B) = 2.03(2) Å, and Cu(B)−N(3B) = 2.00(2) Å for complex **2B**) and one water oxygen at an axial position (Cu(A)−O(1WA) = 2.24(2) Å for complex **2A** and Cu(B)−O(1WB) = 2.25(2) Å for complex **2B**), the resulting

(25) Orpen, A. G.; Brammer, L.; Allen, F. K.; Kennard, O.; Watson, D. G.; Taylor, R. In *Structure Correlation;* Burgi, H.-B., Dunitz, J. D., Eds.; VCH: New York, 1994; Vol. 2.

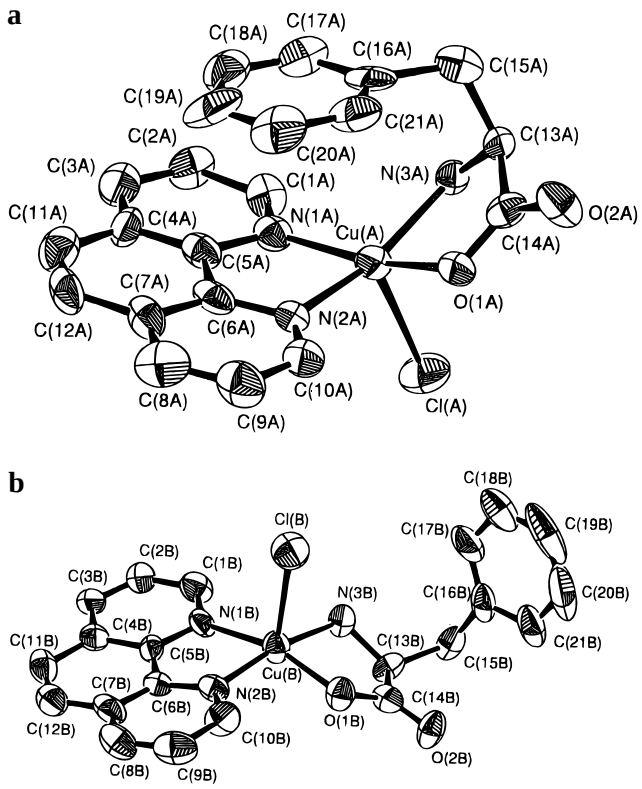

Figure 4. Structures of two crystallographically independent molecules of $[Cu(L\text{-Phe})(phen)Cl]^+$ (**3**) with (a) stacked and (b) unstacked forms. The chloride ion, water molecules, and hydrogen atoms were omitted for clarity.

coordination geometry being described as a square pyramid. All complex structures exhibit the intramolecular stacking between coordinated DA and L-NH_2Phe or L-Tyr. The side chain aromatic ring of the amino acid in both complexes is located approximately parallel to the coordination plane with the intramolecular stacking, with the average spacings of 3.46 Å for **1** and 3.27 and 3.38 Å for **2A** and **2B**, respectively. The distances are comparable with those for Cu(L-Trp)(bpy) (Trp = tryptophanate),[13c] Cu(L-Trp)(phen),[13a,b] and Cu(L-Tyr)(bpy)[12e] with the distances of 3.67, 3.51, and 3.35 Å, respectively. A close contact between the Cu(II) ion and the carbon atom of the side chain aromatic ring is observed (Cu···C(14) = 3.30 Å in **1**, and Cu(A)···C(16A) = 3.03 Å and Cu(B)···C(16B) = 3.18 Å in **2A** and **2B**, respectively).

Interestingly, complex **3** contains two different forms, **3A** and **3B**, in the unit cell (Figure 4); **3A** involves the intramolecular aromatic ring stacking and **3B** does not. The copper coordination sphere of these complex cations (Cu(A)−O(1A) = 1.968(8) Å, Cu(A)−N(1A) = 2.02(1) Å, Cu(A)−N(2A) = 1.988(9) Å, Cu(A)−N(3A) = 2.046(8) Å, and Cu(A)−Cl(A) = 2.486(4) Å for **3A** and Cu(B)−O(1B) = 1.953(9) Å, Cu(B)−N(1B) = 2.018(10) Å, Cu(B)−N(2B) = 2.04(1) Å, Cu(B)−N(3B) = 1.986(9) Å, and Cu(B)−Cl(B) = 2.563(4) Å for **3B**) are similar to those of **1** and **2**, one chloride ion instead of an amino nitrogen or a water molecule occupying an axial position. The mode of the aromatic ring stacking interaction in **3A** is essentially the same as that in **1** and **2**, and the side chain conformation of **3B** is very similar to that of **4**, described below. The side chain aromatic ring of the amino acid in **3A** is stacked approximately parallel to the coordination plane with the average spacing of 3.39 Å. There is also a close contact between the Cu(II) ion and the carbon atom of the stacked aromatic ring (Cu(A)···C(16A) = 3.33 Å).

The crystal of **4** contains two independent $[Cu(L\text{-Phe})(bpy)(H_2O)]^+$ complexes, **4A** and **4B**, having essentially the same

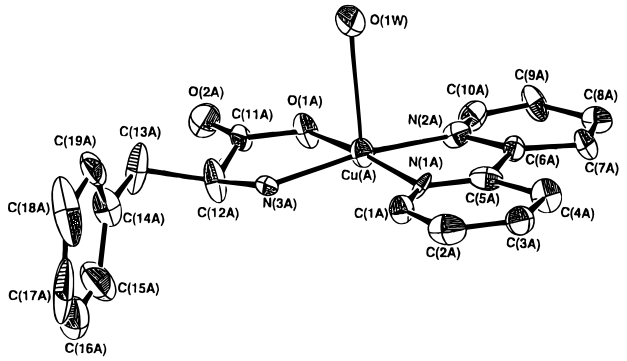

Figure 5. Structure of one of two crystallographically independent molecules of $[Cu(L\text{-Phe})(bpy)(H_2O)]^+$ (**4**). The perchlorate ion and hydrogen atoms were omitted for clarity.

structure. Figure 5 shows a perspective view of **4A**, where each Cu(II) ion coordinates bpy and L-Phe (Cu(A)−O(1A) = 1.94(1) Å, Cu(A)−N(1A) = 1.96(1) Å, Cu(A)−N(2A) = 2.01(1) Å, Cu(A)−N(3A) = 2.00(1) Å, Cu(B)−O(1B) = 1.92(1) Å, Cu(B)−N(1B) = 2.06(1) Å, Cu(B)−N(2B) = 2.00(1) Å, and Cu(B)−N(3B) = 1.99(1) Å) in the square plane in the same manner as above and one water molecule at an axial position (Cu(A)−O(1W) = 2.50(1) Å and Cu(B)−O(2W) = 2.27(1) Å) to form a square pyramid. The bond lengths around the Cu atom agree well with those reported for five-coordinate Cu(II) complexes.[25] The side chain aromatic ring of L-Phe is located approximately perpendicular to the coordination plane, and although there is no intramolecular stacking, it is located above the bpy of the symmetrically related complex molecule. The bpy ligand in turn is stacked with the bpy ligand of a neighboring complex. In this connection, the side chain aromatic ring of L-Phe in **5** extends away from the coordination plane without stacking[26] and that in a similar complex reported very recently, $[Cu(L\text{-Phe})(phen)]ClO_4\cdot H_2O$, is also without stacking.[27]

Substituent Effects on Absorption and CD Spectra and Molecular Orbitals. The intensity of the difference spectra around 320 nm that is observed for the ternary systems increases with the electron-donating properties of the substituent X of L-XPhe. In line with this, the CD magnitude decrease, $\Delta\epsilon_r$, corresponds with the electron-withdrawing ability of X. For example, the CD spectral change for the Cu(II)−L-NO_2Phe−bpy system has a $\Delta\epsilon_r$ value of 31.4% for X = NO_2 while it is 20.2% for X = H (Table 6). This suggests that in the complexes with aromatic ring stacking, coordinated DA, which is electron deficient, serves as a CT acceptor, whereas the side chain aromatic ring of coordinated amino acids acts as a CT donor. However, the relationship between the CT band intensity and the distance between the stacked rings is not straightforward.

The strength of the $\pi-\pi$ stacking interactions in $[Cu(L\text{-XPhe})(phen)]^+$, as seen from the solvent effect on the CD magnitude, may be explained by molecular orbital calculations by the extended Hückel molecular orbital (EHMO) method[28] performed

(26) Ruiz-Ramirez, L.; Martinez, A.; Gasque, L. *Acta Crystallogr.* **1988**, *C44*, 628. X-ray analysis of **5** performed in the present study gave the same structure. *Crystal data*: Monoclinic, $P2_1$, a = 5.777(4) Å, b = 20.663(7) Å, c = 9.338(4) Å, β = 97.61(4)°, V = 1104.9 Å^3, Z = 2, R = 0.056, R_w = 0.070, for 3159 observed reflections [$I > 3\sigma(I)$]. Important bond lengths are as follows: Cu−O(1) = 1.937(4) Å, Cu−N(1) = 2.029(5) Å, Cu−N(2) = 2.013(4) Å, Cu−N(3) = 1.971(4) Å, and Cu−O(1W) = 2.223(5) Å.

(27) Abdel-Rahman, L. H.; Battaglia, L. P. *Polyhedron* **1996**, *15*, 327−334.

(28) (a) Hoffmann, R. *J. Chem. Phys.* **1962**, *36*, 2179−2189. (b) Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397−1412.

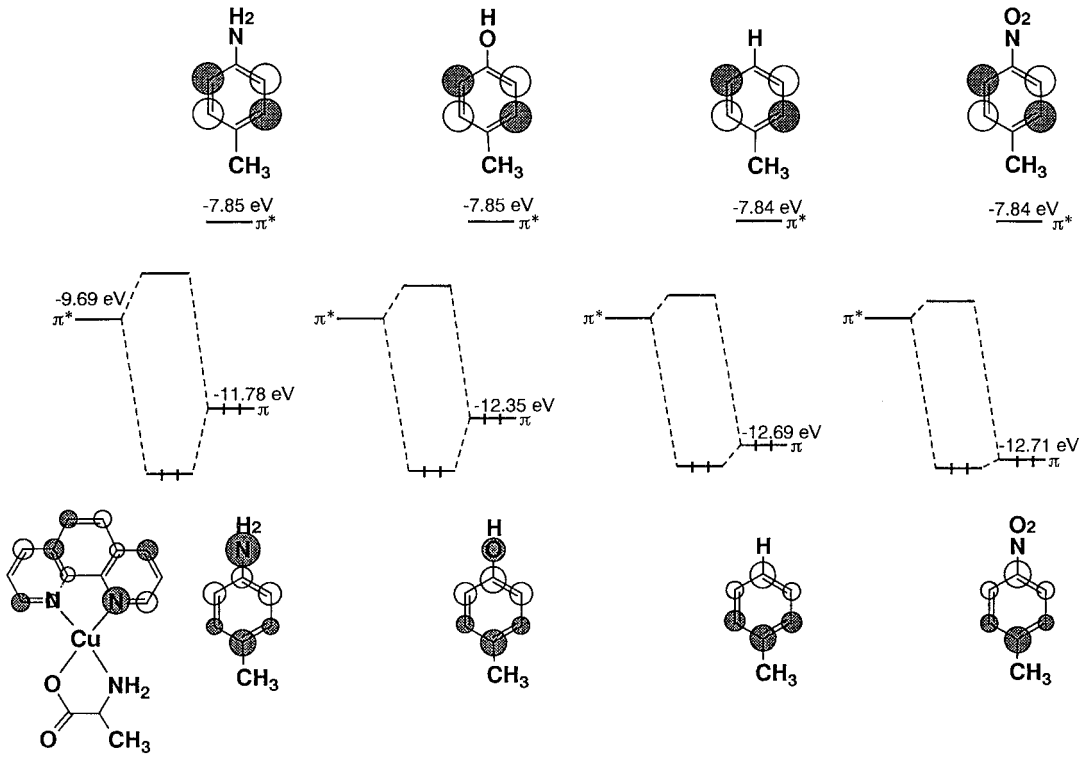

Figure 6. Frontier π and π^* molecular orbitals and energy levels of the [Cu(phen)(L-Ala)]$^+$ and *p*-X-toluenes (X = NH_2, OH, H, NO_2).

by using the program coded by Kitaura.[29] On the basis of the consideration of the symmetry properties of orbitals, the overlap between the π and π^* molecular orbitals with the same signs is considered to affect the $\pi-\pi^*$ transition and its probability: The stronger the interaction between them, the higher the transition probability. The calculations were made for [Cu(phen)(L-Ala)]$^+$ (Ala = alanine) and *para*-X-substituted toluenes (*p*-X-toluene; X = NH_2, OH, H, NO_2), which are considered as models for XPhe, by assuming the idealized geometries of the molecules and the most probable Cu−N bond lengths[25] with the use of the atomic orbital parameters reported by Hoffmann et al.[30] We found that [Cu(phen)(L-Ala)]$^+$ has a large distribution of the lowest unoccupied molecular orbital (LUMO) (π^*) on the phen ring, which was energetically attracted by the central metal atom, and that *p*-X-toluene has a large distribution of the highest occupied molecular orbital (HOMO) (π) on the benzene ring, as depicted in Figure 6. The results indicate that a new bonding orbital is formed by the $\pi-\pi^*$ interaction between these frontier orbitals, because their signs agree well with each other when the aromatic rings are stacked to form the same structures as established by the present studies. A systematic increase in the energy level of the HOMOs with the increase of the electron-donating ability of the substituents was noticed for *p*-X-toluenes: The energy level increase of the HOMOs decreases the energy difference between the HOMO and LUMO and thus favors the CT between them, which results in a more effective stacking interaction between the benzene ring and the phen ring of [Cu(phen)(L-Ala)]$^+$. The changes in the charge transfer bands (Figure 1) reflect this situation. The more intense CT band for complex **1**, as compared with that of the other complexes, may be explained as due to a more favorable structure of **1** for orbital interactions and thus the $\pi-\pi^*$ transition. It may be concluded, therefore, that the stacking occurs through the $\pi-\pi^*$ interaction between the HOMO (π) on the benzene ring and the LUMO (π^*) on the phen ring, which is in line with the conclusion from the spectra.

Interpretation of Structural Differences Due to Substituents. From the structural information described above, we found some differences in intramolecular stacking interactions between the five complexes. Complexes **1** and **2** involve intramolecular stacking, whereas **4** and **5** do not. On the basis of the spectral properties and EHMO calculations, this difference may be regarded as mainly due to the different substituents in the benzene ring of Phe. Such a substituent effect has been reported for the complexes involving halophenylalanines[13e] and the synthesis of their peptides by thermolysin,[31] but there has been no discussion from the viewpoint of molecular orbitals.

On the other hand, **3** exhibits some remarkable structural features. This complex has two typical structures in the solid state, one with intramolecular stacking and the other without it, which shows that the side chain conformation of Phe is affected by the anions, axial ligation, and packing in the crystal. The finding suggests that Phe is intermediate in terms of the ability of intramolecular stacking in ternary Cu(II) complexes.

Concluding Remarks and Biological Implication. Spectral, equilibrium, and X-ray studies have shown that intramolecular aromatic ring stacking occurs between the *para*-substituted phenyl ring of XPhe and coordinated DA in Cu(XPhe)(DA) in solution and in **1**, **2,** and **3A** in the solid state. In biological systems, Phe is important in many ways, some of which are protein stabilization, electron transfer, and formation of a hydrophobic environment, which may be due to the intermediate stability of the stacking it undergoes. According to the crystal structures of proteins, aromatic−aromatic interactions between Phe residues more favorably occur through the edge-to-face stacking rather than the face-to-face stacking,[32] the former of which may be regarded as a CH−π interaction, an interaction

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between partially positively charged hydrogen atoms of the aromatic ring and partially negatively charged carbon atoms of the other interacting ring.[32a,b] Preliminary results of our *ab initio* density functional molecular orbital calculations on [Cu(L-Trp)(bpy)(H_2O)]$^+$ indicated that bonding orbitals are formed between Cu(II) and the indole ring of Trp and between the Cu(II)-coordinated bpy and the indole ring.[33] Stacking involving the Trp indole ring and coordinated DA or other coordinated aromatic rings, such as a phenolate moiety, is considered to be strong due to a large electron density difference and is actually found in proteins; in galactose oxidase, the Cu-coordinated phenolate moiety with a thioether side chain is effectively stacked with an indole ring of a neighboring Trp residue.[9] However, such a strong stacking may not be favorable for certain biological reactions requiring rapid orientation of molecules involved in stacking. The fact that stacking has been detected for **1** and **2**, both having a substituent with a higher electron density on the phenyl ring, suggests that Trp and Tyr residues tend to undergo face-to-face interactions with other aromatic rings whereas Phe is more likely to be involved in edge-to-face interactions. Since protein structures are rigid and, therefore, orientation of aromatic side chains must be limited, Phe may be versatile and preferred for protein stabilization and formation of a hydrophobic environment. Serrano et al. concluded from the studies on mutated ribonuclease barnase that Tyr−Tyr and Phe−Phe interactions make identical contributions to protein stability, although Tyr is preferred at the face of the α-helix that is exposed to the solvent.[34]

On the basis of the present findings, we infer that aromatic rings with a large electron density difference prefer face-to-face stacking whereas those with a small difference prefer edge-to-face stacking. *Ab initio* molecular orbital calculations on ternary Cu(II) complexes will afford more information and substantiate our experimental results.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (Bioinorganic Chemistry, 04225102) from the Ministry of Education, Science, Sports, and Culture of Japan for which we express our thanks.

Supporting Information Available: Tables of atomic coordinates and anisotropic thermal parameters for non-hydrogen atoms, fractional coordinates and isotropic thermal parameters for hydrogen atoms, and bond lengths and angles for complexes **1**, **2**, **3**, **4**, and **5** (39 pages). Ordering information is given on any current masthead page.

IC9608556

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