Structures and Stabilities of Ternary Copper(II) Complexes with 3,5-Diiodo-L-tyrosinate. Weak Interactions Involving Iodo Groups

Feng Zhang,[†] Akira Odani,[†] Hideki Masuda,[‡] and Osamu Yamauchi*[,†]

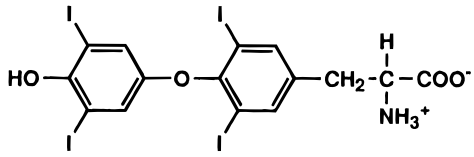
Department of Chemistry, Graduate School of Science, Nagoya University, Chikusa-ku, Nagoya 464-01, Japan, and Department of Applied Chemistry, Faculty of Engineering, Nagoya Institute of Technology, Showa-ku, Nagoya 466, Japan

Received May 22, 1996[⊗]

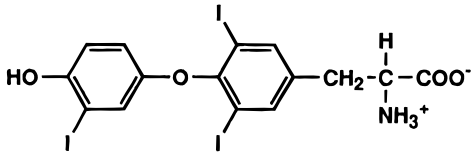
Structures and stabilities of the ternary copper(II) complexes Cu(DA)(AA), where AA refers to 3,5-diiodo-L-tyrosinate (I_2tyr) or L-tyrosinate (Tyr) and DA refers to 1,10-phenanthroline (phen), 2,2′-bipyridine (bpy), 2-(aminomethyl)pyridine (ampy), histamine (hista), or ethylenediamine (en), have been investigated by potentiometric, spectroscopic, and X-ray diffraction methods. The stability constants have been determined by potentiometric titrations at 25 °C and ionic strength $I = 0.1$ M (KNO_3). The equilibrium constants K for a hypothetical equilibrium, Cu(DA)(Ala) + Cu(en)(AA) $\overset{K}{\rightleftharpoons}$ Cu(DA)(AA) + Cu(en)(Ala) where Ala refers to L-alanine, have been calculated from the determined overall stability constants of the ternary complexes for estimating the stability enhancement due to the stacking interaction between the aromatic rings in Cu(DA)(AA). Large positive log K values have been obtained for the Cu(DA)(I_2tyrOH) and Cu(DA)(I_2tyrO$^-$) systems (DA = phen or bpy, OH and O$^-$ refer to the protonated and deprotonated forms of the phenol moiety, respectively), indicating that the complexes are stabilized by effective stacking. Differences between the log K values for Cu(DA)(I_2tyr) and Cu(DA)(Tyr) systems indicate that the iodine substituents greatly contribute to the stability enhancement. A distinct circular dichroism (CD) magnitude anomaly was also observed for the systems with large log K value, supporting the existence of the stacking interaction in Cu(DA)(AA). Two complexes, [Cu(bpy)(I_2tyrO$^-$)(H_2O)]·2H_2O (**1**) and [Cu(bpy)(I_2tyrOH)(NO_3)]·CH_3OH (**2**), have been isolated as crystals and analyzed by the X-ray diffraction method. Both **1** and **2** crystallized in the orthorhombic space group $P2_12_12_1$ with four molecules in a unit cell of dimensions $a = 9.2339(4)$, $b = 16.9230(8)$, and $c = 14.8584(5)$ Å for complex **1**, and $a = 11.2240(8)$, $b = 11.715(1)$, and $c = 17.966(2)$ Å for complex **2**. The central Cu(II) ion for both complexes has a similar distorted five-coordinate square-pyramidal geometry with the equatorial positions occupied by the two nitrogen atoms of bpy and the nitrogen and oxygen atoms of I_2tyr, and the apical position is occupied by a water molecule (for **1**) or a nitrate ion (for **2**). The opposite site to the axial water or nitrate oxygen atom is intramolecularly occupied by the side chain aromatic ring, which is approximately parallel to the copper coordination plane with the average spacing of 3.31 or 3.30 Å for complex **1** or **2**, respectively, directly exhibiting the effective stacking interaction between the aromatic rings in the solid state. Distances between the iodine and one of the pyridine rings of bpy (3.79 Å for **1** and 3.56 Å for **2**) are shorter than the van der Waals distance (3.85 Å), implying that the iodine substituent may be involved in a weak bonding interaction with the pyridine ring. Effects of the iodine substituents on the stacking interactions between the diiodophenol side ring and the coordinated aromatic diamine and their possible biological relevance have been discussed.

Introduction

Thyroid hormones are iodinated derivatives of the amino acid tyrosine, 3,5,3′-triiodo-L-thyronine (T_3) and L-thyroxine (T_4) (Figure 1) and are involved in the control of tissue development and differentiation, the regulation of oxygen consumption, and the promotion of various metabolic processes.[1] They are synthesized by and secreted from the thyroid gland with T_4 as the main secretory product, which can be partly converted to the biologically more active T_3 by isozymes of iodothyronine 5′-deiodinase in the peripheral tissues such as the liver, kidney, and pituitary gland.[2] They are transported to the target cells through the blood circulation by three plasma proteins, thyroxine-binding globulin, transthyretin, and serum albumin.[3,4] They enter all tissues of the body through the circulation and actively persist in the bloodstream or tissue fluids at a tiny but stable



Thyroxine (T_4)



Triiodothyronine (T_3)

Figure 1. Structures of the thyroid hormones.

* Author to whom correspondence should be addressed.
† Nagoya University.
‡ Nagoya Institute of Technology.
⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) Eberhardt, N. L.; Apriletti, J. W.; Baxter, J. D. In *Biochemical Actions of Hormones*; Litwack, G., Ed.; Academic Press: New York, 1980; Vol. 7, p 311.
(2) (a) Braverman, L. E.; Ingbar, S.; Sterling, K. *J. Clin. Invest.* **1970**, *49*, 855. (b) Leonard, J. L.; Visser, T. J. In *Thyroid Hormone Metabolism*; Heinemann, G., Ed.; Marcel Dekker: New York, 1986; p 189.

S0020-1669(96)00599-X CCC: $12.00

free concentration (less than 1% of the total secreted by the thyroid), which is controlled by the dynamic equilibrium between the free and the protein-bound forms.[4,5] Only such a tiny free fraction of the thyroid hormones passes through the cell membranes and binds to some specific intracellular receptor proteins, primarily those located in the nucleus of target cells,[6] exerting significant biological functions.

It has emerged clearly from a large number of investigations that, just as in most other biological processes, the weak thyroid hormone−receptor binding may function as a key step in determining its biological functions, which activate the receptor protein to bind to its DNA response element, leading to the modulation of gene expression.[7] Recently, the crystal structure of the rat α_1 thyroid hormone receptor (rTRα_1) prebound by a thyroid hormone agonist, 3,5-dimethyl-3′-isopropylthyronine (Dimit), in the ligand-binding domain has disclosed that the hormone may act as a hydrophobic core critical for creating the active receptor comformation through stacking and other weak interactions.[8] We have been studying aromatic ring stacking interactions between coordinated ligands in mixed ligand copper(II) and other metal ion complexes,[9,10] where two ligand molecules are close enough to effectively interact with each other in the metal coordination sphere. Use of mixed ligand complexes often makes it possible to study the mode and energy of such weak interactions. Thus, the ternary copper(II) complexes with an aromatic amino acid (AA) such as tyrosinate (Tyr) and an aromatic diamine (DA) such as 2,2′-bipyridine (bpy) were found to be stabilized by aromatic ring stacking relative to the complexes without it,[9b,d,h] and X-ray structure analyses of Cu(bpy)(Tyr), Cu(bpy)(Trp) (Trp = L-tryptophanate), etc., have revealed the molecular structures involving intramolecular stacking,[9e−i,11] further supporting the presence of stacking in the complexes in solution. Although it is not clear from previous investigations whether metal ions are involved in the receptor binding and functioning of the thyroid hormones, the iodo groups of the hormones are particularly intriguing because they are essential for the hormone activity,[1−7] and owing to their bulkiness and polarizability, the iodo groups should have an important role in the hormone−receptor binding through noncovalent interactions.

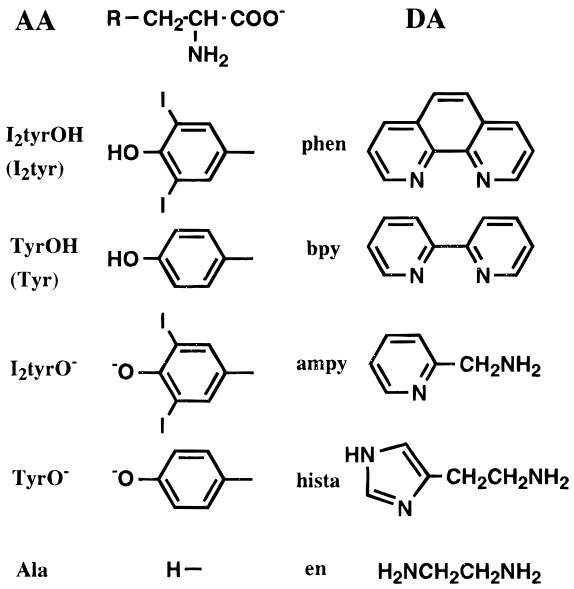


Figure 2. Structures and abbreviations of the ligands.

With a view to obtaining information on weak interactions between diiodophenolic side chain and coordinated aromatic rings, we investigated the structures and stabilities of the ternary copper(II) complexes involving 3,5-diiodo-L-tyrosine, a precursor in the biosynthesis of thyroid hormones,[1] as AA, and a diamine with an aromatic ring (DA) (Figure 2) by X-ray diffraction, potentiometric, and spectroscopic methods. We expected that the iodination of the benzene ring would distinctly change the electron distribution of the phenol group due to the polarizability and charge-transfer of the soft and bulky iodines, making the phenol ring very different from that in tyrosinate in its stacking interaction with DA. The present studies have established that the iodination indeed affect the properties of the phenol group and that the diiodinated phenol ring can interact with the diamine aromatic ring through stacking interactions much more effectively than the phenol ring of tyrosinate. The results may serve as a clue to understanding the specific effects of the iodine substituents on the effective hormone−receptor binding.

Experimental Section

Materials.[12] 3,5-Diiodo-L-tyrosine (I_2tyr) and histamine (hista) dihydrochloride were purchased from Sigma, L-tyrosine (Tyr) was from Ajinomoto, 2,2′-bipyridine (bpy), 1,10-phenanthroline (phen), and ethylenediamine (en) were from Nacalai Tesque, and 2-(aminomethyl)-pyridine (ampy) was from Aldrich. En and ampy were distilled and used as dihydrochlorides. All chemicals used were of the highest grade available. Water was distilled, deionized, and further purified by a Milli-Q Labo.

Preparation of Cu(bpy)(L-I_2tyr). The ternary complex was isolated in two forms according to the following procedures. A solution of 3,5-diiodo-L-tyrosine (0.47 g, 1 mmol) in 0.1 M KOH (20 mL) was gradually added into a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (0.24 g, 1 mmol) and bpy (0.16 g, 1 mmol) in aqueous methanol under moderate stirring.

(3) Robins, J. In *Thyroid Hormone Metabolism*; Harland, W. E., Orr, O. S., Eds.; Academic Press: New York, 1975; p 1.
(4) De La Paz, P.; Burridge, J. M.; Oakley, S. J.; Blake, C. C. F. In *The Design of Drugs to Macromolecular Targets*; Bedell, C. R., Ed.; Wiley: Chichester, New York, 1992; p 119.
(5) (a) Pardridge, W. M. *Endocr. Rev.*, **1981**, *2*, 103. (b) Ekins, P. J. In *Recent Advances in Endocrinology and Metabolism*; O'Riordan, J. L. H., Ed.; Churchill Livingstone: Edinburgh, U.K., 1982; p 289.
(6) (a) Oppenheimer, J. H.; Koerner, D.; Schwartz, H. L.; Surks, M. I. *J. Clin. Endocr. Metab.* **1972**, *35*, 330. (b) Oppenheimer, J. H. In *Molecular Basis of Thyroid Hormone Action*; Oppenheimer, J. H., Samuels, J. H., Eds.; Academic Press: New York, 1983; p 1. (c) Oppenheimer, J. H.; Schwartz, H. L.; Mariash, C. N.; Kinlaw, W. B.; Wong, N. C. W.; Freake, H. C. *Endocr. Rev.* **1987**, *8*, 288.
(7) (a) Evans, R. M. *Science* **1988**, *240*, 889. (b) Chin, W. W. In *Nuclear Hormone Receptors*; Parker, M. G., Ed.; Academic Press: New York, 1991; p 79. (c) Chatterjee, V. K. K.; Tata, J. R. *Cancer Surv.* **1992**, *14*, 147.
(8) Wagner, R. L.; Apriletti, J. W.; McGrath, M. E.; West, B. L.; Baxter, J. D.; Fletterick, R. J. *Nature* **1995**, *378*, 690.
(9) (a) Yamauchi, O.; Odani, A. *Inorg. Chim. Acta* **1985**, *100*, 165. (b) Yamauchi, O.; Odani, A. *J. Am. Chem. Soc.* **1985**, *107*, 5938. (c) Odani, A.; Deguchi, S.; Yamauchi, O. *Inorg. Chem.* **1986**, *25*, 62. (d) Yamauchi, O.; Odani, A. *Nippon Kagaku Kaishi* **1988**, 369. (e) Masuda, H.; Matsumoto, O.; Odani, A.; Yamauchi, O. *Nippon Kagaku Kaishi* **1988**, 783. (f) Yamauchi, O.; Odani, A.; Masuda, H. *Inorg.Chim. Acta* **1992**, 198−200, 749. (g) Masuda, H.; Sugimori, T.; Odani, A.; Yamauchi, O. *Inorg. Chim. Acta* **1991**, *180*, 73. (h) Sugimori, T.; Shibakawa, K.; Masuda, H.; Odani, A.; Yamauchi, O. *Inorg. Chem.* **1993**, *32*, 4951. (i) Sugimori, T.; Masuda, H.; Yamauchi, O. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 131.
(10) Sigel, H.; Tribolet, R.; Yamauchi, O. *Comments Inorg. Chem.* **1990**, *9*, 305.
(11) Aoki, K.; Yamazaki, H. *J. Chem. Soc., Dalton Trans.* **1987**, 2017.

(12) Abbreviations used: T_3, 3,5,3′-triiodo-L-thyronine; T_4, L-thyroxine; rTRα1, rat α1 thyroid hormone receptor; Dimit, 3,5-dimethyl-3′-isopropylthyronine; AA, aromatic amino acid; Tyr, tyrosinate; TyrOH, Tyr with the protonated phenol moiety; $TyrO^-$, Tyr with the deprotonated phenol moiety; Trp, tryptophanate; I_2tyr, 3,5-diiodo-L-tyrosinate; I_2tyrOH, I_2tyr with the protonated phenol moiety; I_2tyrO^-, I_2tyr with the deprotonated phenol moiety; Ala, alanine; DA, aromatic diamine; phen, 1,10-phenanthroline; bpy, 2,2′-bipyridine; ampy, 2-aminomethylpyridine; hista, histamine; en, ethylenediamine.

The mixture was then filtered and kept at room temperature for several days to give [Cu(bpy)(I_2tyrO$^-$)]·2H_2O (**1**) as crystals. [Cu(bpy)(I_2tyrOH)(NO_3)]·CH_3OH (**2**) was obtained as crystals by addition of one equivalent of HNO_3 (0.1 M) and keeping at room temperature.

Spectral Measurements. Absorption spectra were measured at room temperature on a Shimadzu UV-3101PC and a Hitachi 330 recording spectrophotometer in quartz cells with a path length of 50 mm. CD spectra were measured with a JASCO J-720C spectropolarimeter at room temperature in a quartz cell with a path length of 100 mm. Samples for the measurements were freshly prepared in a 1:1:1 Cu(II)−DA−AA molar ratio, and the pH values were adjusted with 0.1 M KOH. The concentrations of Cu(II) were 0.2−0.6 mM.

pH Titrations. Potentiometric titrations were carried out at 25 ± 0.05 °C and ionic strength $I = 0.1$ M (KNO_3) under N_2 atmosphere for solutions containing Cu(II), DA, or I_2tyr in molar ratios of 0:0:1, 1:0:2, and 1:1:1 with an appropriate amount of HNO_3, the concentrations of Cu(II) being 0.2−2.0 mM. Carbonate-free 0.1 M KOH was prepared under N_2 and standardized against standard potassium hydrogen phthalate. Copper(II) nitrate (0.02 M) was standardized by chelatometry with metallic zinc (JIS primary standard) as standard. pH values were measured with a Fisher Scientific Accumet 15 pH meter equipped with a Beckman 39314 glass electrode and a 39419 double-junction reference electrode. Several titrations were made for each system for reproducibility, and about 200−300 data points were collected for each sample. Calibration of the pH meter was made with the NBS standard buffer solutions (pH 4.008, 7.413, and 9.180 at 25 °C). The difference between the pH meter reading and −log [H], where [H] denotes the hydrogen ion concentration, was determined to be 0.068 as reported previously.[9b,13] The apparent ion product of water, pK_w', was determined to be 13.93 under the same conditions. The stability constant, β_{pqrs}, is defined by eq 1 (charges are omitted for clarity), where p, q, r, and s are the moles of Cu, DA, AA, and proton (H), respectively, in the complex $Cu_p(DA)_q(AA)_rH_s$. The log β_{pqrs} values were calculated by the method of nonlinear least-squares using the program SUPERQUAD[14] with the aid of a FACOM M-680 computer at Nagoya University Computation Center. The stability constants for binary Cu(II)−DA and ternary Cu(II)−DA−Tyr and Cu(II)−DA−Ala systems were taken from the literature.[9b,15−20]

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

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

X-ray Structure Determination of [Cu(bpy)(I_2tyrO$^-$)(H_2O)]·2H_2O (1) and [Cu(bpy)(I_2tyrOH)(NO_3)]·CH_3OH (2). Diffraction data for crystals **1** and **2** were obtained with an Enraf Nonius CAD-4 four-circle diffractometer. Crystal data and experimental details for both crystals are summarized in Table 1. Three standard reflections were monitored every 2 h, and the decay of their intensities was within 2%. Reflection data were corrected for both Lorentz and polarization effects. An absorption correction, based on a ψ scan, was applied for each crystal. The structures for both complexes were solved by the heavy-atom method and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. 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 ref 21.[21] All the hydrogen atoms were located from the difference Fourier maps, and their parameters were isotropically refined. The R and R_w values were 0.025 and 0.033 for complex **1** and 0.027 and 0.035 for complex **2**, respectively. The weighting scheme $w^{-1} = [\sigma^2(F_o) + (0.023F_o)^2]$ was employed for both crystals. The final difference Fourier maps did not show any significant features in both cases. All calculations were carried out on a Micro VAX3100 computer by using the program system SDP-MolEN.[22]

Table 1. Crystal Data for [Cu(bpy)(L-I_2tyrO$^-$)(H_2O)]·2H_2O (**1**) and [Cu(bpy)(L-I_2tyrOH)(NO_3)]·CH_3OH (**2**)

	1	**2**
formula	$CuC_{19}H_{21}N_3O_6I_2$	$CuC_{20}H_{20}N_4O_7I_2$
fw	704.75	745.76
cryst syst	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	9.2339(4)	11.2240(8)
b (Å)	16.9230(8)	11.715(1)
c (Å)	14.8584(5)	17.966(2)
V (Å^3)	2321.8(2)	2362.4(4)
Z	4	4
ρ (g cm^{-3})	2.016	2.097
μ (cm^{-1})	36.41	35.89
F(000)	1356	1436
cryst size (mm)	0.3 × 0.2 × 0.2	0.3 × 0.3 × 0.3
λ (Mo Kα (Å))	0.710 69	0.710 69
2θ limit (deg)	60	60
no. of reflcns obsd	3921	2732
no. of reflcns used ($\|F_o\| \geq 3\sigma(\|F_o\|)$)	3179	2547
R	0.025	0.027
R_w	0.033	0.035

Results

Solution Equilibira. Stability constants of the binary and ternary complexes, log β_{pqrs}, calculated from the pH titration data are summarized in Tables 2 and 3, respectively. Stabilization of the ternary complexes Cu(DA)(I_2tyr) and Cu(DA)(Tyr) by the aromatic ring stacking interactions has been evaluated by the log K value for a hypothetical equilibrium defined by eq 2 as described before,[9b] where the ligand−ligand stacking interaction is possible only in Cu(DA)(AA). Most of the ternary systems exhibited large positive log K values (Table 3), suggesting stabilization due to the effective stacking interactions between coordinated DA and the aromatic side group of AA. The systems with protonated I_2tyrOH or TyrOH exhibited much larger log K values than those for deprotonated I_2tyrO$^-$ or TyrO$^-$, and the log K values increased with the number of aromatic rings of DA. These results are in line with our previous observations and hence the existence of the effective aromatic ring stacking.[9a−9d,f,g] Large differences in the log K values between I_2tyr- and Tyr-containing systems suggest that iodination of the phenol ring distinctly favors the stacking, even when the phenol moiety is deprotonated as in Cu(bpy)(I_2tyrO$^-$) or Cu(phen)(I_2tyrO$^-$). Calculated species distributions for a quaternary Cu(II)−bpy−Tyr−I_2tyr system (Figure 3) clearly show the predominance of Cu(bpy)(I_2tyrO$^-$) and Cu(bpy)(I_2tyrOH) over Cu(bpy)(TyrOH) in a wide range of pH. The influence of the iodo groups on the phenol ring can also be clearly seen from comparison of the pK_a values of the phenol

$$\mathrm{Cu(DA)(Ala)} + \mathrm{Cu(en)(AA)} \overset{K}{\rightleftharpoons} \mathrm{Cu(DA)(AA)} + \mathrm{Cu(en)(Ala)}$$

$$\log K = \log \beta_{\mathrm{Cu(DA)(AA)}} + \log \beta_{\mathrm{Cu(en)(Ala)}} - \log \beta_{\mathrm{Cu(DA)(Ala)}} - \log \beta_{\mathrm{Cu(en)(AA)}} \quad (2)$$

(13) Sigel, H.; Zuberbühler, A. D.; Yamauchi, O. *Anal. Chim. Acta* **1991**, *255*, 63.
(14) Gans, P.; Sabatini, A.; Vacca, A. *J. Chem. Soc., Dalton Trans.* **1985**, 1195.
(15) Pettit, L. D.; Swash, J. L. M. *J. Chem. Soc., Dalton Trans.* **1982**, 485.
(16) Brookes, G.; Pettit, L. D. *J. Chem. Soc., Dalton Trans.* **1977**, 1918.
(17) Huber, P. R.; Griesser, R.; Prijs, B.; Sigel, H. *Eur. J. Biochem.* **1969**, *10*, 238.
(18) Huber, P. R.; Griesser, R.; Sigel, H. *Inorg. Chem.* **1971**, *10*, 945.
(19) Fischer, B. E.; Sigel, H. *J. Am. Chem. Soc.* **1980**, *102*, 2998.
(20) Odani, A.; Yamauchi, O. *Inorg. Chim. Acta* **1984**, *93*, 13.
(21) Ibers, J. A.; Hamilton, W. C., Eds. *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, U.K., 1974; Vol. IV.
(22) Frenz, B. A. *Enraf-Nonius Structure Determination Package*; Enraf-Nonius: Delft, The Netherlands, 1985.

Table 2. Stability Constants log β_{pqrs} for Proton−Ligand and Cu(II)−Ligand Binary Systems at 25 °C and $I = 0.1$ M (KNO_3)[a]

	pqrs							
ligand	1011	1010	1022	1021	1020	0011	0012	0013
L-I_2tyr	14.762(1)	8.802(3)	28.864(2)	22.714(3)	15.585(1)	9.611(1)	16.003(1)	18.049(3)
L-Tyr[b]	17.99	10.64	34.90	25.47	15.36	10.142	19.170	21.051

	pqrs							
ligand	1101	1100	1202	1201	1200	0101	0102	0103
en[c]		10.523			19.505	9.976	17.148	
hista[d]		9.67			16.41	9.92	16.06	
ampy[e]		9.72			17.47	8.70	10.75	
bpy[c]		8.10			13.44	4.503		
phen[f]		9.25			16.00	4.95		

[a] Values in parentheses denote estimated standard deviations. [b] Reference 15. [c] Reference 16. [d] Reference 17. [e] Reference 18. [f] Reference 19.

Table 3. Stability Constants log β_{pqrs} and log K[a] for Ternary Complexes $Cu_p(DA)_q(L\text{-}AA)_rH_s$ at 25 °C and $I = 0.1$ M (KNO_3)[b]

		log β_{pqrs}				
AA	*pqrs*	DA = phen	DA = bpy	DA = ampy	DA = hista	DA = en
I_2tyrOH	1111	25.790(2)	24.472(2)	24.516(1)	24.638(1)	24.429(3)
I_2tyrO$^-$	1110	18.996(2)	17.794(2)	18.326(1)	18.084(1)	18.431(2)
TyrOH	1111	28.001[c]	26.838[c]	27.715[c]	27.651[c]	27.772[d]
TyrO$^-$	1110		16.879[c]	18.234[c]	17.944[c]	18.462[d]
Ala	1110	17.131[c]	16.116[c]	17.344[c]	17.321[c]	17.949[d]

		log K				
AA	*pqrs*	DA = phen	DA = bpy	DA = ampy	DA = hista	DA = en
I_2tyrOH	1111	2.18	1.88	0.69	0.84	0.00
I_2tyrO$^-$	1110	1.38	1.20	0.50	0.28	0.00
TyrOH	1111	1.05	0.90	0.55	0.51	0.00
TyrO$^-$	1110		0.25	0.38	0.11	0.00
Ala	1110	0.00	0.00	0.00	0.00	0.00

[a] Calculated according to eq 2. [b] Values in parentheses denote estimated standard deviations. [c] Reference 9b. [d] Reference 20.

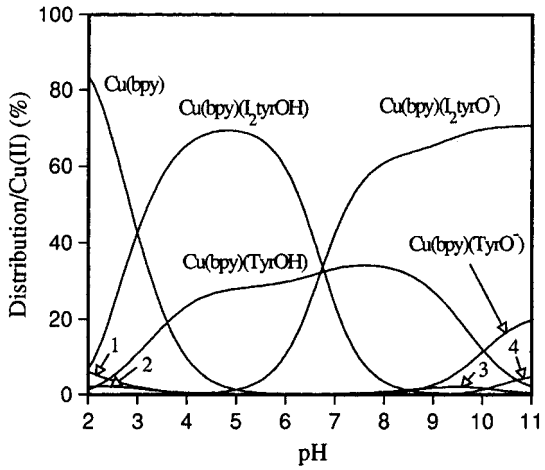


Figure 3. Species distributions as a function of pH in a quaternary 1:1:1:1 Cu(II)−bpy−Tyr−I_2tyr system. Concentration: Cu(II), 1 mM. Curves for minor species: 1, Cu(II); 2, Cu(bpy)$_2$; 3, Cu(I_2tyrO$^-$)(TyrOH); 4, Cu(TyrO$^-$)$_2$. The others are omitted.

OH group: The decrease is as large as about 2.6 log units, from 9.028 of Tyr to 6.392 of I_2tyr (Table 2).

Absorption and CD Spectra. Absorption and CD spectral data obtained for the d−d region in several media are given in Table 4. The ternary Cu(DA)(I_2tyr) and Cu(DA)(Tyr) systems exhibited a d−d absorption peak at 576−619 nm at pH 5.3−8.5. The corresponding CD spectra exhibited an obvious negative maximum at 579−610 nm, and the iodination remarkably enhanced the spectral magnitude. In the absence of ligand−ligand or metal−side chain interactions, the CD magnitude in the d−d region for Cu(II)−oligopeptide systems and ternary Cu(II)−amino acid systems Cu(L-A)(L-B) (A, B: amino acids) is known to be an additive function of the magnitudes of the component binary complexes[23] and can be calculated according to eq (3),[24,25] where $\Delta\epsilon_{Cu(L-A)_2}$ and $\Delta\epsilon_{Cu(L-B)_2}$ are the

$$\Delta\epsilon_{calc} = {}^1/_2(\Delta\epsilon_{Cu(L-A)_2} + \Delta\epsilon_{Cu(L-B)_2}) \quad (3)$$

CD magnitudes of the binary complexes Cu(L-A)$_2$ and Cu(L-B)$_2$, respectively, at the maximum wavelength of Cu(L-A)(L-B). For the ternary complexes containing an optically inactive ligand A (=DA in this paper), eq 3 is simply described as eq 4.

$$\Delta\epsilon_{calc} = {}^1/_2\Delta\epsilon_{Cu(L-B)_2} \quad (4)$$

Table 4 shows that even for the ternary systems with en, the observed $\Delta\epsilon$ values ($\Delta\epsilon_{obs}$) distinctly deviate from the $\Delta\epsilon_{calc}$ values, which may be ascribed to the Cu(II)−aromatic ring interactions in the ternary complexes.[9a] Since the diamine ligands have the same donor atoms and therefore a similar ligand field, we may simply assume that these metal−side chain interactions are approximately identical for all the ternary systems and thus evaluate the CD magnitude anomaly due to the ligand−ligand stacking by comparing the $\Delta\epsilon$ values with those of the corresponding en-containing systems.

CD magnitude anomaly due to stacking is seen from the $\Delta\Delta\epsilon$ values ($= \Delta\epsilon_{obs} - \Delta\epsilon_{calc}$) listed in Table 5. For both Tyr- and I_2tyr-containing systems the deviations become larger with the increase of the ring size, suggesting that the aromatic ring stacking leads to distorsion and increased rigidness of the side chain conformation. Smaller deviations in 50% aqueous dioxane solution indicate that the stacking interaction is weakened in less polar solvents. The $\Delta\Delta\epsilon$ values in Table 5 show that the iodination clearly favors the stacking especially for stacking involving the deprotonated phenol ring. The iodo groups of the phenol ring may effectively protect the negatively charged phenolate oxygen from hydration which is unfavorable for the effective stacking.

Molecular Structures of [Cu(bpy)(I_2tyrO$^-$)(H_2O)]·2H_2O (1) and [Cu(bpy)(I_2tyrOH)(NO_3)]·CH_3OH (2). Molecular structures for complexes **1** and **2** in the solid state are depicted in Figures 4 and 5, respectively. Both complexes have similar structures, directly exhibiting the effective stacking interactions between the aromatic rings. The central Cu(II) ion for both complexes has a distorted five-coordinate square-pyramidal

(23) (a) Tsangaris, J. M.; Martin, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4255. (b) Martin, R. B. *Met. Ions Biol. Sys.* **1974**; *1*, 129.
(24) Yamauchi, O. *J. Mol. Catal.* **1984**, *23*, 255.
(25) Martin, R. B. *Met. Ions Biol. Sys.* **1979**; *9*, 1.

Table 4. Absorption and CD Spectral Data for Cu(DA)(L-I_2tyr) and Cu(DA)(L-Tyr) Systems

		L-I_2tyr						L-Tyr					
			absorption		CD				absorption		CD		
DA	medium	pH	λ_{max}	ϵ_{max}	λ_{max}	$\Delta\epsilon_{obs}$	$\Delta\epsilon_{calc}$[a]	pH	λ_{max}	ϵ_{max}	λ_{max}	$\Delta\epsilon_{obs}$	$\Delta\epsilon_{calc}$
en	H_2O (1.0 M KNO_3)	7.5	576	58	590	−0.357	−0.242	9.6	577	57	583	−0.380	−0.223
		6.2	586	50	593	−0.184	−0.121	7.4	578	55	592	−0.267	−0.198
	H_2O (0.1 M KNO_3)	8.3	578	58	588	−0.405	−0.220	9.7	577	59	585	−0.427	−0.218
		6.4	592	53	589	−0.197	−0.102	7.6	578	57	591	−0.289	−0.192
	H_2O	7.8	577	60	582	−0.417	−0.210	9.6	578	57	584	−0.441	−0.210
		6.1	583	53	589	−0.208	−0.103	7.4	578	57	588	−0.290	−0.193
	50% dioxane−H_2O	8.5	579	62	579	−0.381	−0.149	10.8	583	61	581	−0.424	−0.183
		6.7	579	59	583	−0.139	−0.137	7.8	579	61	588	−0.229	−0.196
hista	H_2O (1.0 M KNO_3)	7.4	597	60	586	−0.720	−0.234	9.8	598	66	589	−0.678	−0.236
		6.1	607	56	591	−0.592	−0.119	7.2	602	67	592	−0.747	−0.198
	H_2O (0.1 M KNO_3)	8.2	597	63	588	−0.731	−0.220	9.9	600	67	592	−0.676	−0.228
		6.0	608	59	593	−0.654	−0.105	7.4	599	66	595	−0.767	−0.196
	H_2O	7.9	598	62	589	−0.728	−0.221	9.7	600	66	591	−0.684	−0.220
		5.9	603	60	594	−0.665	−0.105	7.2	602	66	596	−0.767	−0.200
	50% dioxane−H_2O	8.4	593	66	583	−0.568	−0.154	10.8	594	72	587	−0.460	−0.188
		6.6	597	68	595	−0.451	−0.140	7.9	598	68	591	−0.518	−0.197
ampy	H_2O (1.0 M KNO_3)	7.4	589	62	589	−0.869	−0.240	9.7	590	66	589	−0.732	−0.236
		6.0	602	58	592	−0.709	−0.120	7.1	590	67	590	−0.774	−0.195
	H_2O (0.1 M KNO_3)	8.1	590	64	589	−0.904	−0.222	9.8	591	66	590	−0.740	−0.225
		5.9	598	63	594	−0.789	−0.106	7.3	593	67	591	−0.818	−0.192
	H_2O	7.6	590	63	590	−0.914	−0.222	9.7	592	64	591	−0.760	−0.220
		5.8	598	64	595	−0.821	−0.105	7.1	592	68	591	−0.824	−0.195
	50% dioxane−H_2O	8.3	584	69	588	−0.720	−0.158	10.2	584	80	590	−0.579	−0.190
		6.5	592	71	596	−0.561	−0.140	7.8	590	70	591	−0.616	−0.197
bpy	H_2O (1.0 M KNO_3)	7.5	602	64	597	−1.335	−0.253	10.0	605	71	599	−1.140	−0.250
		5.7	608	66	599	−1.235	−0.124	6.4	607	72	600	−1.203	−0.206
	H_2O (0.1 M KNO_3)	7.9	603	67	598	−1.350	−0.236	9.9	604	70	600	−1.141	−0.238
		5.8	608	67	601	−1.272	−0.110	6.8	608	72	601	−1.200	−0.200
	H_2O	8.0	604	66	599	−1.342	−0.234	10.0	604	70	602	−1.144	−0.233
		5.3	609	69	601	−1.279	−0.108	6.7	608	74	603	−1.212	−0.204
	50% dioxane−H_2O	8.4	600	69	598	−1.215	−0.166	11.0	607	70	600	−0.769	−0.196
		6.4	607	71	599	−1.161	−0.140	7.4	607	76	599	−1.073	−0.200
phen	H_2O (1.0 M KNO_3)	7.4	612	62	608	−1.259	−0.266	10.0	614	71	608	−0.974	−0.259
		5.7	619	66	608	−1.138	−0.130	6.4	618	73	610	−1.058	−0.212
	H_2O (0.1 M KNO_3)	8.0	612	65	609	−1.270	−0.245	10.0	615	71	610	−0.979	−0.246
		5.8	618	68	609	−1.168	−0.113	6.8	617	74	610	−1.059	−0.204
	H_2O	8.1	615	66	610	−1.262	−0.243	10.1	615	69	610	−0.983	−0.237
		5.4	617	69	610	−1.166	−0.111	6.7	617	74	610	−1.059	−0.205
	50% dioxane−H_2O	8.4	612	68	609	−1.168	−0.168	11.1	616	73	608	−0.689	−0.197
		6.5	617	72	606	−1.085	−0.139	7.5	617	77	608	−0.952	−0.199

[a] Calculated according to eq 4.

geometry, in which the equatorial positions are occupied by the two nitrogen atoms of bpy and the nitrogen and oxygen atoms of I_2tyrO^- or I_2tyrOH, and an apical position is occupied by a water molecule (for **1**) or a nitrate ion (for **2**). The copper coordination plane is planar to within 0.19 and 0.18 Å for **1** and **2**, respectively, and the copper atom deviates from the coordination plane toward the apical oxygen atom by 0.16 and 0.23 Å for **1** and **2**, respectively.

Selected bond lengths and angles for **1** and **2** are presented in Tables 6 and 7, respectively. The equatorial Cu−N and Cu−O bond lengths (Cu−N(1) = 1.993(4) Å, Cu−N(1B) = 1.989(4) Å, Cu−N(12B) = 1.989(4) Å, and Cu−O(1) = 1.963(3) Å for complex **1**; Cu−N(1) = 2.001(3) Å, Cu−N(1B) = 1.995(4) Å, Cu−N(12B) = 1.986(4) Å, and Cu−O(1) = 1.949(3) Å for complex **2**) agree well with those generally found in square-planar Cu(II) complexes.[26] The apical Cu−O(1W) (2.356(4) Å) and Cu−O(1N) (2.255(4) Å) bond lengths are slightly longer than the sum of the ionic radii of Cu(II) (0.72 Å) and O^- (1.40 Å), but they are still within the range of 2.2−2.9 Å known for the axial Cu−O bond lengths,[27] so that the oxygen atoms are considered to be coordinated. The opposite site to the axial water or the nitrate oxygen atom is intramolecularly occupied by the aromatic phenol ring of I_2tyrO^- or I_2tyrOH, which is appoximately parallel to the copper coordination plane with average spacing of 3.31 or 3.30 Å, respectively. In spite of the similar spacings, however, the deviations of the phenol ring from the parallel position (11.6° for **1** and 4.8° for **2**) and the distances of I(2) from the plane of one of the pyridine rings of bpy (3.79 Å for **1** and 3.56 Å for **2**) are very different. It is noteworthy that the I(2)−pyridine distances are distinctly shorter than the sum of the van der Waals radii of an aromatic carbon atom (1.70 Å) and an iodine atom (2.15 Å), while those between the phenol oxygen (O(3)) and the pyridine ring (3.85 Å for **1** and 3.60 Å for **2**) are much larger than the sum of the van der Waals radii of an aromatic carbon atom and an oxygen atom (1.40 Å). This suggests that the iodine atom may be involved in weak interactions with the pyridine ring. As can be expected from the charge of the phenolate oxygen, the C(7)−O(3) bond length for **1** is shorter than that for **2**, indicating a double bond character of the C(7)−O(3) bond in **1**. Correspondingly, the I(1)−C(6) and I(2)−C(8) bonds in **1** become longer than those in **2**, which again implies the electron flow

(26) (a) Van der Helm, D.; Tatsch, C. E. *Acta Crystallogr.* **1972**, *B28*, 2037. (b) Freeman, H. C. *Adv. Protein Chem.* **1967**, *22*, 257. (c) Pajunen, A.; Pajunen, S. *Acta Crystallogr.* **1982**, *B38*, 3093.

(27) Wells, A. F. *Structural Inorganic Chemistry*; Oxford University Press: Oxford, U.K., 1975; p 259.

Table 5. CD Magnitude Anomaly ($\Delta\Delta\epsilon^a$) for Cu(DA)(L-AA) Systems

		L-AA			
DA	medium	I_2tyrO^-	$TyrO^-$	I_2tyrOH	TyrOH
en	H_2O (1.0 M KNO_3)	−0.12	−0.16	−0.06	−0.07
	H_2O (0.1 M KNO_3)	−0.19	−0.21	−0.10	−0.10
	H_2O	−0.21	−0.23	−0.11	−0.10
	50% dioxane−H_2O	−0.23	−0.24	0.00	−0.03
hista	H_2O (1.0 M KNO_3)	−0.49	−0.44	−0.47	−0.55
	H_2O (0.1 M KNO_3)	−0.51	−0.45	−0.55	−0.57
	H_2O	−0.51	−0.46	−0.56	−0.57
	50% dioxane−H_2O	−0.41	−0.27	−0.31	−0.32
ampy	H_2O (1.0 M KNO_3)	−0.63	−0.50	−0.59	−0.58
	H_2O (0.1 M KNO_3)	−0.68	−0.52	−0.68	−0.63
	H_2O	−0.69	−0.54	−0.72	−0.63
	50% dioxane−H_2O	−0.56	−0.39	−0.42	−0.42
bpy	H_2O (1.0 M KNO_3)	−1.08	−0.89	−1.11	−1.00
	H_2O (0.1 M KNO_3)	−1.11	−0.90	−1.16	−1.00
	H_2O	−1.11	−0.91	−1.17	−1.01
	50% dioxane−H_2O	−1.05	−0.57	−1.02	−0.87
phen	H_2O (1.0 M KNO_3)	−0.99	−0.72	−1.01	−0.85
	H_2O (0.1 M KNO_3)	−1.03	−0.73	−1.06	−0.86
	H_2O	−1.02	−0.75	−1.06	−0.85
	50% dioxane−H_2O	−1.00	−0.49	−0.95	−0.75

[a] $\Delta\Delta\epsilon = \Delta\epsilon_{obs} - \Delta\epsilon_{calc}$.

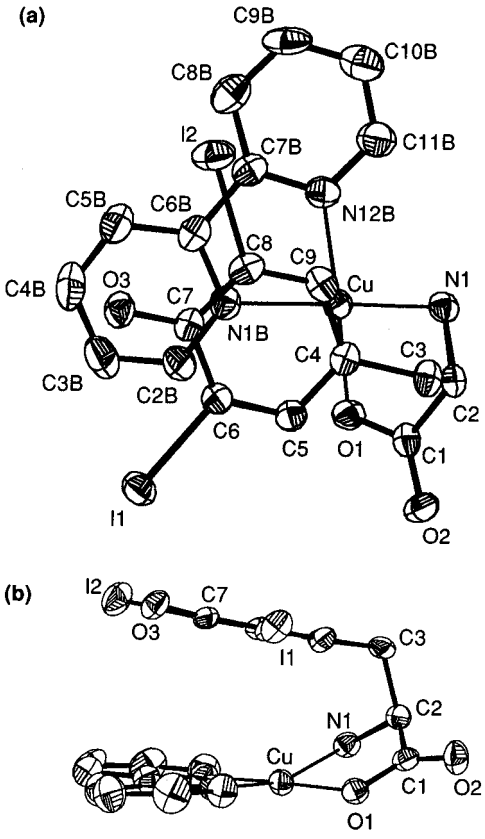


Figure 4. (a) Molecular structure of Cu(bpy)(L-I_2tyrO^-) (**1**) with the atomic numbering scheme. (b) Side view showing the stacking interaction.

from the oxygen to the iodines through the conjugate system of the benzene ring.

On the other hand, a recently reported structure of the binary Cu(L-$I_2tyr)_2$ complex[28] showed that the central Cu(II) ion is equatorially coordinated by an amino nitrogen and a carboxylate oxygen donor atom of one I_2tyr ligand, and a carboxylate oxygen

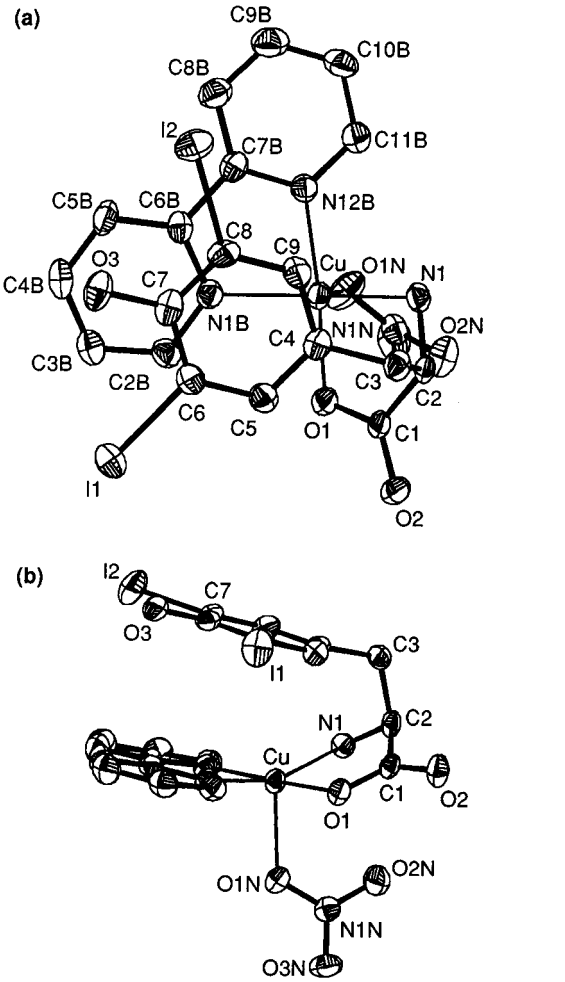


Figure 5. (a) Molecular structure of Cu(bpy)(L-I_2tyrOH) (**2**) with the atomic numbering scheme. (b) Side view showing the stacking interaction.

atom of the other. The two axial positions are inter-molecularly occupied by a phenolate oxygen and an iodine atoms of two I_2tyr ligands from other Cu(L-$I_2tyr)_2$ molecules with a separation of 3.22 Å and 3.248 Å, respectively, from the copper.

Discussion

Aromatic Ring Stacking Interactions Involving Diiodotyrosinate. Remarkable CD magnitude anomaly and distinctly enhanced log *K* values for the ternary complexes with I_2tyr and DA clearly indicate that there exists a stacking interaction between DA and the side chain aromatic ring of AA in solution, as has been substantiated previously by a large body of experimental results,[9−11,29] and the iodo groups here prove to be important for the effectiveness of this interaction, as revealed by the much larger log *K* values for Cu(DA)(I_2tyr) (Table 3) than those for Cu(DA)(Tyr) complexes.[9b] The crystal structures of complexes **1** and **2** clearly demonstrate the stacking interactions between the diiodophenol ring and coordinated bpy with an average spacing of 3.31 and 3.30 Å, respectively. It has been well recognized that stacking in ternary complexes usually gives a charge transfer (CT) absorption band in the region 300−400 nm.[9b,g,i,30] For the present ternary systems, we also observed such CT bands in the difference spectra (Figure 6). Comparison of the difference spectra for Cu(DA)(I_2tyrO^-) and Cu(DA)-

(28) Okabe, N.; Hokaze, M. *Chem. Pharm. Bull.* **1993**, *41*, 605.

(29) (a) Fischer, B. E.; Sigel, H. *J. Am. Chem. Soc.* **1980**, *102*, 2998. (b) Sigel, H. *Pure Appl. Chem.* **1989**, *61*, 923.

(30) Naumann, C. F.; Sigel, H. *J. Am. Chem. Soc.* **1974**, *96*, 2750.

Table 6. Selected Bond Lengths (Å) and Angles (deg) for the Complex [Cu(bpy)(L-I_2tyrO^-)(H_2O)]·2H_2O (**1**)

Bond Lengths			
I(1)−C(6)	2.110(4)	C(3)−C(4)	1.524(6)
I(2)−C(8)	2.108(4)	C(4)−C(5)	1.385(6)
Cu−O(1)	1.963(3)	C(4)−C(9)	1.393(6)
Cu−N(1)	1.993(4)	C(5)−C(6)	1.366(6)
Cu−N(1B)	1.989(4)	C(6)−C(7)	1.415(6)
Cu−N(12B)	1.989(4)	C(7)−C(8)	1.420(6)
O(1)−C(1)	1.291(5)	C(8)−C(9)	1.386(6)
O(2)−C(1)	1.226(5)	C(2B)−C(3B)	1.365(8)
O(3)−C(7)	1.284(5)	C(3B)−C(4B)	1.373(8)
N(1)−C(2)	1.469(5)	C(4B)−C(5B)	1.366(8)
N(1B)−C(2B)	1.344(6)	C(5B)−C(6B)	1.382(7)
N(1B)−C(6B)	1.342(6)	C(6B)−C(7B)	1.479(6)
N(12B)−C(7B)	1.346(6)	C(7B)−C(8B)	1.388(6)
N(12B)−C(11B)	1.327(6)	C(8B)−C(9B)	1.363(7)
C(1)−C(2)	1.531(6)	C(9B)−C(10B)	1.373(8)
C(2)−C(3)	1.530(6)	C(10B)−C(11B)	1.378(7)

Bond Angles			
O(1)−Cu−N(1)	83.7(1)	I(1)−C(6)−C(5)	118.6(3)
O(1)−Cu−N(1B)	96.2(1)	I(1)−C(6)−C(7)	116.7(3)
O(1)−Cu−N(12B)	177.1(1)	C(5)−C(6)−C(7)	124.6(4)
N(1)−Cu−N(1B)	160.3(2)	O(3)−C(7)−C(6)	124.0(4)
N(1)−Cu−N(12B)	99.0(1)	O(3)−C(7)−C(8)	124.2(4)
N(1B)−Cu−N(12B)	81.6(2)	C(6)−C(7)−C(8)	111.8(4)
Cu−O(1)−C(1)	114.2(3)	I(2)−C(8)−C(7)	116.2(3)
Cu−N(1)−C(2)	106.8(3)	I(2)−C(8)−C(9)	118.5(3)
Cu−N(1B)−C(2B)	126.7(3)	C(7)−C(8)−C(9)	125.1(4)
Cu−N(1B)−C(6B)	114.5(3)	C(4)−C(9)−C(8)	119.2(4)
C(2B)−N(1B)−C(6B)	118.7(4)	N(1B)−C(2B)−C(3B)	122.7(5)
Cu−N(12B)−C(7B)	114.6(3)	C(2B)−C(3B)−C(4B)	118.2(5)
Cu−N(12B)−C(11B)	126.4(3)	C(3B)−C(4B)−C(5B)	120.0(5)
O(1)−C(1)−O(2)	123.7(4)	C(4B)−C(5B)−C(6B)	119.2(5)
O(1)−C(1)−C(2)	115.9(3)	N(1B)−C(6B)−C(5B)	121.0(4)
O(2)−C(1)−C(2)	120.2(4)	N(1B)−C(6B)−C(7B)	114.8(4)
N(1)−C(2)−C(1)	108.8(3)	N(12B)−C(7B)−C(6B)	114.4(4)
N(1)−C(2)−C(3)	110.9(3)	N(12B)−C(7B)−C(8B)	120.8(4)
C(1)−C(2)−C(3)	108.7(3)	C(5B)−C(6B)−C(7B)	124.1(4)
C(2)−C(3)−C(4)	116.4(4)	C(6B)−C(7B)−C(8B)	124.8(4)
C(3)−C(4)−C(5)	120.8(4)	C(7B)−C(8B)−C(9B)	119.3(5)
C(3)−C(4)−C(9)	120.9(4)	C(8B)−C(9B)−C(10B)	120.0(4)
C(4)−C(5)−C(6)	121.0(4)	C(9B)−C(10B)−C(11B)	117.9(5)
C(5)−C(4)−C(9)	118.3(4)	N(12B)−C(11B)−C(10B)	122.9(5)

Table 7. Selected Bond Lengths (Å) and Angles (deg) for the Complex [Cu(bpy) (L-I_2tyrOH)(NO_3)]·CH_3OH (**2**)

Bond Lengths			
I(1)−C(6)	2.087(5)	C(1)−C(2)	1.517(6)
I(2)−C(8)	2.082(5)	C(2)−C(3)	1.528(6)
Cu−O(1)	1.949(3)	C(3)−C(4)	1.530(6)
Cu−N(1)	2.001(3)	C(4)−C(5)	1.395(6)
Cu−N(1B)	1.995(4)	C(4)−C(9)	1.384(7)
Cu−N(12B)	1.986(4)	C(5)−C(6)	1.393(6)
O(1)−C(1)	1.266(5)	C(6)−C(7)	1.398(7)
O(2)−C(1)	1.255(6)	C(7)−C(8)	1.402(7)
O(3)−C(7)	1.348(5)	C(8)−C(9)	1.399(6)
O(1N)−N(1N)	1.263(5)	C(2B)−C(3B)	1.385(7)
O(2N)−N(1N)	1.247(5)	C(3B)−C(4B)	1.376(8)
O(3N)−N(1N)	1.227(5)	C(4B)−C(5B)	1.394(8)
O(1M)−C(1M)	1.414(8)	C(5B)−C(6B)	1.382(6)
N(1)−C(2)	1.486(6)	C(6B)−C(7B)	1.473(6)
N(1B)−C(2B)	1.337(6)	C(7B)−C(8B)	1.381(7)
N(1B)−C(6B)	1.355(6)	C(8B)−C(9B)	1.379(8)
N(12B)−C(7B)	1.348(6)	C(9B)−C(10B)	1.356(8)
N(12B)−C(11B)	1.339(6)	C(10B)−C(11B)	1.391(7)

Bond Angles			
O(1)−Cu−N(1)	84.7(1)	C(5)−C(4)−C(9)	118.7(4)
O(1)−Cu−N(1B)	94.0(1)	C(4)−C(5)−C(6)	120.3(4)
O(1)−Cu−N(12B)	174.8(1)	I(1)−C(6)−C(5)	120.0(3)
N(1)−Cu−N(1B)	156.3(2)	I(1)−C(6)−C(7)	118.3(3)
N(1)−Cu−N(12B)	98.5(2)	C(5)−C(6)−C(7)	121.7(4)
N(1B)−Cu−N(12B)	81.4(2)	O(3)−C(7)−C(6)	120.7(4)
Cu−O(1)−C(1)	113.7(3)	O(3)−C(7)−C(8)	121.8(4)
Cu−N(1)−C(2)	106.2(2)	C(6)−C(7)−C(8)	117.4(4)
Cu−N(1B)−C(2B)	125.6(3)	I(2)−C(8)−C(7)	118.8(3)
Cu−N(1B)−C(6B)	114.3(3)	I(2)−C(8)−C(9)	120.4(3)
C(2B)−N(1B)−C(6B)	119.8(4)	C(7)−C(8)−C(9)	120.8(4)
Cu−N(12B)−C(7B)	114.9(3)	C(4)−C(9)−C(8)	121.1(4)
Cu−N(12B)−C(11B)	126.1(3)	N(1B)−C(2B)−C(3B)	121.8(4)
C(7B)−N(12B)−C(11B)	119.0(4)	C(2B)−C(3B)−C(4B)	118.6(5)
O(1N)−N(1N)−O(2N)	119.7(4)	C(3B)−C(4B)−C(5B)	120.0(4)
O(1N)−N(1N)−O(3N)	118.7(4)	C(4B)−C(5B)−C(6B)	118.5(5)
O(2N)−N(1N)−O(3N)	121.5(4)	N(1B)−C(6B)−C(5B)	121.2(4)
O(1)−C(1)−O(2)	123.8(4)	N(1B)−C(6B)−C(7B)	114.4(4)
O(1)−C(1)−C(2)	117.9(4)	C(5B)−C(6B)−C(7B)	124.4(4)
O(2)−C(1)−C(2)	118.2(4)	N(12B)−C(7B)−C(6B)	114.6(4)
N(1)−C(2)−C(1)	108.2(3)	N(12B)−C(7B)−C(8B)	121.2(4)
N(1)−C(2)−C(3)	111.4(4)	C(6B)−C(7B)−C(8B)	124.2(4)
C(1)−C(2)−C(3)	109.0(3)	C(7B)−C(8B)−C(9B)	119.1(5)
C(2)−C(3)−C(4)	115.9(4)	C(8B)−C(9B)−C(10B)	120.1(5)
C(3)−C(4)−C(5)	120.0(4)	C(9B)−C(10B)−C(11B)	118.6(5)
C(3)−C(4)−C(9)	121.2(4)	N(12B)−C(11B)−C(10B)	122.0(4)

($TyrO^-$) (DA = phen or bpy) shows that the iodine substituents shift the CT band to a longer wavelength and increase the intensities, while in Cu(DA)(I_2tyrOH) they exhibit no such effects. These findings may indicate that a CT transition occurs from the electron-rich deprotonated diiodophenolate moiety to the electron-deficient coordinated DA rings. Our previous studies revealed that the stacking in Cu(DA)($TyrO^-$) is greatly weakened relative to that in Cu(DA)(TyrOH)[9b] probably because the hydrophilic phenolate oxygen is hydrated. For I_2tyrO^-, however, effect of the deprotonation on stacking is relatively small because of the two bulky iodines sandwiching the phenolate oxygen. The iodine substituent may also be involved in a weak binding with one of the pyridine rings of DA due to its polarizability (see below) which may also hinder the hydration of the phenolate oxygen. The shorter bond length of C(7)−O(3) (1.284(5) Å) and the longer bond lengths of I(1)−C(6) (2.110(4) Å) and I(2)−C(8) (2.108(4) Å) in complex **1** than those in complex **2** (1.348(5) Å for C(7)−O(3); 2.087(5) and 2.082(5) Å for I(1)−C(6) and I(2)−C(8), respectively) indicate the polarizability of the iodine substituents as electron acceptors (Tables 6 and 7). In accordance with these findings, the $\Delta\Delta\epsilon$ values in Table 5 indicate that the CD magnitude anomaly for Cu(DA)($TyrO^-$) is much smaller than that for Cu(DA)(I_2tyrO^-), and the solvent dependence for Cu(DA)($TyrO^-$) is also much stronger than that for Cu(DA)(I_2tyrO^-) systems.

Weak Interactions Involving Iodine and Pyridine Ring. Although the iodine substituents do not appear to promote the CT in Cu(DA)(I_2tyrOH), as seen from the difference absorption spectra (Figure 6), Table 5 shows that the iodo groups greatly enhance the CD magnitudes in the d−d region for Cu(DA)(I_2-tyrOH) (DA = bpy or phen). The much larger log *K* values for Cu(DA)(I_2tyrOH) than those for Cu(DA)(TyrOH) (DA = bpy or phen) (Table 3) demonstrate that the iodo groups also promote the stacking between the protonated phenol ring and coordinated bpy or phen. We ascribe this promotion effect of the iodines to a cooperative iodine−pyridine weak bonding interaction.

The molecular structure of complex **2** shows that the distance between I(2) and the pyridine ring (3.56 Å) is notably shorter than the sum of the van der Waals radii of an iodine and an aromatic carbon atom (3.85 Å), evidently implying a weak bonding interaction between I(2) and the pyridine ring. Because of the much lower electron density of the phenol ring in protonated I_2tyrOH than in deprotonated I_2tyrO^-, the iodines in Cu(DA)(I_2tyrOH) do not appear to favor the electron flow from the phenol ring to coordinated DA as revealed in the difference absorption spectra (Figure 6). Obviously, the high polarizability of the iodines contributes to the stacking, leading to a weak attraction of the iodine atom to the electron cloud of the pyridine ring of bpy or phen. Halogen−aromatic ring interactions in the solid state have been reported for the 1:1 adducts of benzene−bromine[31] and *p*-xylene−CBr_4,[32] where the

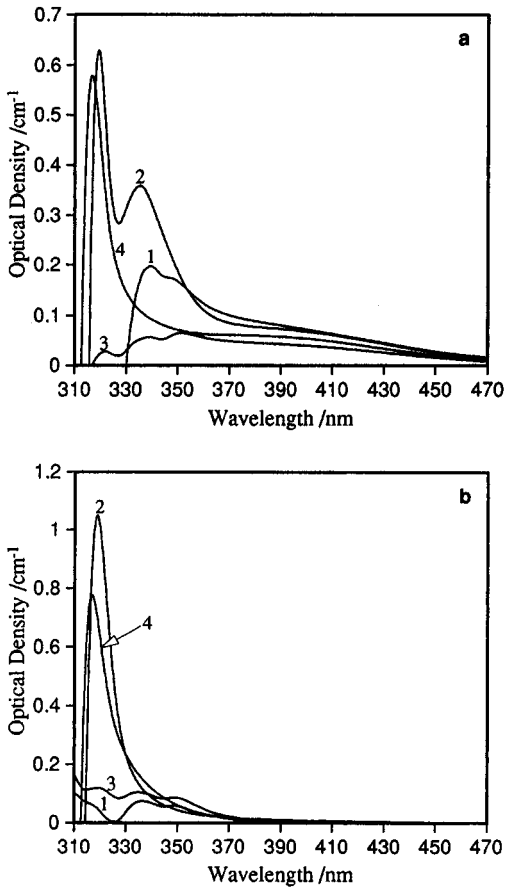


Figure 6. Difference spectra indicating charge transfer between the aromatic ring of phen or bpy and the phenolic ring of I_2tyr or Tyr. Solvent: H_2O. Concentrations: [Cu(II)] = [DA] = [AA] = 0.25 mM. (a) Curves: 1, {Cu(phen)(I_2tyrO$^-$)} − {Cu(phen) (Ala) + (I_2tyrO$^-$)}; 2, {Cu(bpy)(I_2tyrO$^-$)} − {Cu(bpy)(Ala) + (I_2tyrO$^-$)}; 3, {Cu(phen)-(TyrO$^-$)} − {Cu(phen)(Ala) + (TyrO$^-$)}; 4, {Cu(bpy)(TyrO$^-$)} − {Cu-(bpy) (Ala) + (TyrO$^-$)}. (b) Curves: 1, {Cu(phen)(I_2tyrOH)} − {Cu-(phen)(Ala) + (I_2tyrOH)}; 2, {Cu(bpy)(I_2tyrOH)} − {Cu(bpy)(Ala) + (I_2tyrOH)}; 3, {Cu(phen)(TyrOH)} − {Cu(phen)(Ala) + (TyrOH)}; 4, {Cu(bpy)(TyrOH)} − {Cu(bpy)(Ala) + (TyrOH)}.

distances between the bromine atom and the center of the benzene ring are 3.36 and 3.34 Å, respectively.

Concluding Remarks and Possible Biological Relevance. The present investigations clearly indicate that the iodo groups lower the pK_a of the phenol OH group to be mostly deprotonated at neutral pH and hinders the hydration of the phenolate oxygen. Because of this, an effective stacking takes place between the deprotonated as well as protonated diiodophenolate rings and coordinated DA in **1** and **2**. Previous investigations showed that about 82% of the thyroid hormone T_4 exists in the circulation in deprotonated form under the physiological conditions, and nearly 99% of them exists in the protein-bound forms.[3−5] Efficient deprotonation of the phenol hydroxyl group of T_4 at physiological pH may be essential for the free active hormone concentration level in the blood and the effective T_4-carrier protein binding.[4] Although residues with aromatic rings have not been observed in the hormone-binding channel of the plasma protein transthyretin, solution studies[33] and crystal structure analyses[34] on T_4-transthyretin binding showed that the iodo groups contribute to this binding through direct weak interactions with the hydrophobic residues and carbonyl oxygen of the protein. The findings of the present study imply that the iodo groups of thyroid hormones may promote the hormone−receptor binding by directly interacting with the hydrophobic side groups and aromatic rings of the receptor site. The crystal structure of the rTRα_1 receptor with Dimit prebound revealed that the hormone agonist is buried within the hydrophobic core formed by two α helices, where three aromatic side rings of Phe 401, Phe 215, and Phe 218 contact to the outer phenol ring of Dimit in plane-perpendicular fashion.[8] Phe 401 interacts directly with the plane of the outer phenol ring of Dimit in a van der Waals contact. A hydrogen bond is formed from His 381 to the phenol hydroxyl OH group of Dimit (2.64 Å) and is stabilized by Phe 405 and Met 256.[8] We suggest that when T_3 is bound to the receptor in a similar mode, Phe 401 may interact with the outer phenol ring of T_3 through stacking, and in addition, Phe 215 and Phe 218 may be involved in weak bonding with the 3′-iodine atom, further reinforcing the stacking interaction. The hydrogen bonding between His 381 and the phenol hydroxyl group may also contribute to this stacking interaction by withdrawing electrons from the π conjugate system of the benzene ring through the hydroxyl oxygen. Since Phe 405 and Phe 401 are among the key members of the C-terminal activation domain of the receptor which is critical for the hormone-dependent activation,[8] the stacking as well as the hydrogen bonding may play a key role in the biological functions of the thyroid hormone−receptor complex.

Acknowledgment. We thank Tatsuo Yajima for assistance with the experiments. Financial support from The State Education Commission of China and The Hori Information Science Promotion Foundation of Japan to F.Z. is gratefully acknowledged. This work was also supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (Bioinorganic Chemistry, No. 04225102) by the Ministry of Education, Science, Sports, and Culture of Japan, to which our thanks are due.

Supporting Information Available: Tables of atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, atomic parameters for hydrogen atoms, bond lengths and angles, and torsion angles (6 pages). Ordering information is given on any current masthead page.

IC960599X

(31) Hassel, O.; Strømme, K. O. *Acta Chem. Scand.* **1958**, *12*, 1146.
(32) Strieter, F. J.; Templeton, D. H. *J. Chem. Phys.* **1962**, *37*, 161.
(33) (a) Pages, R. A.; Robbins, J.; Edelhoch, H. L. *Biochemistry* **1973**, *12*, 2773. (b) Andrea, T. A.; Cavalieri, R. R.; Goldfine, I. D.; Jorgensen, E. C. *Biochemistry* **1980**, *19*, 55. (c) Somack, R.; Andrea, T. A.; Jorgensen, E. C. *Biochemistry* **1982**, *21*, 163.
(34) (a) Blake, C. C. F.; Geisow, M. J.; Swan, I. D. A.; Rerat, C.; Rerat, B. *J. Mol. Biol.* **1974**, *88*, 1. (b) Blake, C. C. F.; Oatley, S. J. *Nature* **1977**, *268*, 115. (c) Blake, C. C. F.; Burridge, J. M.; Oatley, S. J. *Biochem. Soc. Trans.* **1978**, *6*, 1114. (d) Blake, C. C. F.; Geisow, M. J.; Oatley, S. J.; Rerat, C.; Rerat, B. *J. Mol. Biol.* **1978**, *121*, 339. (e) Oatley, S. J.; Burridge, J. M.; Blake, C. C. F. In *Hormone Antagonists*; Agarwal, M. K., Ed.; Walter de Gruyter and Co.: Berlin, 1982; p 705.