Weak Interactions in Ternary Copper(II) Complexes with Iodotyrosinates. Biological Significance of the Iodines in Thyroid Hormones

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Structures and spectroscopic studies have been carried out on ternary copper(II) complexes, Cu(DA)(AA), with aromatic amino acids (AA = 3,5-diiodo-L-tyrosinate (L-I_2tyr), 3-iodo-L-tyrosinate (L-Ityr), L-tyrosinate) and diamines (DA = 1,10-phenanthroline, 2,2′-bipyridine (bpy), 2-(aminomethyl)pyridine, histamine (hista), or ethylenediamine). The charge transfer (CT) absorption bands observed in the near UV region and the CD spectral magnitude anomaly observed in the d−d region indicated an effective aromatic ring stacking interaction between the side-chain phenol ring of AA and the aromatic diamine DA in the complexes in solution. Two complexes, [Cu(bpy)(L-Ityr)(H_2O)]•NO_3•CH_3OH•H_2O (**1**) and [Cu(hista)(L-I_2tyrO^-)(H_2O)]$_2$•2H_2O (**2**), where O^- represents the deprotonated form of the phenol hydroxyl group, were isolated as single crystals, and their structures were determined by X-ray analysis. Both **1** and **2** crystallized in the monoclinic space group $P2_1$, with $a = 7.549(1)$ Å, $b = 11.431(1)$ Å, $c = 14.292(2)$ Å, $\beta = 100.08(1)°$, and $Z = 2$ for **1** and $a = 9.9642(9)$ Å, $b = 15.825(1)$ Å, $c = 12.451(1)$ Å, $\beta = 91.565(7)°$, and $Z = 2$ for **2**. The molecular structures of **1** and **2** revealed the intramolecular aromatic ring stacking between DA and the iodinated phenol ring of Ityr and I_2tyrO^-, respectively, in correspondence with the solution spectral observations. The stacking with hista was found to be weaker than that with bpy from the interplanar distances in **1** and **2** and the CT band intensities in solution. The molecular and crystal structures revealed some intermolecular iodine−aromatic ring and iodine−oxygen interactions as well as some hydrogen bonds involving the phenol hydroxyl group.

Introduction

Thyroid hormones are biologically active iodothyronines, which exert profound effects on the growth, development, and homeostasis of vertebrate organisms by influencing specific gene expression.[1,2] They are synthesized and secreted by the thyroid gland in two active forms, 3,5,3′,5′-tetraiodo-L-thyronine or L-thyroxine (T_4) and 3,5,3′-triiodo-L-thyronine (T_3). T_4 is the main secretory product, which is subsequently deiodinated in the peripheral tissues by isozymes of iodothyronine 5′-deiodinase to yield biologically more active T_3.[3] It has been suggested by a large body of biochemical and physiological findings that thyroid hormones can regulate the expression of specific genes through binding to specific intracellular receptors, primarily those located in the nucleus of target cells.[4−6] Through binding to the ligand-binding domain (LBD) of the nuclear receptor, the thyroid hormone contributes to the creation of an active receptor conformation, which allows the DNA binding domain of the receptor to effectively bind to its DNA response element in the promoter region of a target gene, achieving the modulation of gene expression.[7−9] It has emerged clearly in recent years that LBD functions through its so called C-terminal activation domain, which, in response to binding T_3, appears to mediate the interactions between the receptors and transcriptional coactivators.[10] The crystal structure of the LBD from the rat α_1 thyroid hormone receptor (rTRα_1) liganded with a T_3 agonist, 3,5-dimethyl-3′-isopropylthyronine, has disclosed that the C-terminal domain forms an amphipathic α-helix, with its hydrophobic face constituting part of the hormone binding cavity for direct interactions with the thyroid hormone agonist through weak bonds.[11]

We have been studying weak interactions between coordinated ligands in ternary copper(II) and other metal ion complexes with biomolecules, where coordinated aromatic amino acids exhibited remarkable properties due to stacking,[12] hydrogen bonding, and metal−aromatic ring interactions. Since 3,5-diiodo-L-tyrosine and 3-iodo-L-tyrosine are the precursors of thyroid hormone biosynthesis and the significance of the iodines in thyroid hormones is still obscure, studies on the ternary metal complexes with the iodotyrosinates should give information on the weak interactions involving the iodines in thyroid hormones, which are the only known biological molecules containing the

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largest essential element. Recently, we have investigated the structures and stabilities of ternary copper(II) complexes with 3,5-diiodo-L-tyrosinate (L-I_2tyr) and an aromatic diamine such as 2,2′-bipyridine (bpy).[12h] The iodo groups have been found to contribute to stabilization of these complexes by strongly favoring the intramolecular aromatic ring stacking interactions. The molecular structures of both Cu(bpy)(L-I_2tyr) and Cu(bpy)(L-I_2tyrO$^-$),[13] where O$^-$ represents the deprotonated form of the phenol hydroxyl group, clearly revealed effective stacking between the diiodophenol ring of L-I_2tyr and bpy.

In order to obtain further information on the weak interactions involving iodines, we performed X-ray crystal structure analysis and UV absorption and circular dichroism (CD) spectral studies on the ternary copper(II) complexes Cu(DA)(AA) (AA = L-I_2-tyr, L-Ityr, or L-Tyr; DA = phen, bpy, ampy, hista, or en).[13] On the basis of the spectral properties and the crystal and molecular structures of isolated ternary complexes, we established the intramolecular aromatic ring stacking interactions, which were distinctly favored by the iodo group, and disclosed some interesting intermolecular iodine−aromatic ring, iodine−oxygen, and other weak interactions.

Experimental Section

Materials.[13] L-I_2tyr and L-Ityr were obtained from Sigma. All other reagents used are the same as those in ref 12h. All chemicals used were of the highest grade available. Purified water was used throughout.

Preparation of [Cu(bpy)(L-Ityr)(H_2O)]·NO_3·CH_3OH·H_2O (1) and [Cu(hista)(L-I_2tyrO$^-$)(H_2O)]$_2$·2H_2O (2). Complex **1** was prepared by mixing an aqueous solution (20 mL) of 0.1 M NaOH containing 1 mmol L-Ityr and an aqueous methanol solution (20 mL) containing Cu(NO_3)$_2$·3H_2O (1 mmol) and bpy (1 mmol). The pH value of the mixture was adjusted to about 7.0 with 0.1 M HNO_3. The mixture was then filtered and kept at room temperature for a few weeks to yield blue crystals, which were collected and recrystallized from aqueous methanol to give [Cu(bpy)(L-Ityr)(H_2O)]·NO_3·CH_3OH·H_2O (**1**). Complex **2** was prepared as blue crystals in a similar manner by mixing 0.1 M NaOH (40 mL) containing 1 mmol L-I_2tyr and an aqueous methanol solution (20 mL) containing $CuCl_2$·2H_2O (1 mmol) and hista·2HCl (1 mmol).

Spectral Measurements. Electronic absorption spectra were measured at room temperature (23 °C) on a Shimadzu UV-3101PC spectrophotometer in quartz cells, and reflectance spectra for the crystalline samples of **1** and **2** were measured on a JASCO UVIDEC-660 spectrophotometer. CD spectra were measured with a JASCO J-720C spectropolarimeter at room temperature (23 °C) in a quartz cell with a path length of 100 mm. Solution samples for absorption and CD spectral measurements were freshly prepared in the 1:1:1 Cu(II)−DA−AA molar ratio. The protonated and deprotonated forms of AA were obtained by adjusting the pH values with an appropriate amount of 0.1 M NaOH. The concentration of Cu(II) was 0.5 mM. The difference spectra were measured in 0.1 M phosphate buffer.

Table 1. Crystal Data for [Cu(bpy)(L-Ityr)(H_2O)]·NO_3·CH_3OH·H_2O (**1**) and [Cu(hista)(L-I_2tyrO$^-$)(H_2O)]$_2$·2H_2O (**2**)

	complex **1**	complex **2**
formula	$CuC_{20}H_{24}N_4O_9I$	$Cu_2C_{28}H_{40}N_8O_{10}I_4$
fw	654.89	1283.38
cryst size/mm	0.15 × 0.25 × 0.30	0.20 × 0.20 × 0.20
crystal system	monoclinic	monoclinic
space group	$P2_1$	$P2_1$
a/Å	7.549(1)	9.9642(9)
b/Å	11.431(1)	15.825(1)
c/Å	14.292(2)	12.451(1)
β/deg	100.08(1)	91.565(7)
V/Å^3	1214.3(3)	1962.6(3)
Z	2	2
ρ/g cm^{-3}	1.791	2.172
μ/cm^{-1}	23.02	42.93
F(000)	652	1228.00
λ(Mo Kα)/Å	0.710 73	0.710 73
$2\theta_{max}$/deg	60	55
no. of reflecns obsd	2596	4935
no. of reflecns used ($\lvert F_o\rvert \geq 3\sigma(\lvert F_o\rvert)$)	2370	4676
R	0.027	0.031
R_w	0.036	0.026

X-ray Structure Determinations of [Cu(bpy)(L-Ityr)(H_2O)]·NO_3·CH_3OH·H_2O (1) and [Cu(hista)(L-I_2tyrO$^-$)(H_2O)]$_2$·2H_2O (2). Diffraction data for crystals **1** and **2** were obtained with an Enraf Nonius CAD-4 and a Rigaku AFC 7R four-circle diffractometer, respectively. The crystallographic data and experimental details are summarized in Table 1. Three standard reflections were monitored every 2 h and 100 reflections for **1** and **2**, respectively, and the decay of their intensities was both within 2%. Reflection data were corrected for both Lorentz and polarization effects. An absorption correction, based on ψ scan, was applied for each crystal. The structures 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 the literature.[14] Hydrogen atoms were located from the difference Fourier maps, and their parameters were isotropically refined. The final R and R_w values were 0.027 and 0.036 for **1**, and 0.031 and 0.026 for **2**, respectively. The weighting schemes $w^{-1} = [\sigma^2(F_o) + (0.023F_o)^2]$ and $w^{-1} = \sigma^2(F_o)$ were employed for **1** and **2**, respectively. The final difference Fourier maps did not show any significant features. The calculations were performed on a Micro VAX3100 computer by using the program system SDP-MolEN[15] for **1** and an IRIS Indigo computer by using the program system teXsan[16] for **2**, respectively.

Results

Absorption and CD Spectra in the d−d Region. Absorption and CD spectral data obtained for the d−d region in various solvents have been deposited as supporting information. All the ternary systems exhibited a d−d absorption peak and an obvious negative CD maximum near 600 nm. Iodination of the benzene ring did not distinctly change the absorption intensity but notably enhanced the CD spectral magnitude. Figure 1 shows the dependence of the observed maximal CD magnitudes ($\Delta\epsilon$) on the dielectric constants (d) of solvents.[17] It has been established by a large body of experimental evidence that in the absence of ligand−ligand or metal−side chain aromatic ring interactions, the CD magnitude in the d−d region for ternary Cu(II), Ni(II), and Pd(II) complexes containing α-amino acids is an additive function of the magnitudes of the

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(13) Abbreviations used: T_3, 3,5,3′-triiodo-L-thyronine; T_4, 3,5,3′5′-tetraiodo-L-thyronine or L-thyroxine; rTRα1, rat α1 thyroid hormone receptor; AA, aromatic amino acid; Tyr, tyrosinate; TyrO$^-$, Tyr with the deprotonated phenol moiety; Ityr, 3-iodotyrosinate; ItyrO$^-$, Ityr with the deprotonated iodophenol moiety; I_2tyr, 3,5-diiodotyrosinate; I_2tyrO$^-$, I_2tyr with the deprotonated diiodophenol moiety; Phe, phenylalaninate; Ala, alaninate; DA, aromatic diamine; phen, 1,10-phenanthroline; bpy, 2,2′-bipyridine; ampy, 2-(aminomethyl)pyridine; hista, histamine; en, ethylenediamine.

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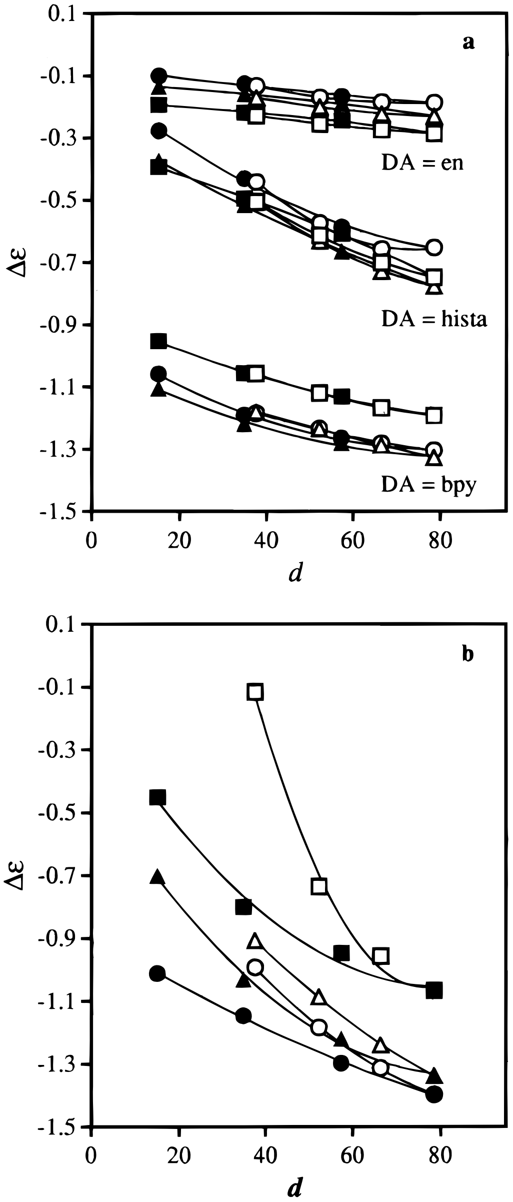

Figure 1. Dependence of the CD magnitudes ($\Delta\epsilon$) on the dielectric constants (*d*) of the solvents for (a) Cu(DA)(AA) systems with DA = bpy, hista, or en and AA = L-I$_2$tyr (●, ○), L-Ityr (▲, △), or L-Tyr (■, □) and (b) Cu(bpy)(AA) systems with AA = L-I$_2$tyrO$^-$ (●, ○), L-ItyrO− (▲, △), or L-TyrO− (■, □). The solid (●, ▲, ■) and open (○, △, □) symbols refer to the $\Delta\epsilon$ values for solvents dioxane−H$_2$O and ethanol−H$_2$O, respectively. The curves are drawn by quadratic curve-fitting.

component binary systems,[18,19] but it deviates from the additivity when there exist such interactions.[12a,b,d−f,h,i,19] The CD magnitudes for the present systems have been estimated from those of the component binary complexes Cu(L-AA)$_2$ by this method,[12h] which showed that for all the systems with an aromatic diamine the observed CD magnitudes seriously deviate from the calculated values, suggesting a hindered side-chain conformation of AA due to the aromatic ring stacking. Since the Cu(II)−aromatic ring interactions can also cause a small CD magnitude deviation,[12,18] we may estimate the CD magnitude anomaly due to the aromatic ring stacking by comparing the $\Delta\epsilon$ value of Cu(DA)(AA) with that of Cu(en)(AA).[12h] Figure 1 shows that the magnitudes of the negative peak for the systems with aromatic DA such as bpy are larger than those with en, which is in line with the aromatic ring stacking interaction between the iodophenol ring and aromatic DA. The $\Delta\epsilon$ values for the systems with I$_2$tyrO$^-$ or ItyrO$^-$ are more negative than those with TyrO$^-$ and decrease in the order I$_2$tyrO$^-$ > ItyrO$^-$ > TyrO$^-$. This indicates that the iodo group strengthens the aromatic ring stacking. On the other hand, Figure 1 shows that the stacking interaction as viewed from the CD magnitudes is weakened in less polar solvents and that the effect of ethanol as a solvent is stronger than that of dioxane, which may result from the hydrogen bonds between the phenol hydroxyl group and ethanol molecules.

Charge Transfer (CT) Absorption Spectra. Aromatic ring stacking usually gives rise to an absorption band in the near ultraviolet region, which has been generally assigned to the CT transition between the stacked aromatic rings and can be observed by recording the difference spectra.[12b,e,g−i,20] Such a CT absorption band was detected for the present Cu(DA)(AA) systems (Figure 2), indicating that a CT transition occurs between the stacked phenol moiety and the aromatic diamines, although the intensities for Cu(hista)(AA) were weaker than those for Cu(bpy)(AA); Cu(DA)(L-Ityr) and Cu(DA)(L-ItyrO$^-$) exhibited a clear CT peak at ~320 nm. The populations of the stacked species in solution are calculated from the stability constants[12h] to be >93% for Cu(bpy)(L-I$_2$tyr) and Cu(bpy)(L-I$_2$tyrO$^-$), 85.5% for Cu(hista)(L-I$_2$tyr), and 47.5% for Cu(hista)(L-I$_2$tyrO$^-$), so that the bands for Cu(hista)(AA) are intrinsically weaker. From the populations of the stacked species and the distributions of the complex species in solution under the conditions of the spectral measurements, the molar absorption coefficients, ϵ, for the completely stacked forms of Cu(bpy)(L-I$_2$tyr) and Cu(hista)(L-I$_2$tyr) are estimated to be ~2300 and ~180, respectively, the value for Cu(hista)(L-I$_2$tyrO$^-$) being ~1400. For the systems with deprotonated AA, iodination of the benzene ring enhances the absorption intensity and shifts the band to a longer wavelength, which is in line with the previous findings on the stabilizing effect of the iodo group on the stacking.[12h] Protonation of the phenol hydroxyl group reduces the CT absorption intensities for the systems with hista but not for the systems with bpy.

Structures of [Cu(bpy)(L-Ityr)(H$_2$O)]·NO$_3$·CH$_3$OH·H$_2$O (1) and [Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)]$_2$·2H$_2$O (2). The unit cell for **1** consists of two [Cu(bpy)(L-Ityr)(H$_2$O)] molecules, two nitrate ions, and two methanol and two water molecules, while that for **2** consists of two crystallographically independent [Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)]$_2$·2H$_2$O units, each of which is composed of isomers **A** and **B** of [Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)] linked together by weak interactions. The molecular structures of [Cu(bpy)(L-Ityr)(H$_2$O)] for **1** and [Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)] for **2** are shown in Figures 3 and 4, respectively. The central Cu(II) ion for both **1** and **2** has a similar distorted five-coordinate square-pyramidal geometry with the two nitrogen atoms of bpy or hista and the amino nitrogen and carboxylate oxygen atoms of Ityr or I$_2$tyrO$^-$ in the equatorial positions and an oxygen atom

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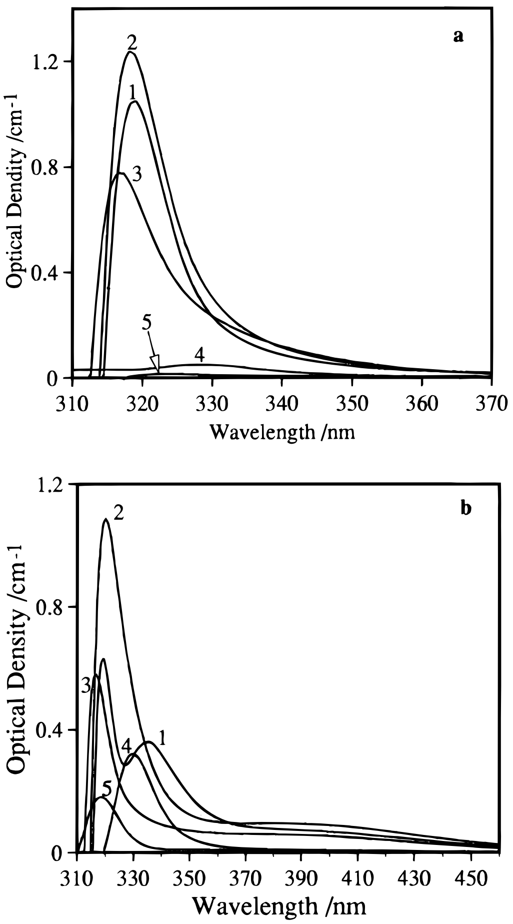

Figure 2. Difference spectra showing the CT transitions between the stacked aromatic rings for Cu(DA)(AA) systems, obtained by subtracting the absorbances of Cu(DA)(L-Ala) and AA from the absorbance of Cu(DA)(AA). The spectra were measured in 0.1 M phosphate buffer solution in a quartz cell with a path length of 10 mm at the Cu(II), DA, and AA concentrations of 0.5 mM. The pH value was adjusted to the value that corresponds to the highest percentage of the ternary species. Curves in a: 1, (Cu(bpy)(L-I_2tyr); 2, Cu(bpy)(L-Ityr); 3, Cu(bpy)(L-Tyr); 4, Cu(hista)(L-I_2tyr); 5, Cu(hista)(L-Ityr). Curves in b: 1, Cu(bpy)(L-I_2tyrO^-); 2, Cu(bpy)(L-$ItyrO^-$); 3, Cu(bpy)(L-$TyrO^-$); 4, Cu(hista)(L-I_2tyrO^-); 5, Cu(hista)(L-$ItyrO^-$).

of water in an apical position. Selected bond lengths and angles are given in Tables 2 and 3. The equatorial Cu−N and Cu−O bond lengths observed for **1** and **2** agree well with the corresponding bond lengths found for Cu(bpy)(L-I_2tyr) and Cu(bpy)(L-I_2tyrO^-) reported previously[12h] and the Cu(II) complexes with amino acids.[21] The axial Cu(II)−O(1W) distances are 2.268(6) Å for **1** and 2.715(7) and 2.406(6) Å for **A** and **B** of **2**, respectively, which are longer than the sum of the ionic radii of Cu(II) and an oxygen atom (2.13 Å),[22] but still within the range of 2.2−2.9 Å known for axial Cu−O bond length,[23] so that the oxygen atom of water is considered to be coordinated in these complexes. The obvious difference between the distances for **A** and **B** (0.31 Å) may result from the intermolecular interactions involved in **2** (see below). The axial position opposite to the coordinated oxygen in both **1** and **2** is intramolecularly occupied by the iodinated phenol ring. For complex **1**, the iodophenol ring is approximately parallel to the Cu(II) coordination plane with the dihedral angle of 3.7° and the average spacing of 3.36 Å. The ring is positioned over one of the two pyridine rings of bpy with the iodine atom located over the other pyridine ring with the distance of 3.73 Å, which is shorter than the sum of the van der Waals radii of an aromatic carbon atom and an iodine atom (3.85 Å)[24] and is indicative of an iodine−pyridine ring weak bonding interaction. For complex **2**, however, the diiodophenol ring of I_2tyrO^- deviates from the parallel position with the average spacings of 3.91 and 3.97 Å and the dihedral angles of 23.8 and 30.9° for **A** and **B**, respectively.[25] The differences of the average spacings (0.06 Å) and the dihedral angles (7.1°) may be caused by the conformational change in the chelate ring puckering of hista (Figure 4b). The torsion angles of Cu(1)−N(1)−C(3)−C(4)

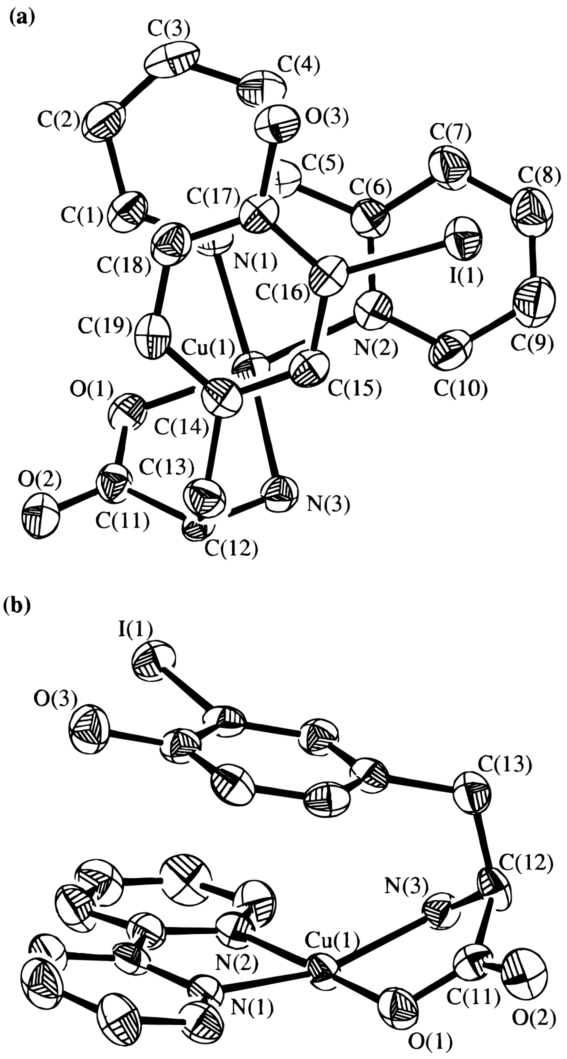

Figure 3. (a) Molecular structure of [Cu(bpy)(L-Ityr)(H_2O)] (**1**) with the atomic numbering scheme. (b) Side view showing the aromatic ring stacking. The coordinated water molecule is omitted for clarity.

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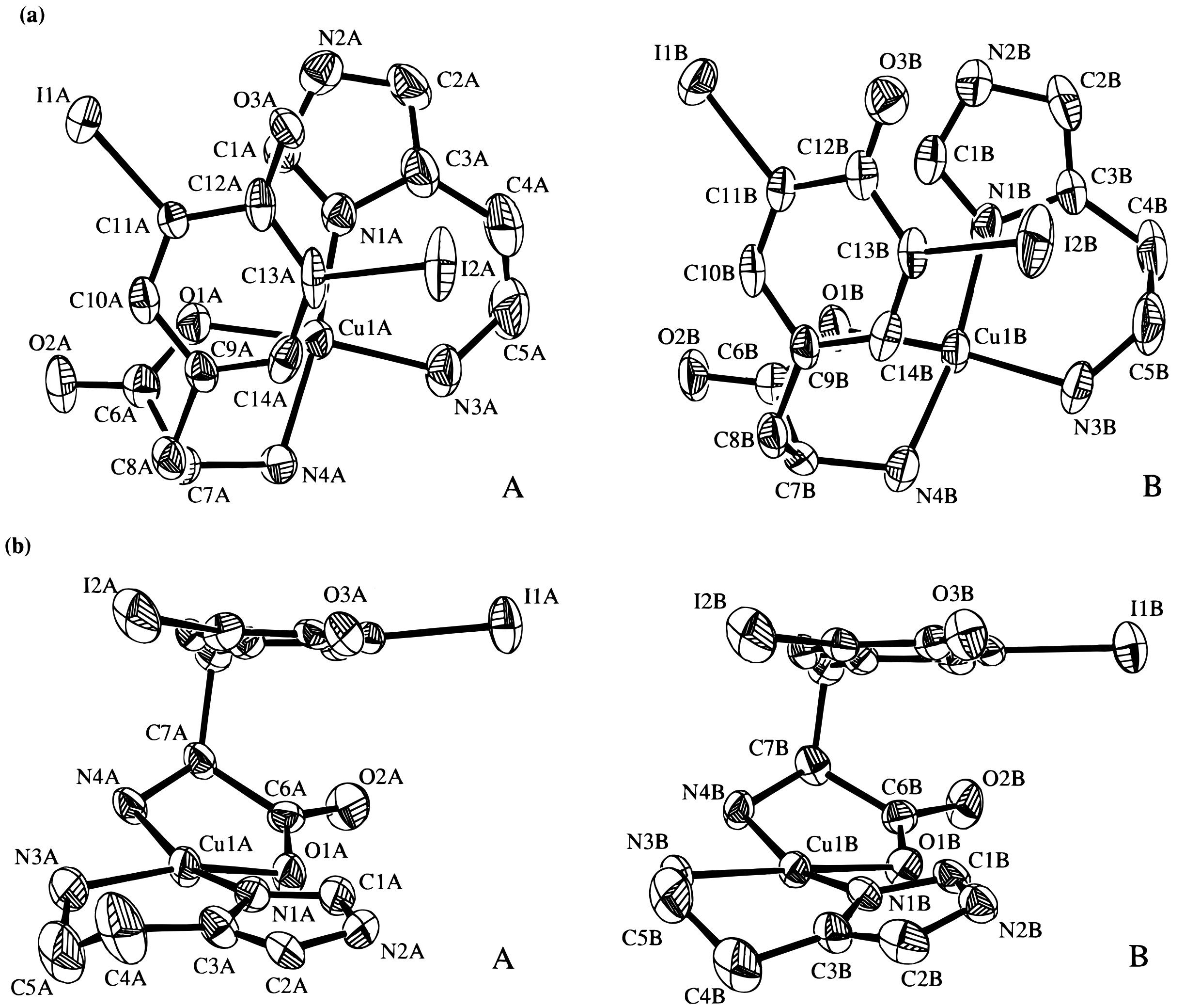

Figure 4. (a) Molecular structures of isomers **A** and **B** of [Cu(hista)(L-I_2tyrO^-)(H_2O)] with the atomic numbering scheme. (b) Side view showing the intramolecular aromatic ring stackings. The coordinated water molecules are omitted for clarity.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for [Cu(bpy)(L-Ityr)(H_2O)]·NO_3·CH_3OH·H_2O (**1**)

Bond Lengths			
Cu(1)−O(1)	1.947(4)	Cu(1)−N(3)	2.020(4)
Cu(1)−N(1)	2.003(4)	Cu(1)−O(1W)	2.268(6)
Cu(1)−N(2)	2.002(5)	I(1)−C(16)	2.081(6)
Bond Angles			
O(1)−Cu(1)−N(1)	92.8(2)	O(1W)−Cu(1)−N(1)	110.6(2)
O(1)−Cu(1)−N(2)	173.7(2)	O(1W)−Cu(1)−N(3)	89.1(2)
O(1)−Cu(1)−N(3)	82.7(2)	O(1W)−Cu(1)−N(2)	93.4(2)
N(1)−Cu(1)−N(3)	159.9(2)	O(1W)−Cu(1)−O(1)	91.2(2)
N(1)−Cu(1)−N(2)	81.4(2)	I(1)−C(16)−C(15)	117.7(3)
N(3)−Cu(1)−N(2)	101.7(2)	I(1)−C(16)−C(17)	122.2(4)

and N(1)−C(3)−C(4)−C(5) are −11(1)° and 36(2)° for **A** and 2(1)° and −50(1)° for **B**, respectively. On the other hand, the iodine atoms in complex **2** are found to be intermolecularly in contact with the aromatic diiodophenol and imidazole rings (Figure 5). The closest iodine−aromatic carbon atom distances are 3.587−3.715 Å, which are shorter than the van der Waals distance of 3.85 Å and indicate weak iodine−aromatic ring interactions. In addition, some intermolecular hydrogen bonds involving the phenol hydroxyl group were also observed (Table 4). Interestingly, the iodine atom of Ityr in **1** and of I_2tyrO^- in **2** is in contact with the oxygen atom of a solvent methanol molecule and the oxygen atom of the coordinated water molecule, respectively, with the distances of 3.08 and 3.28 Å (Table 4). These distances are notably shorter than the sum of the van der Waals radii of an iodine and an oxygen atom (3.55 Å)[24] and are in line with the weak iodine−oxygen interactions.

Discussion

Intramolecular Aromatic Ring Stacking and Iodine−Aromatic Ring Interactions. As suggested by the CD magnitude anomaly and its solvent dependence as well as the CT absorption bands near 320 nm, an effective intramolecular stacking interaction occurred between the side-chain iodophenol ring of AA and aromatic DA in the ternary Cu(DA)(AA) complexes. The molecular structures of Cu(bpy)(L-Ityr)(H_2O) (**1**) and Cu(hista)(L-I_2tyrO^-)(H_2O) (**2**) demonstrate such effective stacking interactions in the solid state, supporting the presence of the stacking in solution. Our previous equilibrium studies on ternary Cu(DA)(L-I_2tyr) complexes showed that the iodines remarkably contribute to the stabilization of the complexes, which corresponded well with the CD magnitude anomaly.[12h] In the present study, the CD magnitudes observed for Cu(DA)-(AA) decreased in the order I_2tyrO^- > $ItyrO^-$ > $TyrO^-$ (Figure 1b), further suggesting that the bulky iodine atoms may assist the stacking by interacting with the pyridine ring and by protecting the phenol hydroxylate group from hydration.[12h] The same CD magnitude sequence was observed in aqueous dioxane and aqueous ethanol, and their solvent dependence (I_2tyrO^- < $ItyrO^-$ < $TyrO^-$) suggested that the presence of the iodine atoms may also be effective for stacking in less polar solvents. The

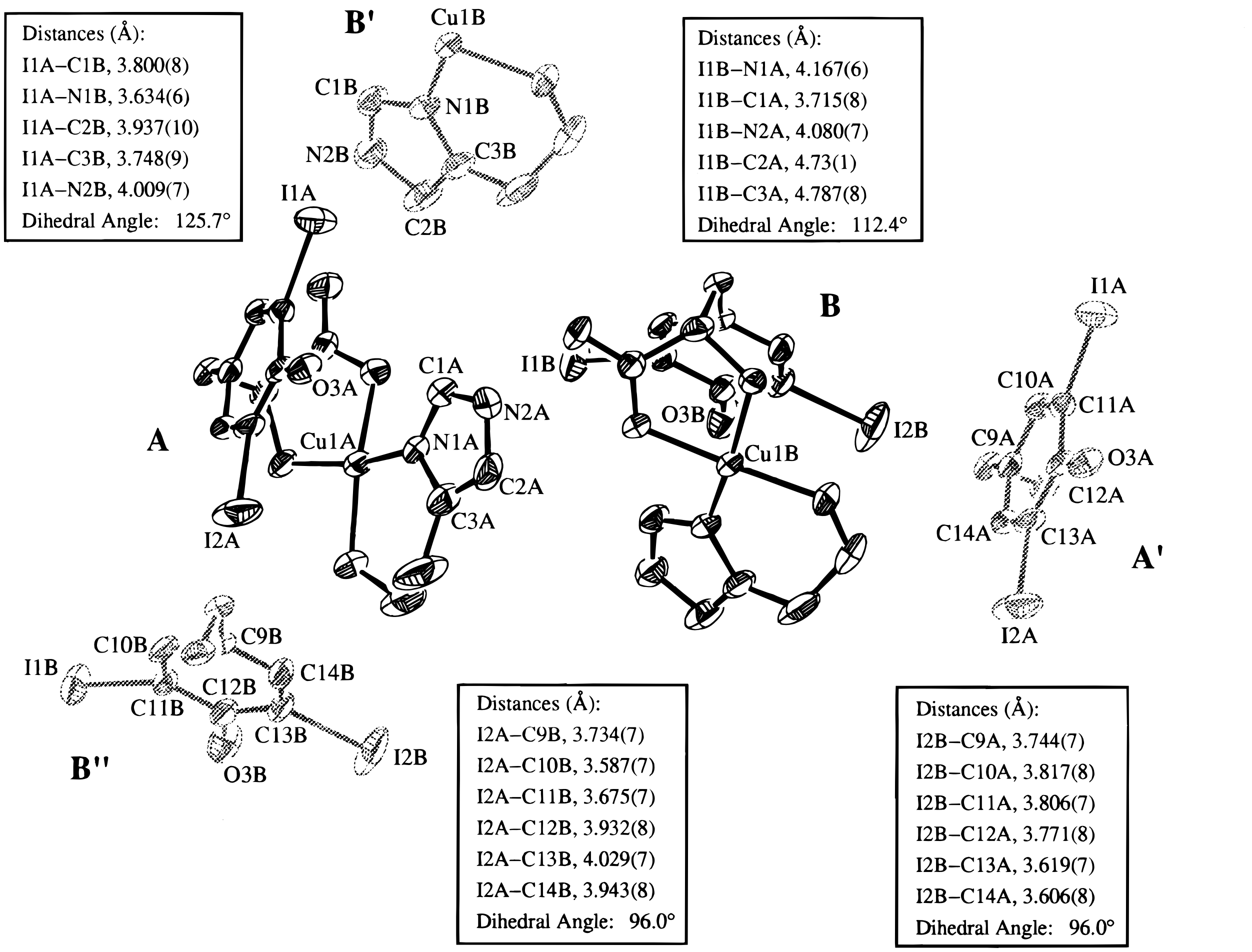

Figure 5. Structure of [Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)]$_2$ (**2**) with the atom–atom distances and dihedral angles between the related aromatic rings showing the intermolecular iodine–aromatic ring interactions. The coordinated water molecules are omitted for clarity.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for [Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)]$_2$·2H$_2$O (**2**)

	Bond Lengths		
I(1A)–C(11A)	2.088(7)	I(1B)–C(11B)	2.087(7)
I(2A)–C(13A)	2.094(7)	I(2B)–C(13B)	2.089(7)
Cu(1A)–O(1A)	1.966(5)	Cu(1B)–O(1B)	1.975(5)
Cu(1A)–N(1A)	1.946(7)	Cu(1B)–N(1B)	1.946(7)
Cu(1A)–N(3A)	1.999(6)	Cu(1B)–N(3B)	2.009(6)
Cu(1A)–N(4A)	1.994(6)	Cu(1B)–N(4B)	2.011(7)
Cu(1A)–O(1WA)	2.715(7)	Cu(1B)–O(1WB)	2.406(6)
	Bond Angles		
O(1A)–Cu(1A)–N(1A)	93.2(2)	O(1B)–Cu(1B)–N(1B)	92.7(2)
O(1A)–Cu(1A)–N(3A)	164.6(3)	O(1B)–Cu(1B)–N(3B)	173.6(3)
O(1A)–Cu(1A)–N(4A)	83.0(2)	O(1B)–Cu(1B)–N(4B)	82.7(2)
O(1A)–Cu(1A)–O(1WA)	82.7(2)	O(1B)–Cu(1B)–O(1WB)	85.4(2)
N(1A)–Cu(1A)–O(1WA)	97.2(2)	N(1B)–Cu(1B)–O(1WB)	102.9(2)
N(3A)–Cu(1A)–O(1WA)	82.9(2)	N(3B)–Cu(1B)–O(1WB)	90.5(2)
N(4A)–Cu(1A)–O(1WA)	95.7(2)	N(4B)–Cu(1B)–O(1WB)	92.5(2)
N(1A)–Cu(1A)–N(3A)	94.2(3)	N(1B)–Cu(1B)–N(3B)	93.1(3)
N(1A)–Cu(1A)–N(4A)	165.9(2)	N(1B)–Cu(1B)–N(4B)	163.6(3)
N(3A)–Cu(1A)–N(4A)	92.9(3)	N(3B)–Cu(1B)–N(4B)	92.6(3)
I(1A)–C(11A)–C(10A)	118.7(5)	I(1B)–C(11B)–C(10B)	117.7(5)
I(1A)–C(11A)–C(12A)	118.0(6)	I(1B)–C(11B)–C(12B)	118.5(6)
I(2A)–C(13A)–C(12A)	117.4(6)	I(2B)–C(13B)–C(12B)	117.3(6)
I(2A)–C(13A)–C(14A)	119.4(6)	I(2B)–C(13B)–C(14B)	118.5(6)

much stronger solvent dependence of the magnitudes observed in aqueous ethanol than that in aqueous dioxane suggests that ethanol molecules may weaken the stacking through hydrogen bonds with the phenol hydroxyl or hydroxylate group, as has been evidenced by the crystal structures in the solid state (see below). In addition, the molecular structure of **1** also revealed an intramolecular iodine–pyridine ring interaction with the distance of 3.73 Å. A similar weak interaction was detected in Cu(bpy)(L-I$_2$tyr) with the distance of 3.56 Å.[12h] Such interactions may be responsible for the large CD magnitude anomaly and strong CT absorption intensity observed for these complexes.

The molecular structures of **1** and **2** revealed that the average spacing between the stacked aromatic rings for **1** (3.36 Å) is comparable with the values previously found for Cu(bpy)(L-I$_2$tyr) (3.30 Å) and Cu(bpy)(L-I$_2$tyrO$^-$) (3.31 Å)[12h] as well as for

Table 4. Selected Distances (Å) for Cu(DA)(AA) Showing the Iodine−Oxygen and Hydrogen-Bonding Interactions[a]

complexes	distances			
[Cu(bpy)(L-I$_2$tyrO$^-$)(H$_2$O)]·2H$_2$O[b]	I(1)−O(1W)	3.23	O(2)−O(3W)	2.83
	I(1)−O(3)	3.19	O(1)−O(3W)	2.77
	I(2)−O(3)	3.18	O(3)−N(1)	2.80
	O(3)−O(1W)	2.64	O(2W)−O(3W)	2.77
[Cu(hista)(L-I$_2$tyrO$^-$)(H$_2$O)]$_2$·2H$_2$O(**2**)	I(1A)−O(1WB)	3.28	O(3B)−O(1WB)	2.65
	I(1A)−O(3A)	3.17	O(2A)−O(2WA)	2.70
	I(2A)−O(3A)	3.18	O(2B)−O(2WB)	2.74
	I(1B)−O(3B)	3.19	N(2B)−O(2WA)	2.83
	I(2B)−O(3B)	3.18	O(1WA)−O(2WA)	2.75
	O(3A)−O(1WA)	2.55	O(1WB)−O(2WB)	2.94
[Cu(bpy)(L-I$_2$tyr)(NO$_3$)]·CH$_3$OH[b]	I(1)−O(3)	3.15	O(3)−O(2)	2.54
	I(2)−O(3)	3.19	O(3)−O(1M)	2.77
[Cu(bpy)(L-Ityr)(H$_2$O)]·NO$_3$·CH$_3$OH·H$_2$O (**1**)	I(1)−O(1M)	3.08	O(2)−O(1M)	2.68
	I(1)−O(3)	3.23	O(1W)−O(2N)	2.81
	O(3)−O(2W)	2.67	O(2W)−O(1M)	2.77
[Cu(bpy)(L-Tyr)(ClO$_4$)]·2H$_2$O[c]	O(3)−O(2W)	2.62	O(2)−O(2W)	2.81
	O(3)−O(1W)	2.86	O(1W)−O(2W)	2.78

[a] Atomic numbering schemes are the same as those used in the papers cited; W, M, and N in parentheses refer to water, methanol, and nitrate, respectively. [b] Reference 12h. [c] Reference 12f.

Cu(bpy)(L-Tyr) (3.35 Å)[12f] but is much smaller than the values for **2** (3.91 Å for **A** and 3.97 Å for **B**). On the other hand, the spacings for **2** are smaller than those previously found for Cu(hista)(L-Tyr) (4.20 Å) and Cu(hista)(L-Phe) (4.15 Å),[26] and the dihedral angles between the stacked aromatic rings for **2** (23.8° for **A** and 30.9° for **B**) are also smaller than those observed for Cu(hista)(L-Tyr) (38.1°) and Cu(hista)(L-Phe) (38.5°). The stacking interactions of the phenol moieties with the imidazole ring may be concluded to be much less effective than that with bpy, which may be related with the weak CT band observed for the Cu(hista)(AA) systems. In this connection, the reflectance spectra of **1** and **2** showed, in addition to a d−d peak at ∼610 nm, a broad band at <450 nm, probably indicating the CT due to the stacking revealed in the solid state.

Intermolecular Iodine−Aromatic Ring Interactions. The crystal structure of **2** revealed that the iodines of I$_2$tyrO$^-$ intermolecularly contact with the imidazole and diiodophenol rings with the closest distances of 3.587−3.715 Å (Figure 5). These distances are shorter than the van der Waals distance of 3.85 Å, indicating weak iodine−aromatic ring interactions. A similar contact has previously been observed for Cu(bpy)(DL-Iphe) (Iphe = (*p*-iodophenyl)alaninate) with the closest distance of 3.54 Å.[12g] Some other halogen-aromatic ring contacts in the solid state have been reported for the 1:1 adducts of benzene−bromine[27] and *p*-xylene−CBr$_4$[28] and the ternary complex Cu(bpy)(DL-Brphe) (Brphe = (*p*-bromophenyl)alaninate)[12g] with the closest distances of 3.36, 3.34, and 3.47 Å, respectively. Figure 5 suggests that interactions of the iodine atom with the electron-rich diiodophenol ring may be more effective than those with the imidazole ring.

Iodine−Oxygen Interactions. In addition to the aromatic rings, the iodine atoms in **1** and in **2** were also found to contact with the oxygen atom of a methanol molecule and the oxygen atom of a water molecule with the distances of 3.08 and 3.28 Å, respectively (Table 4).[29] These distances are notably shorter than the calculated distance of 3.55 Å, which is indicative of the iodine−oxygen interactions and is comparable with the similar iodine−oxygen contact observed for Cu(bpy)(L-I$_2$tyrO$^-$) (3.23 Å).[12h] Iodine−oxygen interaction has also previously been observed for other complexes,[12g,30−32] which has generally been interpreted as the donor−acceptor charge-transfer interaction that often occurs between the heavier p block elements such as iodine and some nucleophiles with lone pairs such as oxygen, nitrogen, and sulfur.[30] Extensive analyses of the features of C−I···X contacts (X = O, N, S) have shown that the C−I···O angle ranges from 180° to even less than 90°,[31] and it appears that the donor oxygen atom, where possible, is arranged so that one of its lone pairs is directed toward the iodine atom for the most effective interaction.[32] The iodine−oxygen distances observed for **1** and **2** (3.08 and 3.28 Å, respectively) as well as for Cu(bpy)(L-I$_2$tyr) (3.23 Å)[12h] are within the range of 2.99−3.45 Å known for some thyroactive compounds[33] but shorter than the value previously observed for free solvent water (3.43 Å).[32] Interestingly, the intramolecular iodine−oxygen distances for the phenol hydroxyl group (3.15−3.23 Å, Table 4) are also much shorter than the calculated distance of 3.55 Å. A space-filling model shows that the phenol hydroxyl group of I$_2$tyr is partly buried within the bulky iodines, suggesting that the iodine atoms nestling the hydroxyl oxygen may not only hinder the water molecules from approaching the oxygen as suggested by the CD spectral findings but also exert a direct influence on its lone pairs and thus its hydrogen bond formation.[34]

Intermolecular Hydrogen Bonds Involving the Phenol Hydroxyl Group. The hydrogen bonds detected in **1** and **2** as well as those found in [Cu(bpy)(L-I$_2$tyr)(NO$_3$)]·CH$_3$OH,[12h] [Cu(bpy)(L-I$_2$tyrO$^-$)(H$_2$O)]·2H$_2$O,[12h] and [Cu(bpy)(L-Tyr)(ClO$_4$)]·2H$_2$O[12f] indicated a high efficiency of the phenol hydroxyl group in forming hydrogen bonds with other side groups and solvent molecules. Table 4 shows that, indeed, the iodines influence the hydrogen bond formations by the phenol hydroxyl group. The phenol O$^-$ group in **2** and Cu(bpy)(L-I$_2$tyrO$^-$)[12h] formed

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hydrogen bonds with the coordinated water molecule but not with the solvent water molecules. In addition, the water molecules of crystallization involved in the hydrogen bonds with the phenol OH group are dramatically 2, 1, and 0 for Cu(bpy)(AA) with AA = L-Tyr, L-Ityr, and L-I_2tyr, respectively. Interestingly, instead of the water molecules in **1** and [Cu(bpy)(L-Tyr)(ClO_4)]·$2H_2O$,[12f] a methanol molecule is involved in the hydrogen bond with the phenol OH group in [Cu(bpy)(L-I_2tyr)(NO_3)]·CH_3OH.[12h]

For the hydrogen bonds involving the phenol O^- group, the observed O···O distances (2.55 and 2.65 Å for **2** and 2.64 Å for Cu(bpy)(L-I_2tyrO^-)[12h]) are the same or slightly shorter than the average O···O distance 2.66 Å observed for crystalline thyroid hormone analogs.[35] The phenol O^- group in Cu(bpy)(L-I_2tyrO^-) formed another hydrogen bond with the coordinated amino group (N(1)) in addition to that with the water molecule, with the O···N distance of 2.80 Å,[12h] which is slightly shorter than the average O···N distance of 2.87 Å observed for T_4−diethanolamine.[36] For the phenol OH group, on the other hand, two hydrogen bonds were detected in both [Cu(bpy)(L-I_2tyr)(NO_3)]·CH_3OH and [Cu(bpy)(L-Tyr)(ClO_4)]·$2H_2O$[12f] with the bond lengths of 2.54 and 2.77 Å for the former and 2.62 and 2.86 Å for the latter, which agree well with those observed for the 4′-OH group of crystalline thyroid hormone analogs (2.66 and 2.81 Å for the OH group as a proton donor and an acceptor in the hydrogen bond, respectively).[35] However, only one hydrogen bond was observed for **1** with the bond length of 2.67 Å, which is in correspondence with the proton donor distance.[35,36] The iodine atoms may affect the lone pairs of the phenol oxygen.

Conclusions and Possible Biological Significance of the Iodines in Thyroid Hormones. As has been clearly indicated by the difference spectra and the CD magnitude anomaly as well as the X-ray structural observations, the iodines exhibit a distinct influence on the iodophenol ring in the weak interactions. By effectively protecting the phenol hydroxyl group from hydration and affecting its lone pairs, the iodines appear not only to promote the aromatic ring stacking of the iodophenol rings with DA but also to affect the hydrogen bond formation of the hydroxyl group. In addition, they also exhibit a high activity in directly forming weak bonds with aromatic rings and other groups containing a nucleophilic atom through donor-acceptor interactions. These findings may imply that the iodines of thyroid hormones play an important role in the thyroid hormone−receptor binding under physiological conditions. As has previously been expected,[12h] the possible aromatic ring stacking interaction between the outer phenol ring of hormone T_3 and Phe 401 may be crucial for creating the active conformation of the C-terminal activation domain in the thyroid hormone-receptor binding. The 3′ iodine may contribute to the stacking by stabilizing the outer phenol ring of the hormone through multiply interacting with the carbonyl oxygen of Gly 290 and/or Gly 291 and the aromatic rings of Phe 215 and/or Phe 218 as well as the hydroxyl oxygen of Thr 219. Similar iodine−carbonyl oxygen and iodine−hydroxyl oxygen interactions have previously been detected for thyroxine-transthyretin[37] and 3,3′-diiodothyronine-transthyretin,[38] respectively. On the other hand, the 3,5 iodines may be of significance for maintaining the active conformation of the hormone molecule by hindering the rotation of the diphenyl ether moiety through steric hindrance to the outer phenol ring[35] and direct interactions with the ether oxygen. Thus, the iodine atoms in thyroid hormones may be essential for the hormone−receptor binding from the structural point of view, which is in accordance with physiological studies.[39]

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Supporting Information Available: Tables of absorption and CD spectral data, atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, atomic parameters for hydrogen atoms, bond lengths and angles, and torsion angles (9 pages). Ordering information is given on any current masthead page.

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