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Properties of the indole ring in metal complexes. A comparison with the phenol ring

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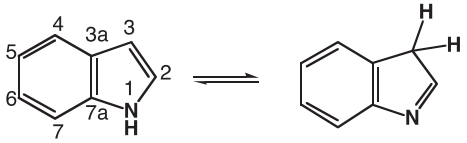
ABSTRACT

Tryptophan (Trp), an essential amino acid, has an indole ring with a high electron density and is frequently seen at the proximal position of the metal site in metalloproteins. For example, the indole ring of Trp has been reported to interact weakly with Cu(I) in a Cu chaperone CusF. Another aromatic amino acid, tyrosine (Tyr), has a phenol ring, which is an important metal binding site in various metalloproteins. Although the structures of the aromatic rings are different, they both have a weakly acidic moiety and perform some similar roles in biological systems, such as radical formation and electron transfer. In this review, we focus on these and other properties of the indole and phenol rings in metal-containing systems.

1. Introduction

The indole and phenol rings are important components of tryptophan (Trp) and tyrosine (Tyr), respectively. The pyrrole NH moiety of the indole ring is very weakly acidic with a pK_a value of 16.82 for Trp (25 °C) [1] and is known to form a hydrogen bond as seen for Trp191 of cytochrome *c* peroxidase [2]. On the other hand, the phenol group of Tyr is more acidic (pK_a = 10.14) [3] than the Trp indole and is well known as an important metal binding site in metalloproteins. In addition to the metal binding properties, the unique radical formation from the Cu(II)-bound phenolate moiety of a copper protein galactose oxidase (GO) [4,5] has prompted intense studies on the redox properties of the coordinated phenolate ligands [6–11].

Trp is the most hydrophobic amino acid providing a lipophilic environment [12] but was not known as a metal binding site in proteins until recently. Indole exists in the tautomeric forms, 1*H*- and 3*H*-indoles, shown below:



1*H*–indole 3*H*–indole

In 3*H*-indole the nitrogen atom (N(1)) is regarded as an imine nitrogen, and the carbon(3) (C(3)) atom becomes tetrahedral. While the pyrrole moiety of 1*H*-indole is known to give salts with alkali metal ions, an early work on bonding of the indole ring with transition metal ions was reported for the palladium(II) complexes of indole and 3-methylindole, the 3*H*-indole forms of which were reported to bind with a sulfur-bridged dinuclear Pd(II) complex through the nitrogen and deprotonated C(2) atoms to form another bridge [13]. The structures of metal–indole complexes were established by X-ray analysis for the first time for the Pd(II) complexes of 2-methylindole and 2,5-dimethylindole, both of which have a σ-bond between Pd(II) and the pyridine-like nitrogen of the 3*H*-indole tautomer [14]. The involvement of the C(3) atom of 3*H*-indole by deprotonation was revealed for an indole-N,C(3)-bridged dimeric Pd(II) complex of 3-indoleacetate [15]. There have since been reported various metal complexes of indole derivatives bound through the pyridine-like nitrogen atom and/or a carbon atom by cyclometalation [16], and the binding of Pd(II) and Pt(II) complexes with the peptidase activity (metallopeptidases) to the Trp indole moiety of peptides has also been reported [17].

Recently the Ru(II) and Ir(III) complexes of a ligand having a 2-(2′-pyridyl)indole partial structure, which was inspired by the natural product staurosporine, have been prepared by deprotonation from the pyrrole NH moiety [18]. The redox properties of the Trp residue in proteins have been reported for the radical formation in the catalytic cycle such as compound I of cytochrome *c* peroxidase [2,19] and for the electron transfer such as in azurin [20,21] and MauG/pre-methylamine dehydrogenase complex [22]. On the other hand, Cu(II) binding by

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the octarepeat domain of prion proteins has been studied in detail [23–26], and the observation that the Trp residue of the octarepeat unit may be necessary for the reduction of bound Cu(II) is currently attracting much attention [27–30].

In view of the above properties and similarities between the indole and phenol rings, we will review comparatively the metal binding abilities and reactivities of the indole and phenol rings incorporated into the side chain of chelating N- and N,O-donor ligands and discuss their biological relevance mainly on the basis of our studies.

2. Stacking interaction in ternary complexes containing an α-amino acid with the aromatic side chain residue

α-Amino acids coordinate to transition metal ions such as Cu(II) and Pd(II) as bidentate ligands through the amino and carboxylate groups, forming a five-membered N,O-chelate ring [31,32]. Their side chain may have an influence on the properties of the complexes. When the aromatic amino acids (AA), phenylalanine (Phe), Tyr, and Trp, in the mono-negative form are coordinated to metal(II)–aromatic dinitrogen ligand (DA) complexes to form ternary complexes M(AA)(DA) (M = Cu(II), Pd(II), etc.; AA = Phe, Tyr, or Trp; DA = 2,2′-bipyridine (bpy), 1,10-phenanthroline (phen), etc.; charges are omitted for clarity), their aromatic side chain may be involved in weak intramolecular interactions with DA and/or the coordination plane, thereby stabilizing the ternary complexes compared to similar complexes without such interactions [33–36]. In fact, already in the binary Cu(II) complexes of Phe and Trp, formation of the complexes $Cu(AA)_2$ from Cu(AA) is favored due to stacking as compared with that of the bis(alaninato) complex $Cu(Ala)_2$ from Cu(Ala) (Ala = alanine) [37]. Slightly higher redox potentials have been reported for the same complexes $Cu(AA)_2$ in comparison with those of $Cu(Ala)_2$ and $Cu(Gly)_2$ (Gly = glycine) and ascribed to various effects of the aromatic rings [38]. The interactions in M(AA)(DA) may not be simply assigned as the aromatic–aromatic stacking interaction but are considered to involve various forces such as van der Waals forces, electrostatic interactions, hydrophobic interactions, and interactions between the metal d-orbitals and the ligand π-system. However, we will describe the weak interactions in M(AA)(DA) as a stacking interaction hereafter.

The crystal structure analyses of the ternary complexes with DA and Trp etc. disclosed a stacking interaction or a close contact between the side chain aromatic ring and the coordination plane in the solid state as shown in Fig. 1[35,36,39–41]. The intramolecular stacking interaction in solution has been concluded from various lines of evidence, such as the stability enhancement ascribed to the interactions, circular dichroism (CD) spectral magnitude anomaly arising from increased asymmetry due to fixed conformation, the charge transfer band around 300–400 nm, and ^{1}H-NMR upfield shifts due to the ring current effect in the stacked structure as observed for Pd(II) complexes [33–36,39,42,43]. For example, the UV–vis absorption and CD spectra of the ternary complexes, $[Cu(L\text{-}mTrp)(en)]^+$ and $[Cu(L\text{-}mTrp)(bpy)]^+$ (Fig. 1(B)) (mTrp = 1-methyltryptophan; en = ethylenediamine), in water (Fig. 2) show that, while both $[Cu(L\text{-}mTrp)(en)]^+$ and $[Cu(L\text{-}mTrp)(bpy)]^+$ exhibit the d-d absorption band at 590–600 nm with a similar intensity, the CD magnitude of $[Cu(L\text{-}mTrp)(bpy)]^+$ in this region is much larger than that of $[Cu(L\text{-}mTrp)(en)]^+$. This is in line with the previous observations [35,36,43] that intramolecular stacking in ternary Cu(II) complexes causes anomaly of the magnitudes of the CD spectra in the d-d region due to the vicinal effect; for Cu(II)- and Ni(II)–oligopeptide complexes, the CD magnitudes are known to be an additive function of the magnitudes for the complexes of the component amino acids without an interacting side chain group [44], and this holds also for ternary Cu(II) complexes involving a simple amino acid [35].

The extent of the stacking interaction in the ternary complexes in solution depends on the side chain aromatic residues. We estimated the stability enhancement of Cu(AA)(DA) relative to Cu(Ala)(en) (en = ethylenediamine) due to the intramolecular stacking interaction from the stability constants according to the following hypothetical equation [35,43,45]:

$$Cu(Ala)(DA) + Cu(AA)(en) \overset{K}{\rightleftharpoons} Cu(AA)(DA) + Cu(Ala)(en) \quad (1)$$

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

where $\log \beta_{Cu(AA)(DA)}$ etc. denote the overall stability constants expressed in log units for respective complexes and stacking is possible only in Cu(AA)(DA). The log K value gives an estimate of the stability enhancement mainly due to aromatic ring stacking between DA and the side chain aromatic ring of AA. Table 1 shows the stability constants, $\log \beta_{Cu(AA)(DA)}$, and log K values for some selected ternary complexes. Because of the larger ring size and higher electron density, the stacking of the Trp indole ring with electron-deficient DA is more effective than that of the Tyr phenol and Phe benzene rings, the log K values for DA = bpy and phen being in the order Trp > Tyr > Phe. The stacking with coordinated histamine (hista) also stabilizes complexes Cu(AA)(hista), which suggests that imidazole–indole stacking may be possible at the protein metal site.

The order of the log K values of Cu(AA)(DA) is dependent on the substituents of the aromatic rings of both AA and DA [43]. For example, the ternary complexes containing diiodotyrosine with a 2,6-diiodophenol moiety show a higher stability than those of Trp, while the complexes containing Tyr with the deprotonated phenolate moiety ($TyrO^-$) exhibit a lower stability in comparison to the Tyr complexes. On the other hand, the complexes containing 5-hydroxytryptophan (hTrp) with a 5-hydroxyindole ring and those containing mTrp exhibit higher stabilities as compared with the Trp complexes; the log K value for the mTrp

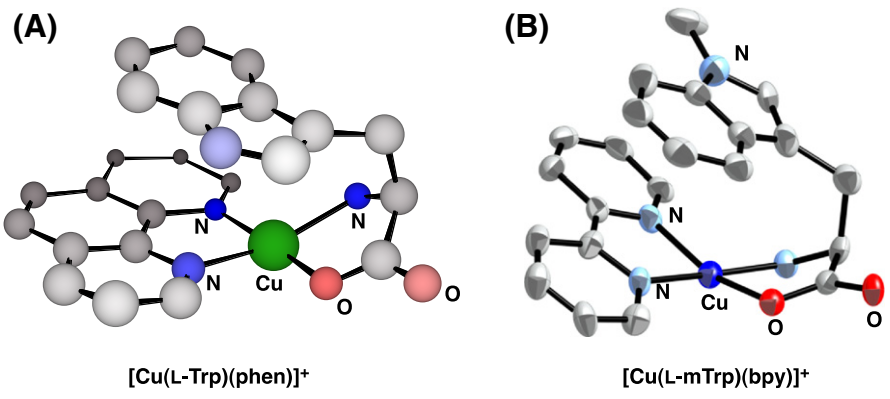

Fig. 1. X-ray structures of the ternary Cu(II) complexes of (A) L-Trp (ball and stick view) [34] and (B) L-mTrp (ORTEP view with 50% probability) [41].