*Inorg. Chem.* **2007**, *46*, 9975–9978


# An Attempt to Discriminate between the Hydrophobic and Aromatic $\pi$–$\pi$ Interactions in the Copper(II) Ternary Complexes CuLA with L = 1,10-Phenanthroline or 2,2′-Bipyridyl and A = *para*-X-Substituted Phenylalaninates

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Received June 27, 2007

For the title complexes, the value of formation constant $K$(CuL + A) is higher than that of $K_1$(CuA$_2$). According to the mechanistic consideration, log $K$(CuL + A) is calculated for *regular* Cu(II) complexes with neither special enhancement nor diminution of the stability constant. Then, the difference of log $K$(CuL + A)(obs) − log $K$(CuL +A)(calc) represents extrastabilization due to the hydrophobic interactions and the aromatic $\pi$–$\pi$ interactions. The former has been found to be proportional to the free energy of the transfer of side chains of aminocarboxylates A. The discrimination between the hydrophobic and the aromatic $\pi$–$\pi$ interactions has been attempted.

## Introduction

Ternary metal complexes have been the subjects of extensive studies for coordination chemists, including bioinorganic chemists.[1−20] Ligand pairs utilized in these studies include amino acids,[3,5−7,9−11,13,15,17,18] peptides,[2,8,18] pterin,[6] 2′-deoxyguanidine-5′-monophosphate,[1] and catechol.[10] In an early stage of study on the ternary complexes, a general and methodological account for the study of mixed-ligand complexes of amino acids and peptides was outlined and the stability constants of ternary complexes of Cu, Ni, Co, Cd, Zn, Pb, and Ca were tabulated.[18] Structural aspects of mixed-ligand complex formation have been given together with the biological importance of ternary complexes.[19] Later on, aromatic diamines such as 2,2′-bipyridine (bpy) and 1,10-phenanthroline (phen) together with aliphatic analogues such as 2,2′-diaminoethane have been utilized to discuss the aromatic stacking interactions between the side chains of amino acids and the aromatic diamine in the complex in solution.[1−9]

In these studies, stability constants enhanced by noncovalent interactions between coordinated ligands have attracted the interest of these chemists. The noncovalent interactions include the interactions between two aromatic rings, the

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10.1021/ic701261e CCC: $37.00 
Published on Web 10/20/2007

interactions between metal ion and aromatic ring in the coordinated ligand, the electrostatic interactions between charged groups of the coordinated ligands, and the hydrophobic interactions between coordinated ligands. The present paper describes the extent of the hydrophobic interactions and the aromatic $\pi-\pi$ interactions in the ternary complexes CuLA with L = phen or ′bpy and A = *para*-X-substituted phenylalaninate, where the stacking or aromatic ring interactions have been observed between phen or bpy and the aromatic side chains of *para*-X-substituted phenylalaninates.[1,3,4,8,12] Noncovalent interactions between two neutral aromatic molecules involve the interplay of several different effects including (a) van der Waals interactions, (b) electrostatic interactions for molecular charge distributions, (c) induced energy transfer, (d) charge transfer, and (e) deaquation.[21] However, they are usually divided into two main categories: nonspecific hydrophobic interactions[22] and aromatic $\pi-\pi$ interactions mainly occurring through delocalized aromatic $\pi$ systems through stacked molecules.

## Results and Discussion

On the basis of the mechanistic consideration,[20] we have the following equation for the formation constants of ternary copper(II) complexes CuLA:

$$\log K(\mathrm{CuL + A}) = \log K(\mathrm{CuA}) + \{\log K_{\mathrm{OS}}(\mathrm{CuL, A}) - \log K_{\mathrm{OS}}(\mathrm{Cu, A})\} + \sum_{I<}^{I}\sum_{J}^{J} \delta_{ij} X_i(\mathrm{A}) Y_j(\mathrm{L}) \quad (1)$$

where charges are omitted for simplicity and the formation constants are defined as

$$K(\mathrm{CuL + A}) = [\mathrm{CuLA}][\mathrm{CuL}]^{-1}[\mathrm{A}]^{-1}$$

$$K(\mathrm{CuA}) = [\mathrm{CuA}][\mathrm{Cu}]^{-1}[\mathrm{A}]^{-1}$$

and $K_{\mathrm{OS}}$(CuL, A) and $K_{\mathrm{OS}}$(Cu, A) denote formation constants of outer-sphere complexes [CuL, A] and [Cu, A], respectively. In the last term of eq 1, $\delta_{ij}$ denotes the effect of the donor atom $X_i$ in the ligand A on the donor atom $Y_j$ in the ligand L, and $X_i$(A) and $Y_j$(L) denote the number of the donor atoms $X_i$ in A and $Y_j$ in L, respectively. With L = noncharged amines such as bpy and phen, the second term involving formation constants of outer-sphere complexes is dropped. Then we have the simpler equation

$$\log K(\mathrm{CuL + A}) = \log K(\mathrm{CuA}) + \sum_{I<}^{I}\sum_{J}^{J} \delta_{ij} X_i(\mathrm{A}) Y_j(\mathrm{L}) \quad (2)$$

On the basis of the same consideration, we have the following for the formation constant of $CuA_2$:

$$\log K_2(\mathrm{CuA_2}) = \log K(\mathrm{CuA}) + \{\log K_{\mathrm{OS}}(\mathrm{CuA, A}) - \log K_{\mathrm{OS}}(\mathrm{Cu, A})\} + \sum_{I<}^{I}\sum_{J}^{J} \delta_{ij} X_i(\mathrm{A}) Y_j(\mathrm{A}) - \log 2 \quad (3)$$

where the term log 2 provides the statistical correction for the number of ways through which $CuA_2$ can dissociate.

We have the following interaction terms between the donor atoms of coordinated ligands (revised on the basis of the preferential coordination of carboxylate oxygen in A[24] instead of the previously postulated preferential coordination of the terminal nitrogen of aminocarboxylate:[20] $\delta_{\mathrm{N(CH)N(AL)}} = -0.36$, $\delta_{\mathrm{N(HC)O(AL)}} = +0.08$, $\delta_{\mathrm{N(AL)O(AL)}} = \delta_{\mathrm{O(AL)O(AL)}} = -0.10$, with N(CH), heterocyclic N; N(AL), aliphatic N; and O(AL), aliphatic carboxylate O.

At an ionic strength of 0.1 mole $dm^{-3}$ (=M), values of log $K_{\mathrm{OS}}$ are calculated as −0.1 for [$CuA^{+1}$, $A^{-1}$] and 0.3 for [$Cu^{2+}$, $A^{-1}$] at 25 °C and ionic strength of 0.1 M[35]. Then we have

$$\log K(\mathrm{Cu-phen + A})(\mathrm{calc}) = \log K(\mathrm{Cu-bpy + A})(\mathrm{calc}) = \log K_1(\mathrm{CuA})(\mathrm{obs}) - 0.56 \quad (4)$$

$$\log K_2(\mathrm{CuA_2})(\mathrm{calc}) = \log K_1(\mathrm{CuA})(\mathrm{obs}) - 1.33 \quad (5)$$

$$\log K(\mathrm{Cuen + A})(\mathrm{calc}) = \log K_1(\mathrm{CuA})(\mathrm{obs}) - 0.86 \quad (6)$$

These equations enable us to successfully calculate the stability constants of *regular complexes* with neither special enhancement of stability constant by noncovalent ligand−ligand interactions nor special diminution of stability constant by steric hindrance between coordinated ligands. Noncovalent ligand−ligand interaction includes the electrostatic interactions, the aromatic $\pi-\pi$ interactions,[1,3,4,8,12] and the hydrophobic interactions[13,25] of the coordinated ligands.

In the ternary complexes CuLA with L = phen or ′bpy and A = *para*-X-substituted phenylalaninates,[4] hydrophobic interactions and aromatic $\pi-\pi$ interactions are both anticipated to operate and the electrostatic interactions has already been involved in eq 1. In Table 1, stability constants log $K$(Cu + A), log $K$(CuL + A), and log $K_2$($CuA_2$) are collected.[4]

By the use of log $K$(Cu + A)(obs), values of log $K$(CuL + A) for L = bpy and phen are calculated. The difference of log $K$(CuL + A)(obs) − log $K$(CuL + A)(calc) is then given in Table 2. These values represent extrastabilization due to the aromatic $\pi-\pi$ interactions and/or hydrophobic interactions.

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(22) It is, of course, difficult to discriminate clearly between the $\pi-\pi$ interaction and the hydrophobic interaction, but the latter, especially nonspecific hydrophobic interaction, is defined as the tendency of hydrocarbons (or of *lipophilic* hydrocarbon-like groups in solutes) to form *intermolecular* aggregates or analogous intramolecular interactions in aqueous solution. The name arises from the attribution of the phenomenon to the apparent repulsion between water and hydrocarbons (Müller, P. *Pure Appl. Chem.* **1994**, *66*, 1077−1184). The hydrophobicity scale proposed by Nozaki and Tanford[23] is the transfer energy (solubility) of amino-acid side chains from water to ethanol or dioxane. The hydrophobic parameters calculated by using the effects of the substituents on the partition[24] for the side chains of *para*-X-substituted phenylalanines are also a nonspecific hydrophobicity scale, while aromatic $\pi-\pi$ interaction is a specific or enhanced hydrophobic interaction that mainly occurs with delocalized $\pi$ systems between stacked molecules.

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**Table 1.** Stability Constant of the Copper(II) Ternary Complexes CuLA with L = bpy or phen and A = *para*-X-Substituted L-Phenylalaninate

| | | log *K*(CuL + A)(obs) | | |
|---|---|---|---|---|
| A | log *K*(Cu + A)(obs) | L = phen | L = bpy | L = A |
| Ala | 8.330 | 7.881 | 8.016 | 6.940 |
| $NH_2$−Phe | 7.874 | 8.541 | 8.960 | 6.596 |
| $NO_2$−Phe | 7.421 | 7.754 | 7.915 | 6.241 |
| Tyr | 7.848 | 8.609 | 8.596 | 4.720 |
| Phe | 7.931 | 8.320 | 8.413 | 6.903 |
| F−Phe | 7.403 | 7.931 | 7.965 | 6.422 |
| Cl−Phe | 7.314 | 8.131 | 8.192 | 6.504 |
| Br−Phe | 7.340 | 8.252 | 8.324 | 6.558 |
| I−Phe | 7.623 | 8.642 | 8.616 | 7.362 |
| $I_2$−Tyr | 5.151 | 6.929 | 6.761 | 4.491 |

**Table 2.** Stability of Copper(II) Ternary Complexes CuLA with L = phen or bpy and A (A = *para*-X-Substituted L-Phenylalaninate) as Related with the Free Energy of the Transfer of Side Chains of Amino Acids ($\Delta G_t$/kJ mol$^{-1}$)

| | | log *K*(CuL + A)(obs) − log *K*(CuL + A)(cal) | | |
|---|---|---|---|---|
| A | $\Delta G_t$/kJ mol$^{-1}$ | L = phen | L = bpy | L = A |
| Ala | 2.1 | 0.111 | 0.246 | −0.06 |
| $NH_2$−Phe | 3.5 | 1.227 | 1.146 | 0.05 |
| $NO_2$−Phe | 8.9 | 0.893 | 1.054 | 0.20 |
| Tyr | 9.6 | 1.321 | 1.308 | 0.25 |
| Phe | 10.5 | 0.949 | 1.042 | 0.302 |
| F−Phe | 11.3 | 1.088 | 1.122 | 0.349 |
| Cl−Phe | 14.5 | 1.377 | 1.436 | 0.520 |
| Br−Phe | 15.4 | 1.472 | 1.544 | 0.548 |
| I−Phe | 16.8 | 1.579 | 1.553 | |
| $I_2$−Tyr | 22.4 | 2.372 | 2.304 | 0.67 |

On the other hand, Nozaki and Tanford have measured the free energy of the transfer of hydrophobic side chains of some amino acids and proposed to use the value as a measure of the hydrophobicity of amino-acid side chains.[23] Among the amino acids given in Table 1, they have given the values only for alanine, phenylalanine, and tyrosine.[23] Then, by using the effect of substituents on the partition,[24] we have calculated the free energy of the transfer of side chains of *para*-X-substituted phenylalanines, and the values are given in Table 2.

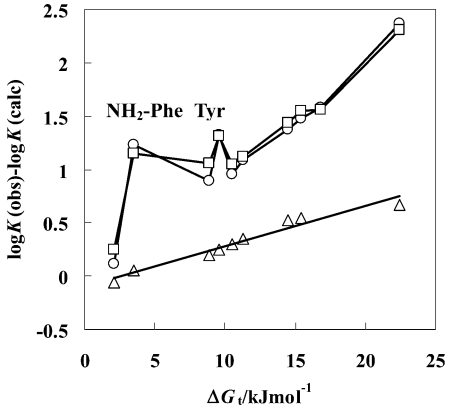


**Figure 1.** Stability constant of copper(II) ternary complexes CuLA with L = phen (○) or bpy (□) and A (Δ) = *para*-X-substituted phenylalaninates as a function of the free energy of the transfer of side chains of amino acids ($\Delta G$t/kJ mol$^{-1}$). Each point (left to right) refers to the amino acid reported in Table 2 in the order they are listed in the first column (top to bottom).

**Table 3.** Ratio (the Enhanced Stability of (CuLA)/(Free Energy of the Transfer of Side Chains of A) for *para*-X-Substituted Phenylalanines

| | A | | | | | |
|---|---|---|---|---|---|---|
| L | $NH_2$−Phe | $NO_2$−Phe | Tyr | Phe | F−Phe | Cl−Phe |
| phen | 0.351 | 0.100 | 0.138 | 0.0904 | 0.096 | 0.095 |
| bpy | 0.327 | 0.118 | 0.136 | 0.099 | 0.099 | 0.099 |

| | A | | |
|---|---|---|---|
| L | Br−Phe | I−Phe | $I_2$−Tyr |
| phen | 0.096 | 0.0934 | 0.106 |
| bpy | 0.100 | 0.0924 | 0.103 |

Now it appears interesting to see how the enhanced stability of these ternary copper(II) complexes is related to the free energy of the transfer of side chains of amino acids involved. The enhanced stability is plotted against the free energy of the transfer of side chains of amino acids in Figure 1.

From this figure, it is evident that the enhanced stability correlates with the free energy of the transfer of amino-acid side chains except for $NH_2$−Phe and Tyr with $[Cu(phen)]^{2+}$ or $[Cu(bpy)]^{2+}$. Then, the ratio (the enhanced stability)/(the free energy of the transfer of amino-acid side chain) for *para*-X-substituted phenylalanine (X−Phe) is calculated and given in Table 3, where alanine is omitted because it is not needed for determining the aromatic $\pi-\pi$ interactions on the enhanced stability constants of [Cu(phen)A] or [Cu(bpy)A].

It is evident from Table 3 that for CuLA with X−Phe for X = electron-donating substituents such as $NH_2$− or −OH, the ratio is higher than that for the other X−Phe groups, for which the enhanced stability is almost proportional to the free energy of the transfer of amino-acid side chain ($\Delta G_t$/kJ mol$^{-1}$). Then, it is reasonable to assume that

$$\text{enhanced stability} = a\Delta G_t + P \qquad (7)$$

(25) Rate constants of formation of copper(II) aminocarboxylate chelates and related complexes are as follows ($10^9$ $k$/M$^{-1}$ sec$^{-1}$ at 25 °C and ionic strength of 0.1 M): $NH_3$, 0.2;[26] acetate, 1.5;[27] glycinate, 4;[28] sarcosinate, 2.8;[29] α-alaninate, 1.3;[30] β-alaninate, 0.2;[30] leucinate, 1.6:[31] L-tyrosinate, 1.1;[32] L-prolinate, 2.5;[33] L-hydroxyprolinate, 0.74;[33] serine, 2.5;[34] valinate, 1.1;[35] bicinate, 0.95.[35] The values for five-member-ring chelates are about 1 order of magnitude higher than that of the ammine complex, whereas they are all similar to that of the acetate complex. Thus, it follows that the formation of these chelates should proceed by the dissociative interchange mechanism via the preferential coordination of the carboxylate O end instead of the N end of aminocarboxylates.[20] Then, the stability constant of chelates with aminocarboxylates should be calculated with revised $\delta$ terms. On the other hand, previously given $\delta$ terms[20] should be utilized if we postulate the preferential coordination of the N end of aminocarboxylates.[13]

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**Table 4.** Enhanced Stability Constant of the Copper(II) Ternary Complexes CuLA with L = phen or bpy′ and A = *para*-X-Substituted Phenylalaninates: log *K* (Free Energy/kJ mol$^{-1}$)

| | aromatic $\pi-\pi$ interaction | | hydrophobic interaction | |
|---|---|---|---|---|
| A | L = phen | L = bpy | L = phen | L = bpy |
| Ala | <0.1(<0.5) | <0.1(<0.5) | 0.2(1.1) | 0.2(1.1) |
| $NH_2$−Phe | 0.9(5.1) | 0.8(4.6) | 0.3(1.7) | 0.35(2.0) |
| $NO_2$−Phe | <0.1(0.5) | 0.2(1.1) | 0.85(4.6) | 0.9(5.1) |
| Tyr | 0.4(2.3) | 0.35(2.0) | 0.9(5.1) | 0.96(5.5) |
| Phe | <0.1(<0.5) | <0.1(<0.5) | 1.0(5.7) | 1.1(6.3) |
| F−Phe | <0.1(<0.5) | <0.1(<0.5) | 1.1(6.3) | 1.1(6.3) |
| Cl−Phe | <0.1(<0.5) | <0.1(<0.5) | 1.4(8.0) | 1.45(8.3) |
| Br−Phe | <0.1(<0.5) | <0.1(<0.5) | 1.5(8.5) | 1.55(8.8) |
| I−Phe | <0.1(<0.5) | <0.1(<0.5) | 1.6(9.1) | 1.7(9.7) |
| $I_2$−Tyr | 0.3(1.7) | 0.1(0.6) | 2.1(12) | 2.2(12.5) |

where *P* denotes the enhancement due to the aromatic $\pi-\pi$ interaction[22] and given by the deviation from the straight lines in Figure 1. The value of *P* is close to 0 for X = $-NO_2$, −H, −F, −Cl, −Br, and −I. From the above figures we obtain

$$a = 0.095 \text{ for L = phen and } a = 0.10 \text{ for L = bpy}$$

Then it is possible to discriminate between the aromatic $\pi-\pi$ interactions and the hydrophobic interactions as given in Table 4.

Crystal structures showing the aromatic stacking and the $\pi-\pi$ charge-transfer interactions of A with L have been reported for A = $NH_2$Phe and Tyr.[4] This is in accord with the results given in Table 4. The ternary complex with L = phen and A = Phe, however, showed two different crystal structures, one with aromatic stacking and the other without it.[4] In aqueous solution, the UV spectrum of the ternary complex shows a weak charge-transfer absorption, which disappears by the addition of acetonitrile. As given in Table 4, Cu(phen)(Phe) is stabilized by hydrophobic interaction *in solution*.

Finally, some words should be added for the figures given in Table 4. The electron-withdrawing substituent I makes the aromatic $\pi-\pi$ interaction lower with bpy or phen bound to the copper(II) atom. This is why the aromatic $\pi-\pi$ interaction for tyrosine is higher than that for $I_2$−Tyr. On the other hand, I substitution makes higher the free energy of the transfer of amino-acid side chain higher and then the stability enhancement by hydrophobic interaction for CuLA is higher for $I_2$−Tyr than for tyrosine, and it is higher for I−Phe than for phenylalanine as observed.[4,6]

**Acknowledgment.** We thank Dr. Osamu Yamauchi, Emeritus Professor of Nagoya University, for helpful discussions.

IC701261E