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Structures and Properties of Ternary Copper(II) Complexes Involving a Halogen Substituted Phenylalanine and 2,2′-Bipyridine. Intermolecular Interactions between Halo and Organic Groups

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Structural and spectroscopic studies have been performed on the ternary Cu(II) complexes containing 4-halophenylalanines (XPhe) (X=I or Br) and 2,2′-bipyridine (bpy). The absorption spectra of the 1:1:1 Cu(bpy)(XPhe) systems exhibited a single d–d peak at 605—608 nm (pH 6—7), and the band centered at ca. 320 nm due to the charge transfer interaction between the substituted phenyl ring and bpy was observed in the difference spectra in the near ultraviolet region. Three complexes with XPhe, [Cu(bpy)(DL-IPhe)(NO_3)] (**1**), [Cu(bpy)(DL-BrPhe)(NO_3)] (**2**), and [Cu(bpy)(L-IPhe)]ClO_4 (**3**) were isolated as crystals, and the structures were determined by the X-ray diffraction method. Complex **1** crystallizes in the monoclinic space group, $P2_1/n$, with four molecules in a unit cell of dimensions a=5.292(1), b=27.315(8), c=13.848(2) Å, β=90.05(2)°. Complex **2** also crystallizes in the monoclinic space group, $P2_1/n$, with four molecules in a unit cell of dimensions a=5.293(5), b=27.18(1), c=13.540(6) Å, β=90.03(6)°. The Cu(II) ion in each complex is in a five-coordinate distorted square-pyramidal geometry. Complex **3** crystallizes in triclinic space group $P1$ with two independent molecules in the asymmetric unit in a unit cell of dimensions a=18.329(4), b=10.701(1), c=5.9287(9) Å, α=73.91(1), β=90.02(2), γ=105.93(2)°. The Cu(II) ion is in a four-coordinate, slightly distorted square-planar geometry. The phenyl ring of XPhe in **1** and **2** is located perpendicular to the bpy plane, and no intramolecular stacking was observed. The phenyl ring of L-IPhe in **3** is tilted over the coordination plane to be stacked with bpy with the average spacing of 3.23 and 3.24 Å. The crystal structures revealed close contacts between the halogen atoms and the carbon atoms of the bpy ring in complexes **1** and **2**, with the distances of I···C=3.54 Å and Br···C=3.47 Å for **1** and **2**, respectively. A close contact between the iodine and carbonyl oxygen was also detected in the crystal structure of **3** with the I···O distance of 3.1 Å. Possible significance of these interactions has been discussed in relation to thyroid hormone-receptor bonding.

Intermolecular interactions involving amino acid side groups and other biological functional groups are vital for such biological events as protein structuring, specific and efficient catalysis by enzymes, and molecular recognition in hormone-receptor bonding.[1,2] Biological systems with a metal center show intramolecular hydrogen bonds and aromatic ring stacking interactions that can be regarded as ligand–ligand interactions around the central metal ion, a classical example of which is provided by the carboxypeptidase A–substrate complex.[3] Recent studies have revealed unique interactions between DNA and DNA-binding proteins such as TFIIIA containing zinc fingers,[4] whose binding with DNA at a specific site upon Zn(II) complex formation has been revealed for Zif268 to occur through the hydrogen bonds between the arginine guanidinium group of the zinc fingers and the guanine moiety of DNA.[5]

On the other hand, there is a different type of noncovalent interactions involving biological molecules. Thyroid hormones, thyroxine and other thyronine derivatives, have iodo substituents as essential components for their biological activity, and the X-ray structural study of 3,3′-diiodo-L-thyronine bound to human serum transthyretin[6] has disclosed that the iodo groups are involved in the interactions with the carbonyl and hydroxyl oxygens. The I_2–benzene charge-transfer (CT) interactions have been known for a long time and are explained by a polar bond due to high polarizability of the iodine atom.[7] However, in spite of the fact that the iodo groups in thyroid hormones are the only well established biological use of the iodine atom, its significance in thyroxine-receptor bonding is largely unknown. We have been studying noncovalent interactions in mixed ligand metal complexes containing amino acids and peptides. By X-ray crystal structure determinations and spectroscopic and thermodynamic investigations we have revealed aromatic ring stacking between aromatic amino acid side chains and 2,2′-bipyridine (bpy) etc. and hydrogen bonds or electrostatic interactions between polar or charged groups, e. g., the arginine guanidinium and the aspartate carboxylate group.[8] The complexes with these weak interactions have been found to be stabilized relative to those without the interactions,[8—12] indicating that they exist in solution as well as in the solid state and contribute to the stability.

With a view to obtaining basic information on the weak bonds involving a halo group and/or aromatic rings, we now carried out X-ray structural and spectroscopic investigations on aromatic ring stacking and possible aromatic ring-halogen interacions in the Cu(II) complexes containing bpy and 4-bromo- or 4-iodophenylalanine (XPhe, X=Br or I), Cu(bpy)(XPhe). To our knowledge, these are the first ternary metal complexes exhibiting noncovalent interactions involving the C–X moiety.

Table 1. Crystallographic Data for [Cu(bpy)(DL-IPhe)(NO_3)] (**1**), [Cu(bpy)(DL-BrPhe)(NO_3)] (**2**) and [Cu(bpy)(L-IPhe)]ClO_4 (**3**)

	1	**2**	**3**
Formula	$ICuO_5N_4C_{19}H_{17}$	$BrCuO_5N_4C_{19}H_{17}$	$ICuClO_6N_3C_{19}H_{17}$
Formula weight	571.82	524.82	609.27
Color	Purple	Purple	Blue
Crystal size/mm	0.1×0.2×0.4	0.1×0.3×0.4	0.1×0.1×0.5
Crystal system	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	$P2_1/n$	$P1$
a/Å	5.292(1)	5.293(5)	18.329(4)
b/Å	27.315(8)	27.18(1)	10.701(1)
c/Å	13.848(2)	13.540(6)	5.9287(9)
α/deg.	—	—	73.91(1)
β/deg.	90.05(2)	90.03(6)	90.02(2)
γ/deg.	—	—	105.93(2)
V/Å^3	2001.5	1947.8	1070.8
Z	4	4	2
D_c/g cm^{-3}	1.898	1.790	1.890
λ /Å	0.71073 (Mo $K\alpha$)	0.71073 (Mo $K\alpha$)	0.71073 (Mo $K\alpha$)
μ/cm^{-1}	26.58	31.94	26.14
F(000)	1124.0	1052.0	598.0
Scan method	ω–2θ	ω–2θ	ω–2θ
$2\theta_{max}$/deg.	60	60	60
Scan speed/deg min^{-1}	4—12	4—12	4
Scan range/deg.	1.2	1.2	1.0
No. of refls. used	2492	3295	5142
R	0.097	0.072	0.079
R_w	0.113	0.060	0.134

Experimental

Materials. DL-IPhe, DL-BrPhe, and L-IPhe were purchased from Sigma. $Cu(NO_3)_2 \cdot 3H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, L-phenylalanine (L-Phe), and bpy were obtained from Nacalai Tesque. All other chemicals used were of analytical grade or highest grade available.

Synthesis of Ternary Cu(II) Complexes [Cu(bpy)(DL-IPhe)(NO_3)] (1), [Cu(bpy)(DL-BrPhe)(NO_3)] (2), and [Cu(bpy)(L-IPhe)]ClO_4 (3). These complexes were prepared by the following procedure. To a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (121 mg, 0.5 mmol) or $Cu(ClO_4)_2 \cdot 6H_2O$ (185 mg, 0.5 mmol) was added an aqueous methanol solution of bpy (78 mg, 0.5 mmol), XPhe (0.5 mmol), and aqueous NaOH. The resulting solutions were kept for a few week at room temperature, when single crystals suitable for X-ray analysis were obtained as needle-like crystals.

Spectroscopic Measurements. Electronic spectra were measured at room temperature on a Shimadzu UV-3101PC spectrophotometer in quartz cells with a path length of 10 mm. Samples for the measurements were freshly prepared at pH 6—7 in the 1 : 1 : 1 ratio of Cu(II), bpy, and XPhe, the concentrations of Cu(II) being 1—5 mM (M=mol dm^{-3}).

X-Ray Structure Determinations of Complexes 1, 2, and 3. Crystal data and experimental details for the complexes are summarized in Table 1. Diffraction data for **1** and **2** were obtained with an Enraf–Nonius CAD4 and those for **3** with a Rigaku AFC-5R four-circle automated diffractometer. The reflection intensities were monitored by three standard reflections at every 2 h for **1** and **2** and at every 150 measurements for **3**, respectively, and the decays of intensities for these crystals were within 2%. Reflection data were corrected for Lorentz and polarization effects. Absorption corrections were empirically applied in all the cases.

The structures were solved by the heavy-atom method and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. All refinements were 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 literature.13) All hydrogen atoms for the three structures were included as isotropic in the structure factor calculations at the final stage of refinement; their positions were located on the calculated positions. The final R and R_w values were 0.097 and 0.113 for **1**, 0.072 and 0.060 for **2**, and 0.079 and 0.134 for **3**. The weighting scheme $w^{-1} = (\sigma^2(F_o) + (0.015F_o)^2)$ was employed for all crystals. The final difference Fourier map did not show any significant features except the ghost peaks close to Cu, Br, and I atoms. 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.14)

The final atomic parameters for non-hydrogen atoms for **1**,**2**, and **3** are given in Tables 2, 3, and 4, respectively, and the selected bond lengths and angles are summarized in Table 5. Tables of the final parameters for all non-hydrogen atoms and positions of hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond lengths and angles, torsion angles, and observed and calculated structure factor amplitudes are deposited as Document No. 67005 at the Office of the Editor of Bull. Chem. Soc. Jpn.

Table 2. Positional Parameters and Equivalent Isotropic Temperature Factors for the Non-Hydrogen Atoms of [Cu(bpy)(DL-IPhe)NO_3] (**1**)

Atom	x	y	z	B_{eq}
I	0.2220(5)	0.90081(8)	0.6035(1)	4.60
Cu	0.4120(7)	0.8790(1)	1.0209(2)	2.06
O(1)	0.277(3)	0.9415(6)	0.049(1)	2.8
O(2)	0.847(3)	0.4864(6)	0.618(1)	3.4
O(3)	0.672(4)	0.6563(7)	0.653(1)	4.6
O(4)	0.464(4)	0.8124(7)	0.238(1)	4.3
O(5)	0.669(4)	0.7327(7)	0.676(2)	5.2
N(1)	0.517(4)	0.8102(7)	0.986(1)	2.2
N(2)	0.671(3)	0.6329(6)	0.414(1)	1.8
N(3)	0.677(3)	0.8967(6)	0.118(1)	1.9
N(4)	0.265(4)	0.8073(8)	0.190(1)	3.4
C(1)	0.207(5)	0.715(1)	0.531(2)	3.0
C(2)	0.750(6)	0.737(1)	1.006(2)	3.8
C(3)	0.611(6)	0.717(1)	0.935(2)	4.0
C(4)	0.416(5)	0.7406(9)	0.890(2)	2.9
C(5)	0.382(4)	0.7904(8)	0.917(2)	1.9
C(6)	0.681(5)	0.6805(8)	0.376(2)	2.4
C(7)	0.515(5)	0.6933(9)	0.302(2)	2.7
C(8)	0.338(5)	0.662(1)	0.272(2)	3.2
C(9)	0.320(5)	0.6141(8)	0.312(2)	2.2
C(10)	0.492(5)	0.6035(9)	0.384(1)	2.4
C(11)	0.410(5)	1.9713(9)	0.098(1)	2.3
C(12)	0.678(4)	0.953(1)	0.125(2)	2.5
C(13)	0.777(4)	0.9711(9)	0.218(2)	2.5
C(14)	0.648(5)	0.9539(8)	0.309(2)	2.6
C(15)	0.428(6)	0.979(1)	0.342(2)	3.5
C(16)	0.309(6)	0.962(1)	0.427(2)	4.4
C(17)	0.381(6)	0.923(1)	0.474(2)	4.1
C(18)	0.611(6)	0.895(1)	0.441(2)	4.5
C(19)	0.718(5)	0.9122(9)	0.355(2)	3.3

Table 3. Positional Parameters and Equivalent Isotropic Temperature Factors for the Non-Hydrogen Atoms of [Cu(bpy)(DL-BrPhe)NO_3] (**2**)

Atom	x	y	z	B_{eq}
Cu	0.9255(1)	0.1195(1)	0.5205(1)	2.2
Br	0.7617(2)	0.1027(1)	1.1023(1)	5.4
O(1)	0.7780(6)	0.0574(1)	0.5503(3)	2.6
O(2)	0.8482(8)	−0.0143(1)	0.6242(3)	3.5
O(3)	0.6779(8)	0.1532(2)	0.6558(4)	4.4
O(4)	0.6887(9)	0.2317(2)	0.6770(4)	5.2
O(5)	0.9799(9)	0.1864(2)	0.7401(4)	4.7
N(1)	0.6826(8)	0.1334(2)	0.4127(3)	2.2
N(2)	1.0393(8)	0.1878(2)	0.4859(3)	2.5
N(3)	1.1891(8)	0.0993(2)	0.6169(3)	2.6
N(4)	0.7822(9)	0.1910(2)	0.6924(3)	3.3
C(1)	0.5050(11)	0.1022(2)	0.3791(4)	2.7
C(2)	0.3384(11)	0.1152(2)	0.3050(4)	2.9
C(3)	0.3563(12)	0.1615(2)	0.2652(4)	3.2
C(4)	0.5362(11)	0.1939(2)	0.2989(4)	2.8
C(5)	0.6959(10)	0.1789(2)	0.3729(4)	2.3
C(6)	0.8934(10)	0.2103(2)	0.4165(4)	2.4
C(7)	0.9309(11)	0.2590(2)	0.3920(5)	3.2
C(8)	1.1212(12)	0.2846(2)	0.4368(5)	3.5
C(9)	1.2667(12)	0.2622(2)	0.5074(5)	3.5
C(10)	1.2221(11)	0.2135(2)	0.5301(4)	3.0
C(11)	0.9179(10)	0.0269(2)	0.6011(4)	2.5
C(12)	1.1811(10)	0.0450(2)	0.6254(4)	2.3
C(13)	1.2795(11)	0.0265(2)	0.7252(4)	2.9
C(14)	1.1486(10)	0.0464(2)	0.8145(4)	2.5
C(15)	0.9360(11)	0.0232(2)	0.8517(4)	3.1
C(16)	0.8198(12)	0.0405(3)	0.9366(5)	3.8
C(17)	0.9183(12)	0.0812(2)	0.9835(4)	3.6
C(18)	1.1292(13)	0.1051(2)	0.9481(5)	4.0
C(19)	1.2419(11)	0.0873(2)	0.8640(5)	3.4

Results and Discussion

Molecular Structures of [Cu(bpy)(DL-IPhe)(NO_3)] (1) and [Cu(bpy)(DL-BrPhe)(NO_3)] (2). Crystals of **1** and **2** are isomorphic. Figure 1a shows a perspective view of **1** with the atom numbering scheme. The copper atom coordinates two nitrogen atoms of bpy and one nitrogen and one oxygen atom of DL-IPhe in the equatorial positions (Cu–N(1)=2.02(2), Cu–N(2)=1.98(2), Cu–N(3)=2.00(2), and Cu–O(1)=1.89(2) Å) and one nitrate oxygen in an apical position (Cu–O(3)=2.43(2) Å), the resulting coordination polyhedron being described as a square-pyramid. The molecular structure of **2** is given in Fig. 2. The coordination geometry around the copper atom is considered to be square-pyramidal with the same ligand atoms as in **1** in equatorial (Cu–N(1)=2.007(5), Cu–N(2)=1.981(5), Cu–N(3)=1.988(5), and Cu–O(1)=1.903(4) Å) and apical (Cu–O(3)=2.432(5) Å) positions.

These complex structures are very similar to each other. The side chain aromatic ring of the amino acids is located perpendicular to the Cu coordination plane, so that there is no such intramolecular aromatic ring stacking as is observed in the crystal structure of **3** described below. The halogen atom of XPhe contacts with the bpy ring of a neighboring molecule in the crystal structure with the separations of 3.54 and 3.47 Å for **1** and **2** (Fig. 1b), respectively, which are shorter than the sums of the van der Waals radii of X (=I, Br) and bpy carbon atoms, C···I=3.75 and C···Br=3.62 Å.15)

Molecular Structure of [Cu(bpy)(L-IPhe)]ClO_4 (3). Complex **3** crystallizes in space group $P1$ with two independent molecules in the asymmetric unit. The structures of the complex cations are very similar to each other, and one of them is illustrated in Fig. 3. The central Cu(II) ion in each cation, five-coordinated, has an approximately square-pyramidal geometry, where the two nitrogen atoms of bpy and the amino nitrogen and carboxylate oxygen atoms of L-IPhe constitute the slightly distorted square-planar base (Cu(A)–N(1A)=2.01(2), Cu(A)–N(2A)=2.04(2), Cu(A)–N(3A)=2.01(2), Cu(A)–O(1A)=1.92(1), Cu(B)–N(1B)=1.98(2), Cu(B)–N(2B)=2.04(1), Cu(B)–N(3B)=2.04(1), and Cu(B)–O(1B)=1.94(1) Å) and the perchlorate oxygen atom loosely occupies the apical position with a long Cu–O distance (Cu(A)···O(P1A)=3.00, and Cu(B)···O(P1B)=2.88 Å). The dihedral angles between the planes formed by Cu–O(1)–N(3) and Cu–N(1)–N(2)

Table 4. Positional Parameters and Equivalent Isotropic Temperature Factors for the Non-Hydrogen Atoms of [Cu(bpy)(L-IPhe)]ClO_4 (**3**)

Atom	x	y	z	B_{eq}
I(A)	0	0	0	4.1
I(B)	0.2305(1)	0.6615(1)	0.1692(3)	4.2
Cu(A)	−0.1534(1)	0.4417(2)	−0.2489(4)	2.7
Cu(B)	0.3848(1)	0.2203(2)	0.3620(4)	2.6
Cl(A)	0.7502(4)	0.7183(5)	0.4401(10)	4.2
Cl(B)	−0.5206(4)	0.9435(5)	0.3275(10)	4.1
O(1A)	−0.1057(9)	0.5163(13)	−0.5638(21)	3.1
O(2A)	−0.0200(10)	0.6936(14)	−0.8036(23)	4.0
O(1B)	0.3339(9)	0.1439(13)	0.1238(20)	3.2
O(2B)	0.2492(10)	−0.0330(14)	0.0626(21)	4.0
O(P1A)	0.7347(13)	0.6026(21)	0.6143(31)	6.5
O(P2A)	0.6957(12)	0.7884(21)	0.4829(42)	6.3
O(P3A)	0.8223(13)	0.8057(18)	0.4422(40)	6.4
O(P4A)	0.7321(18)	0.7017(18)	0.2114(34)	8.5
O(P1B)	−0.5081(11)	1.0653(18)	0.3767(33)	5.1
O(P2B)	−0.5943(12)	0.8548(17)	0.4160(41)	6.3
O(P3B)	−0.4656(11)	0.8750(19)	0.4428(40)	6.0
O(P4B)	−0.4945(25)	0.9480(24)	0.0957(39)	12.9
N(1A)	−0.2281(10)	0.3518(17)	0.0357(28)	3.3
N(2A)	−0.1827(10)	0.2459(14)	−0.2607(27)	2.8
N(3A)	−0.0978(10)	0.6240(15)	−0.2132(24)	2.9
N(2B)	0.4120(9)	0.4173(14)	0.1585(24)	2.7
N(1B)	0.4566(11)	0.3092(17)	0.5585(26)	3.3
N(3B)	0.3254(10)	0.0370(15)	0.5823(25)	2.9
C(1A)	−0.2537(14)	0.4214(22)	0.1658(36)	3.7
C(2A)	−0.3107(15)	0.3476(30)	0.3569(39)	4.8
C(3A)	−0.3345(16)	0.1965(33)	0.4156(46)	5.9
C(4A)	−0.3146(15)	0.1210(29)	0.2782(42)	5.1
C(5A)	−0.2591(12)	0.2065(23)	0.0853(34)	3.4
C(6A)	−0.2285(11)	0.1590(14)	−0.0778(31)	2.6
C(7A)	−0.2490(20)	0.0138(22)	−0.0551(39)	5.3
C(8A)	−0.2207(20)	−0.0271(23)	−0.2136(48)	5.5
C(9A)	−0.1711(17)	0.0602(25)	−0.3918(40)	4.8
C(10A)	−0.1534(15)	0.1933(29)	−0.4121(36)	4.5
C(11A)	−0.0515(14)	0.6335(19)	−0.6069(29)	3.2
C(12A)	−0.0303(12)	0.6829(17)	−0.3928(29)	2.6
C(13A)	0.0393(12)	0.6403(19)	−0.3024(31)	3.0
C(14A)	0.0294(11)	0.4890(18)	−0.2290(30)	2.6
C(15A)	0.0546(13)	0.4280(23)	−0.3828(35)	3.5
C(16A)	0.0421(12)	0.2874(19)	−0.3226(32)	2.9
C(17A)	0.0098(13)	0.2102(18)	−0.1023(35)	3.2
C(18A)	−0.0088(12)	0.2627(20)	0.0579(33)	3.2
C(19A)	0.0002(13)	0.4052(19)	−0.0028(30)	3.2
C(1B)	0.4816(14)	0.2380(25)	0.7598(35)	4.0
C(2B)	0.5366(10)	0.3143(18)	0.8720(30)	2.9
C(3B)	0.5701(10)	0.4571(20)	0.7805(33)	3.2
C(4B)	0.5420(11)	0.5251(18)	0.5784(31)	3.1
C(5B)	0.4894(12)	0.4548(25)	0.4660(35)	3.5
C(6B)	0.4595(16)	0.5191(31)	0.2448(37)	4.9
C(7B)	0.4781(11)	0.6447(17)	0.1341(33)	3.1
C(8B)	0.4467(19)	0.6897(21)	−0.0667(42)	5.4
C(9B)	0.3991(19)	0.5997(27)	−0.1535(39)	5.5
C(10B)	0.3798(13)	0.4612(22)	−0.0439(32)	3.5
C(11B)	0.2805(13)	0.0288(17)	0.1944(29)	2.9
C(12B)	0.2597(12)	−0.0198(17)	0.4582(28)	2.7
C(13B)	0.1881(13)	0.0209(19)	0.5099(32)	3.4
C(14B)	0.1991(12)	0.1735(21)	0.4333(32)	3.2
C(15B)	0.1757(12)	0.2346(24)	0.2120(35)	3.6
C(16B)	0.1863(12)	0.3734(19)	0.1345(33)	2.9
C(17B)	0.2182(13)	0.4555(19)	0.2711(35)	3.2
C(18B)	0.2391(13)	0.3991(21)	0.4927(35)	3.3
C(19B)	0.2271(15)	0.2563(22)	0.5690(33)	3.8

were 21.8° and 22.8° for cations A and B. The aromatic ring of L-IPhe is tilted over the coordination plane to be involved in the intramolecular stacking with the coordinated bpy rings, being approximately parallel to the bpy plane with the average spacing of 3.24 and 3.23 Å for cations A and B, respectively. The Cu(II) ion is in close contact with the carbon atoms of the iodophenyl ring with the distances Cu(A)$\cdots$C(19A)=3.24, Cu(A)$\cdots$C(14A)=3.26, Cu(B)$\cdots$C(19B)=3.30, and Cu(B)$\cdots$C(14B)=3.31 Å, which are slightly longer than those reported previously for Cu(bpy)(L-tyrosinate),[12] probably because of the steric hindrance due to the bulky iodo group. There are also some close contacts between the iodine atom and the carbon atoms of the bpy ring (I(A)$\cdots$C(9A)=3.99 and I(B)$\cdots$C(9B)=3.93 Å). The iodo group of L-IPhe is in close van der Waals contact with the carbonyl oxygen atom of the neighboring molecule (I(A)$\cdots$O(2A$'$)=3.08 and I(B)$\cdots$O(2B$'$)=3.07Å), which are significantly smaller than the sum of their van der Waals radii (I$\cdots$O=3.50 Å).[15]

Absorption Spectra of Ternary Complexes. The ternary Cu(bpy)(XPhe) (XPhe=L-Phe, DL-BrPhe, and DL-IPhe) systems in aqueous solution at pH 6—7 exhibited d–d absorption peaks at 606 nm (ε 72), 607 nm (ε 75), and 605 nm (ε 75) for L-Phe, DL-BrPhe, and DL-IPhe, respectively, which correspond to a planar complex with a CuN_3O chromophore.[11a)] The difference spectra obtained by subtracting the spectral magnitudes for 1 : 1 : 1 Cu(II)–bpy–L-alaninate and XPhe from those for [Cu(bpy)(XPhe)(NO_3)] gave a weak broad peak at ca. 320 nm, which is ascribable to the charge transfer (CT) between stacked aromatic rings in the complexes (Fig. 4).[16] Similar CT bands have also been reported for the systems [Cu(bpy)(L-tryptophanate)]$^+$,[17] [H(phen)(L-tryptophan)],[11a)] and indole-oxidized nicotinamide adenine dinucleotide.[18] The CT band shifted to longer wavelengths in the order Phe< BrPhe<IPhe with concomitant increase in the intensity, on which the difference in the counter anions had no effect. The shift to a longer wavelength and the intensity increase may result from a more effective stacking interaction, because the large uncharged substituent that has high polarizability could contribute to the expansion of the interacting area. Higher absorption intensity exhibited by [Cu(bpy)(DL-IPhe)(NO_3)] and [Cu(bpy)(DL-BrPhe)(NO_3)] compared with that by [Cu(bpy)(L-Phe)(NO_3)] suggests the presence of halogen atom-bpy ring interactions, which is further supported by the close contact between them as illustrated in Fig. 3.

Table 5. Selected Bond Lengths (Å) and Angles (°) for Complexes **1**, **2**, and **3**

a) [Cu(DL-IPhe)(bpy)(NO$_3$)] (**1**)		b) [Cu(DL-BrPhe)(bpy)(NO$_3$)] (**2**)		c) [Cu(L-IPhe)(bpy)]ClO$_4$ (**3**)	
Bond length		Bond length		Bond length	
Cu–O(1)	1.89(2)	Cu–O(1)	1.903(4)	Cu(A)–O(1A)	1.92(1)
Cu–O(3)	2.43(2)	Cu–O(3)	2.432(5)	Cu(A)–N(1A)	2.01(2)
Cu–N(1)	2.02(2)	Cu–N(1)	2.007(5)	Cu(A)–N(2A)	2.04(2)
Cu–N(2)	1.98(2)	Cu–N(2)	1.981(5)	Cu(A)–N(3A)	2.01(2)
Cu–N(3)	2.00(2)	Cu–N(3)	1.988(5)	Cu(B)–O(1B)	1.94(1)
				Cu(B)–N(1B)	1.98(2)
				Cu(B)–N(2B)	2.04(1)
				Cu(B)–N(3B)	2.04(1)
Bond angle		Bond angle		Bond angle	
O(1)–Cu–O(3)	90.3(6)	O(1)–Cu–O(3)	87.3(2)	O(1A)–Cu(A)–N(1A)	164.8(7)
O(1)–Cu–N(1)	173.7(8)	O(1)–Cu–N(1)	173.2(2)	O(1A)–Cu(A)–N(2A)	94.7(6)
O(1)–Cu–N(2)	93.4(7)	O(1)–Cu–N(2)	93.4(2)	O(1A)–Cu(A)–N(3A)	84.0(6)
O(1)–Cu–N(3)	84.7(7)	O(1)–Cu–N(3)	84.4(2)	N(1A)–Cu(A)–N(2A)	79.5(7)
O(3)–Cu–N(1)	87.3(7)	O(3)–Cu–N(1)	89.4(2)	N(1A)–Cu(A)–N(3A)	105.2(7)
O(3)–Cu–N(2)	99.2(7)	O(3)–Cu–N(2)	97.7(2)	N(2A)–Cu(A)–N(3A)	164.5(8)
O(3)–Cu–N(3)	87.6(7)	O(3)–Cu–N(3)	89.3(2)	O(1B)–Cu(B)–N(1B)	167.6(7)
N(1)–Cu–N(2)	81.2(7)	N(1)–Cu–N(2)	81.2(2)	O(1B)–Cu(B)–N(2B)	95.6(6)
N(1)–Cu–N(3)	101.0(7)	N(1)–Cu–N(3)	101.4(2)	O(1B)–Cu(B)–N(3B)	82.7(6)
N(2)–Cu–N(3)	173.0(8)	N(2)–Cu–N(3)	172.6(2)	N(1B)–Cu(B)–N(2B)	79.6(6)
				N(1B)–Cu(B)–N(3B)	105.4(6)
				N(2B)–Cu(B)–N(3B)	161.3(7)

Crystal Structures and Weak Interactions Involving Aromatic Rings and Halogen Atoms. The crystal structures of **1**, **2**, and **3** exhibit various weak interactions involving aromatic rings, halogen atoms, and polar groups as schematically summarized in Fig. 5. Aromatic ring stacking in the solid state can be affected by various factors including the polarity of the solvent used for crystallization, presence of coordinating groups such as small anions and neighboring groups, and differences in crystal packing energies due to chirality of ligands. Since water was used as solvent throughout the experiments, the latter factors may account for the presence of the stacking interaction only in **3**. Interestingly the halogen atom of XPhe in all the complexes are involved in weak interactions with the bpy ring with the interatomic distances of 3.54, 3.47, and 3.93 and 3.99 Å for **1**, **2**, and **3**, respectively. The distances for **1** and **2** are 0.21 and 0.15 Å shorter than the values expected from the van der Waals radii,[15] respectively, indicating that there is an X···bpy noncovalent bonding interaction. Similar contacts have been found between Br and an aromatic ring in the crystal structures of the 1 : 1 adducts of benzene–bromine[19] and *p*-xylene–CBr$_4$[20] with the distances between Br and the center of the benzene ring=3.36 and 3.34 Å, respectively. In addition, the iodine atom in **3** is definitely in a bonding distance from the carbonyl oxygen of the coordinated carboxylate group of L-IPhe (I···O=C = ca. 3.1 Å) (Fig. 3b). A short I···O=C distance (2.94 Å) has been observed for the crystal structure of the 1 : 1 diiodoacetylene–cyclohexane-1,4-dione adduct.[21] Cody and Murray-Rust reported an extensive survey of the Cambridge Crystallographic Data Base for compounds containing C–I bonds that have C–I···O (N, S) distances less than 3.55 Å.[22] They found the contacts between I and the nucleophiles are such that the distances are the shortest with the C–I···O (N, S) angles close to 180°. On the other hand, a recent X-ray structure determination of Cu(II)–3,5-diiodo-L-tyrosinate showed the Cu(II)···I interaction (3.248 Å) at an axial position.[23]

Biological Significance of Halogen Substituents. In biological systems, the iodine atom plays an important role as an essential component of thyroid hormones. The above observations indicate that halogen substituents in the benzene ring exhibit versatile interactions with polar or polarizable groups and thus may be bound to a variety of protein side groups. The interactions between the oxygen and iodine atoms have been observed in the complexes of transthyretin with thyroxine[24] and 3,3′-diiodo-thyronine,[6] where close contacts were detected between the carbonyl oxygen of alanine 109 and I (I···O=2.96 Å) and between the hydroxyl oxygen of serine 177 and I (I···O=2.86 Å), respectively. The importance of the substituent of thyroxine was investigated by Koerner et al.,[25] who concluded that the iodine substituent is not always a unique requirement for thyroid hormone activity. They studied the nuclear binding abilities of some 3,5,3′-derivatives of thyronine relative to 3,5,3′-triiodothyronine (T$_3$) and found that 3′-isopropyl-3,5-diiodothyronine had a stronger nuclear binding ability (the binding constant $K=10^4$) than that of T$_3$ ($K=10^2$). However, 3′-iodo-3,5-diisopropylthyronine exhibited almost no binding ability ($K=0.2$).

The present and previous findings suggest that the iodine substituents in thyroid hormones may have dif-

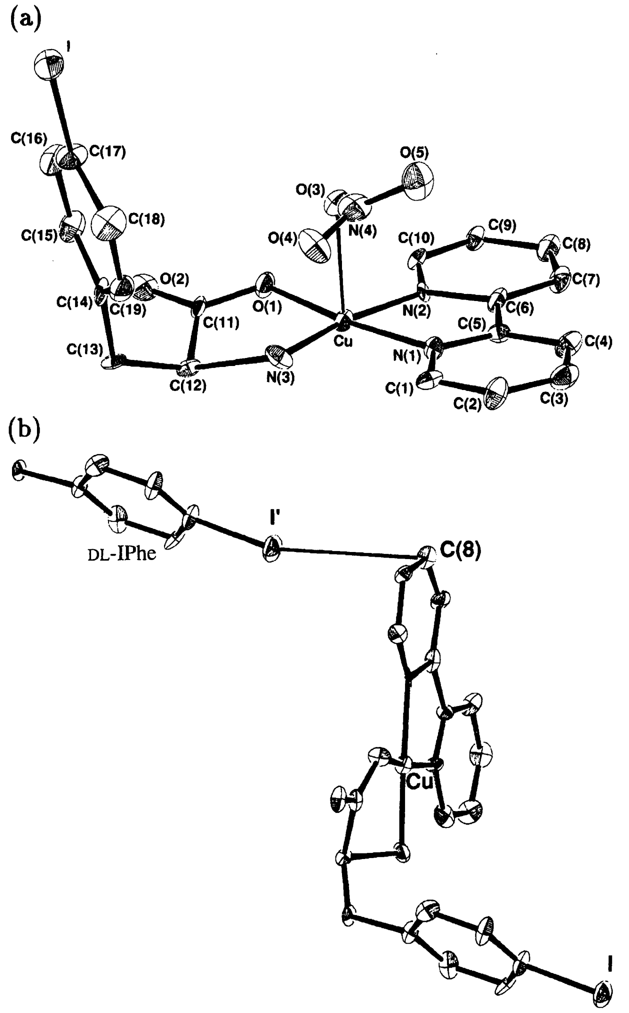

Fig. 1. Molecular structure of [Cu(bpy)(DL-IPhe)-(NO_3)] (**1**) with the atom numbering scheme (a) and an intermolecular C–I···C contact between symmetry related molecules (b). Hydrogen atoms are omitted for clarity.

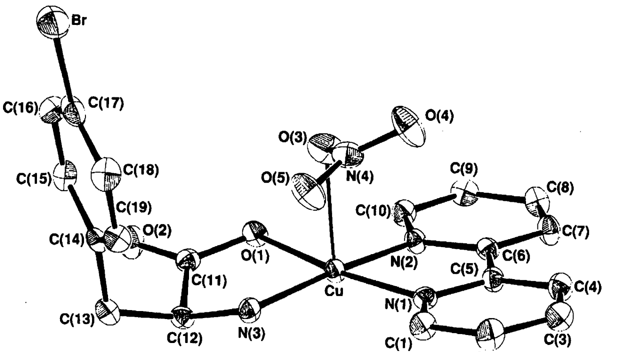

Fig. 2. Molecular structure of [Cu(bpy)(DL-BrPhe)-(NO_3)] (**2**) with the atom numbering scheme. Hydrogen atoms are omitted for clarity.

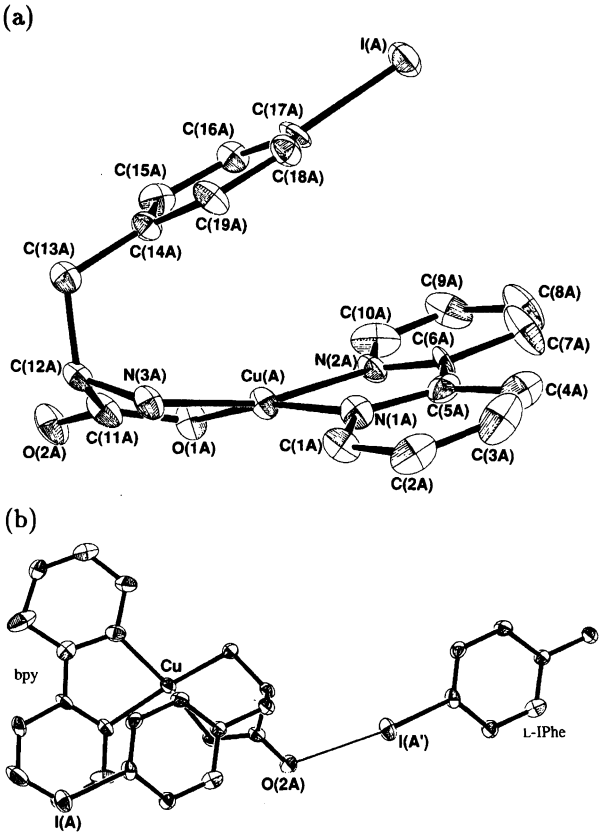

Fig. 3. Molecular structure of $[Cu(bpy)(L\text{-}IPhe)]^+$ (**3**) with the atom numbering scheme (a) and an intermolecular C–I···O contact between symmetry related molecules (b). Hydrogen atoms are omitted for clarity.

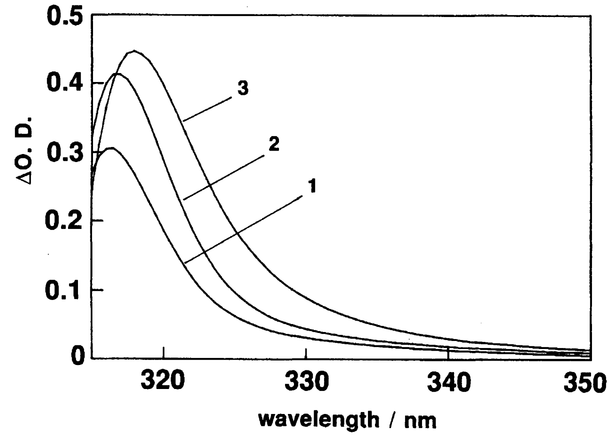

Fig. 4. Difference spectra of 1 : 1 : 1 Cu–bpy–XPhe systems. XPhe for curves: 1, Phe; 2, BrPhe; 3, IPhe.

ferent effects depending on the positions, i. e. the steric effect or the bulkiness of the iodine atoms probably in 3′ and 5′ positions and noncovalent interactions of the iodine atoms in 3 and 5 positions with the receptor groups. Combination of these effects may contribute to molecular recognition in receptor binding of thyroid hormones in addition to their peculiar structure. Since the iodine atom is the largest and most polarizable atom available in the biological environment and can covalently bind with the carbon atom, we may understand

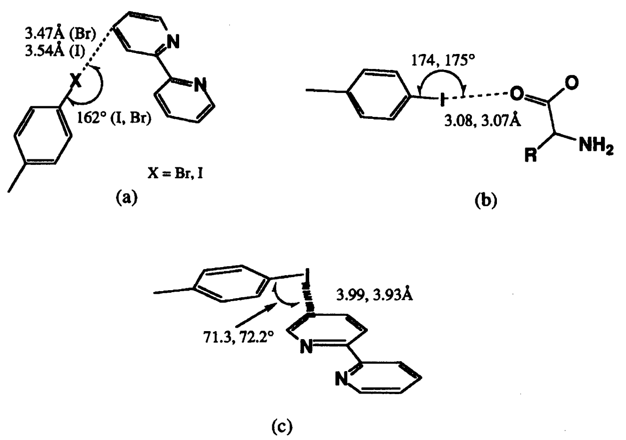

Fig. 5. Schematic representation of inter- and intramolecular contacts, (a) halogen–aromatic carbon, (b) iodine–carbonyl oxygen, and (c) iodine–aromatic ring, detected in **1**, **2**, and **3**.

that it is certainly the right choice for biological functions because of the mentioned effects it has inherently.

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