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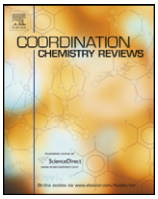

Review

Metal complexes involving indole rings: Structures and effects of metal–indole interactions

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ABSTRACT

Indole is an electron-rich aromatic compound with characteristic properties and is widely distributed in natural products and in proteins as the important constituent of essential amino acid tryptophan. It is known to form a hydrophobic environment in proteins and to be involved in enzymatic reactions. In addition to the redox activities and various weak interactions, it shows versatile metal binding abilities through the nitrogen and carbon atoms. This review focuses on the properties of the indole ring in and around the coordination sphere and the structures and bonding modes of Cu(I), Cu(II), Pd(II), and Pt(II) complexes of indole-containing ligands. Reactivities of indole-containing Cu(I) complexes with dioxygen, indole-radical formation by oxidation of Pd(II) and Pt(II) complexes, and the effects of the proximal indole ring on the reactivity of the Cu(I) center are also reviewed.

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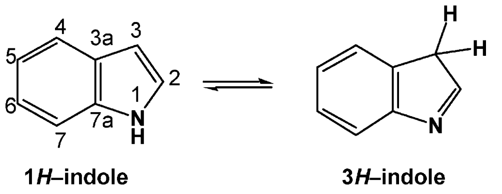
1. Introduction

Indole is an electron-rich aromatic compound with characteristic properties due to the presence of an electron-rich pyrrole moiety. It is widely distributed in biological systems as an important constituent of biomolecules and natural products such as an essential amino acid, tryptophan (Trp), and ergot alkaloids [1]. As a constituent of proteins, Trp has the highest hydrophobicity among the amino acids [2] and forms a hydrophobic environment, stabilizing the protein structure [3]. The indole ring of the Trp residue near the active site of metalloenzymes has been reported to be involved in the electron-transfer pathways as in cytochrome *c* peroxidase (C*c*P) [4]. The Trp residue near the active site of galactose oxidase (GO), which is a type II copper protein having an equatorially bound tyrosine phenolate oxygen, is stacked with this phenolate ring and is considered to stabilize the phenoxyl radical formed in the course of the catalytic cycle among other functions [5,6]. Thus, Trp residues in proteins not only provide a hydrophobic environment but also take part in enzymatic reactions, showing that the indole ring can be an active component of reactions. Until very recently no evidence was reported for its metal binding and related functions in biological systems, while it is well established for chemical systems that the indole ring exhibits its ability to coordinate to certain metal ions [7,8]. On the other hand, the indole ring of Trp in planar ternary Cu(II) complexes containing an aromatic diimine (DA) such as 1,10-phenanthroline (phen), M(DA)(Trp) (M = Cu(II)), undergoes intramolecular aromatic ring stacking with DA [7–10], and the Trp residue in some peptides is known to stack with nucleotides and intercalate into DNA base pairs through π–π interactions [11].

This review is intended to focus on the metal binding properties, structures, and reactivities of the indole ring as observed for the metal complexes with various ligands including 3N-, 2N1O-, and 2N-tripod-like ligands containing one or two proximal indole rings (Fig. 1). We will first overview the metal binding modes and weak interactions of indoles and then describe some properties of the indole ring in the metal coordination sphere mainly on the basis of our recent studies.

2. Metal binding properties and noncovalent interactions of the indole ring

The indole ring exists in two tautomeric forms, 1*H*- and 3*H*-indoles:



1*H*-Indole has a pyrrole NH moiety, which is very weakly acidic with the pK_a value of 16.82 for Trp (25 °C) [12] and is known to bind with alkali metal ions and Grignard reagents to form their salts by deprotonation [13,14]. In 3*H*-indole the nitrogen atom (N(1)) is regarded as an imine nitrogen, and the carbon(3) atom (C(3)) becomes an sp^3 carbon, so that the behavior of 3*H*-indole toward metal ions may be different from that of 1*H*-indole due to the coordinating ability of the imine nitrogen. Pd(II) binds with N(1) in the 3*H*-indole form, shifting the NH proton to C(3) to convert it to an sp^3 carbon [15]. The indole ring is capable of various noncovalent interactions with other molecules by hydrogen bonding through the NH moiety and by π–π stacking, cation–π interactions, etc., through the aromatic moiety.

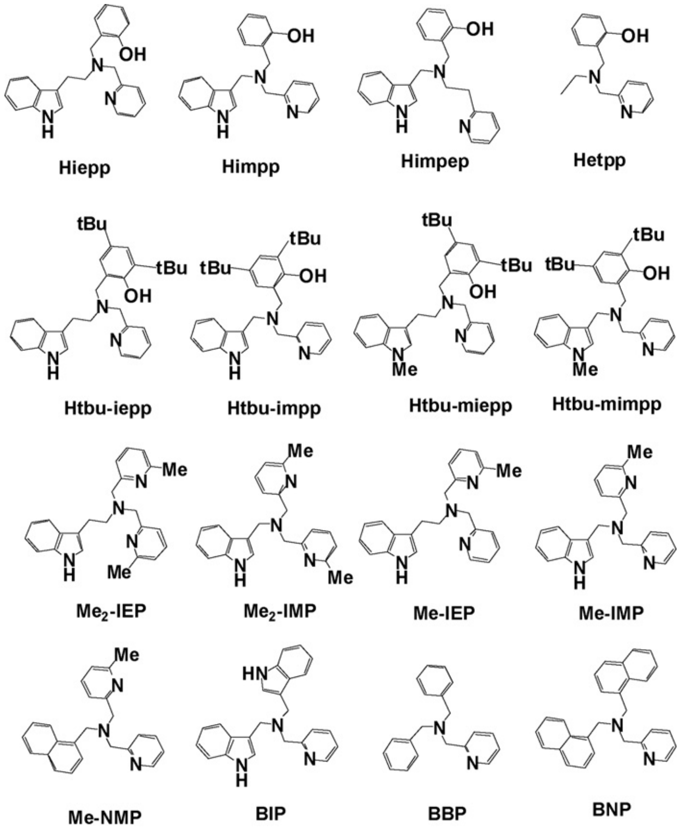


Fig. 1. Structures of ligands. H in Hiepp, etc., denotes a phenol proton which dissociates upon coordination.

2.1. Metal–indole σ-bonding

Indole and 3-methylindole were concluded by ^{1}H NMR spectra to form dimeric Pd(II) complexes by bridging two Pd(II) ions through the N(1) and C(2) atoms in the 3*H*-indole form [16]. Reactions of Na_2PdCl_4 with 2-methylindole (MI) and 2,5-dimethylindole (DMI) in methanol gave the corresponding complexes, $[Pd(MI)_2Cl_2]$ (**1**) and $[Pd(DMI)_2Cl_2]$, respectively, where Pd(II) binds with two indole rings through the N(1) atoms in a square-planar geometry with two chloride ions in a trans configuration (Fig. 2(A)) [15]. The C(2)–C(3) bond distances (1.52–1.57 Å) were close to the value for a single bond, and in line with this the ^{13}C NMR signal for C(3) (ca. 47 ppm vs. TMS) corresponded with the sp^3 carbon signal. Considering that Pd(II) has a high affinity for N donors, similar modes of binding may be expected for metal ions such as Pt(II). The indole ring attached close to the metal binding site may interact with the metal ion under suitable conditions. Thus, while Trp is an efficient glycine-like bidentate ligand and indole-3-acetate (IA) can normally bind with a metal ion by the carboxylate oxygen, the indole ring could also take part in metal binding. It is well known that Pd(II) undergoes cyclopalladation reactions to give a Pd–C bond. IA reacted with Na_2PdCl_4 in methanol to give a complex with the composition $Na[Pd(IAH_{-1})Cl]$ (IAH_{-1} = deprotonated IA), which was converted to $[Pd_2(IAH_{-1})_2(py)_2]$ (**2**) upon addition of pyridine (py) [17] (Fig. 2(B)). Complex **2** has a dimeric structure, where Pd(II) binds with the carboxylate oxygen and N(1) of a neighboring complex molecule in a square-planar geometry and further with C(3) by cyclopalladation to form a *spiro*-ring composed of the indole ring and the C,O-donor chelate ring, resulting in the N(1),C(3)-bridging of two Pd(II) ions [17]. This indicates that $Na[Pd(IAH_{-1})Cl]$ also has a dimeric structure with coordinated chloride ions in

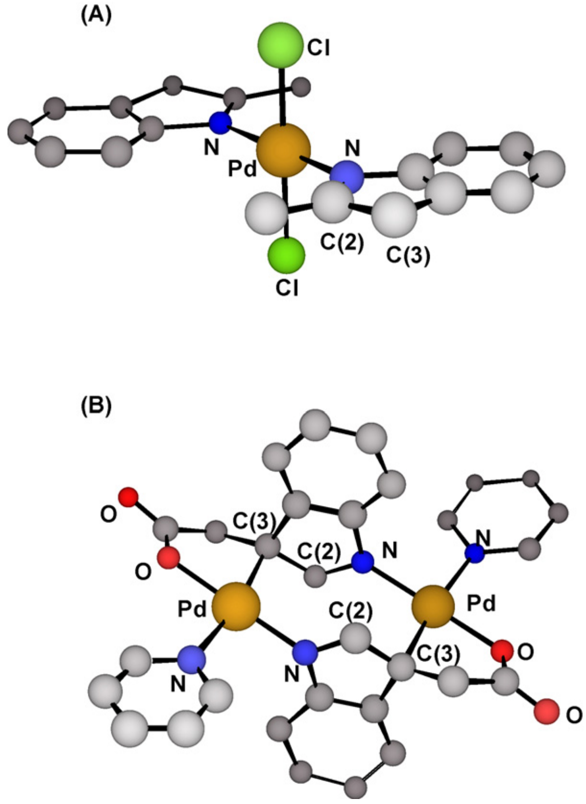


Fig. 2. Structures of indole-binding Pd(II) complexes: (A) $[Pd(MI)_2Cl_2]$ (**1**) [15]; (B) $[Pd_2(IAH_{-1})_2(py)_2]$ (**2**) [17].

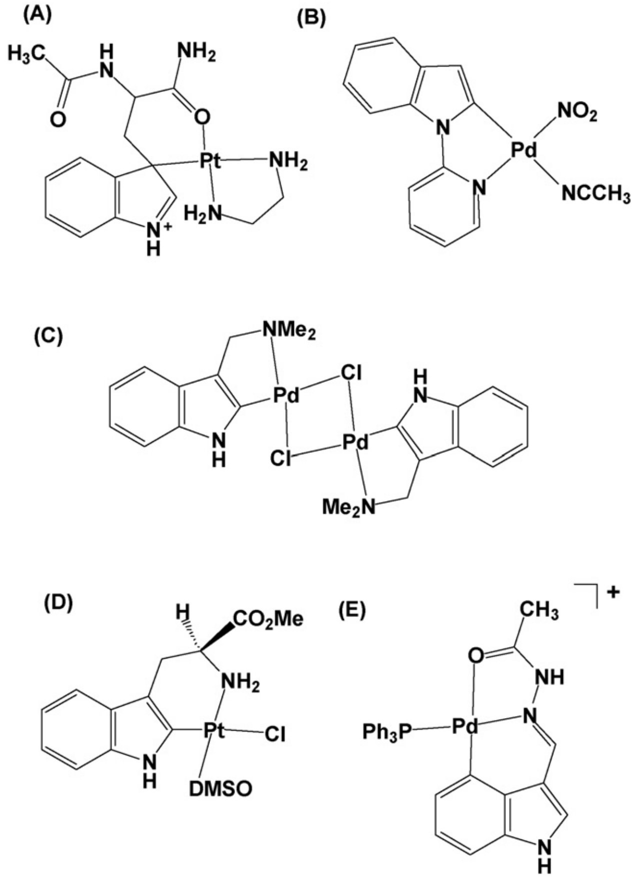


Fig. 3. Examples of indole-binding M(II) complexes (M = Pd, Pt): (A) complex **3** [20]; (B) complex **4** [22]; (C) complex **5** [24]; (D) complex **6** [26]; (E) complex **7** [28].

place of the py molecules in **2**. Kostić and co-workers studied the Pd(II) and Pt(II) complexes of indole-3-acetamide [18,19] and *N*-acetyltryptophanamide [20] and concluded by molecular mechanics simulations that the indole ring binds with the metal ions through the C(3) atom (**3**) and substantiated the conclusion by the NMR spectra (Fig. 3(A)). They developed Pd(II) and Pt(II) complexes as artificial peptidases, which recognize the indole moiety of the Trp residues in peptides by binding at the C(3) atom and specifically cleave the C-terminal amide or peptide bond [20,21]. Pd(II) was found to form a chelate ring as shown in **4** by binding with 1-(2′-pyridyl)indole and 1-(2′-pyrimidyl)indole at the side-chain N and the indole C(2) atom by cyclopalladation (Fig. 3(B)), and Rh(III) gave the octahedral complexes having the same chelate ring [22]. 1-Dimethylaminomethylindole [23] and 3-dimethylaminomethylindole (gramine) [24] react with Li_2PdCl_4 similarly at the side-chain N and C(2) atoms to form chloride-bridged dimers such as **5** (Fig. 3(C)) [24]. The halide-bridged dimeric Pd(II) complex of 1-(2′-pyridyl)indole reacted with monodentate nitrogen and phosphorus ligands to form a neutral, monomeric complex similar to **4**, which exhibited growth inhibitory activity against the mouse lymphoid leukemia cell line L1210 [25]. The Pt(II) complexes of gramine, tryptamine, and Trp methyl ester (**6**) were also formed by cyclometalation at C(2) (Fig. 3(D)) [26]. Pd(II) and Pt(II) bind with 2-(2′-pyridyl)indole at the indole N(1) and pyridine N atoms, and the M(II)–C(3) bond was formed when the indole ring had an N(1)-substituent [27]. Cyclometalation involving the C(4) atom of indole was revealed for the Pd(II) complex of a hydrazone of indole-3-carboxaldehyde (**7**) (Fig. 3(E)) [28], while its thiosemicarbazone was found to bind with Pd(II) through the side-chain N and S atoms without Pd(II)–indole binding [29]. Metal–indole binding is often implicated in the synthesis of indole derivatives catalyzed by palladium and other metal complexes; for example, Pd(II)-catalyzed C(2)- and C(3)-arylation of indoles [30–32] and C-arylation of 1*H*-indole and pyrrole by Rh(III) complexes [33] are considered to take place through metal–indole intermediates.

2.2. Stereochemistry and metal binding modes of the sp^3 C(3) atom

Pd(II) binding at N(1) causes the shift of the N(1) proton to C(3) to form 3*H*-indole [15]. Ligands with a metal binding substituent at C(3) may undergo cyclopalladation, as seen for **2**, and the metal binding at C(3) of 3*H*-indole gives rise to stereoisomers depending on the stereochemistry of the attack by the metal ion. Such isomers were isolated for the complex of IEP which is the condensation product of tryptamine with acetylacetone, $[Pd_2(IEPH_{-2})_2]$ (**8**) ($IEPH_{-2}$ = doubly deprotonated IEP), by silica gel column chromatography [34]. They were structurally characterized to be a *syn* form (**8a**) and an *anti* form (**8b**) as shown in Fig. 4. In both complexes the C(3) atoms of the two indole moieties are at the centers of the *spiro*-rings and have the same chirality in **8a** but are enantiomeric in **8b**, resulting in pseudo-C_2 and C_i symmetry, respectively. The molecular structures (Fig. 4) show that only the five-membered pyrrole moieties are involved in stacking in the *anti* isomer **8b**, and the C(2) proton of one pyrrole moiety is located close to the other, exhibiting a 0.56 ppm upfield shift of the NMR signal relative to the signal of the ligand due to the ring current effect. In the *syn* isomer **8a**, on the other hand, the two indole rings are juxtaposed to be in face-to-face stacking interaction, so that the C(5), C(6), and C(7) proton signals shifted upfield by 0.22–0.59 ppm while the C(2) proton signals shifted downfield by 1.04 ppm. These NMR spectral changes

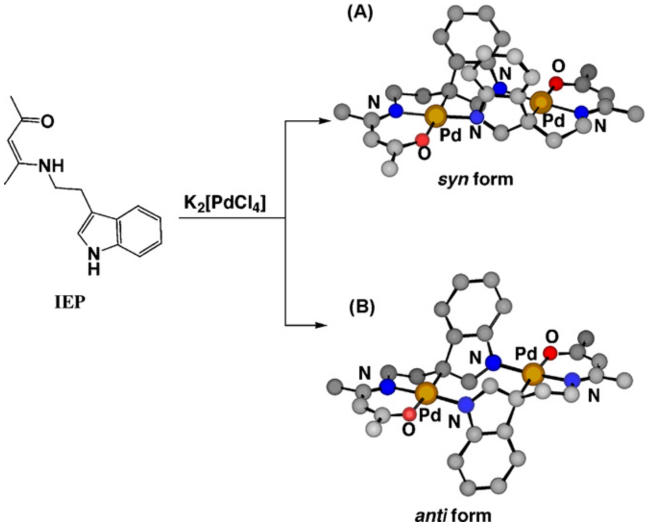


Fig. 4. Structures of ligand IEP and $[\mathrm{Pd(IEPH_{-2})}]_2$ (**8**): (A) *syn* form (**8a**); (B) *anti* form (**8b**) [34].

as well as the mass spectra showed that the indole-bridged dipalladium structures and the *syn* and *anti* forms of **8** are maintained in $CHCl_3$ [34]. A chiral ligand, IEU, derived from tryptamine and D-usnic acid from lichens (Fig. 5), which has β-diketone moieties comparable with acetylacetone and is widely known as a biomonitor of environmental pollution for its metal binding ability [35,36] as well as antibiotic activities [37,38], etc., also reacted with Pd(II) to give two isomeric complexes, $[\mathrm{Pd(IEUH_{-2})}]_2$ (**9**) ($\mathrm{IEUH_{-2}}$ = doubly deprotonated IEU), whose NMR spectral behavior was very similar to that of **8a** [34]. The isomers of **9**, which exhibited CD spectra with opposite signs, were concluded to be the enantiomers of the *syn* isomers as shown in Fig. 5(A) due to the presence of another asymmetric atom C(9b). Two diastereomeric complexes corresponding to the *anti* isomer, one of which is shown in Fig. 5(B), were not isolated but detected by the NMR spectra. These results clearly illustrate the stereochemistry of the metal binding at the tetrahedral C(3) atom of 3*H*-indole by deprotonation.

Pd–C(3) bonds of the 3*H*-indole complexes in **2**, **8a**, and **8b** (2.122–2.157 Å) [17,34] are longer than the Pd–C(2) bonds of cyclopalladated indoles (1.942–1.983 Å) [22,39]. The C(2)–C(3) bonds of C(3)-bound Pd(II) complexes of 3*H*-indole (1.426–1.448 Å) [34] are also longer than those of C(2)-bound Pd(II) complexes (1.362–1.379 Å) [22,39]. Pd–C(2) bond formation was observed also for the other Pd(II)–2N1O-donor ligand systems [40].

2.3. Weak interactions involving the indole ring

The side-chain groups of amino acid residues are involved in noncovalent or weak interactions, which are essential for the structures and functions of proteins [3,41,42]. The molecular environment of the metalloprotein active site and weak interactions with the surrounding groups may modulate the properties of the metal center. For example, the coordinated imidazole ring is hydrogen-bonded to a neighboring aspartic acid residue in CcP [4] and undergoes π–π stacking with a phenylalanine residue in plastocyanin from fern [43,44], and both interactions are considered to affect the redox potential of the metal center. The indole ring is known to undergo intra- and intermolecular π–π stacking and cation–π interactions [45–47], and its NH moiety may be involved in hydrogen bonding as seen for Trp191 in CcP [4].

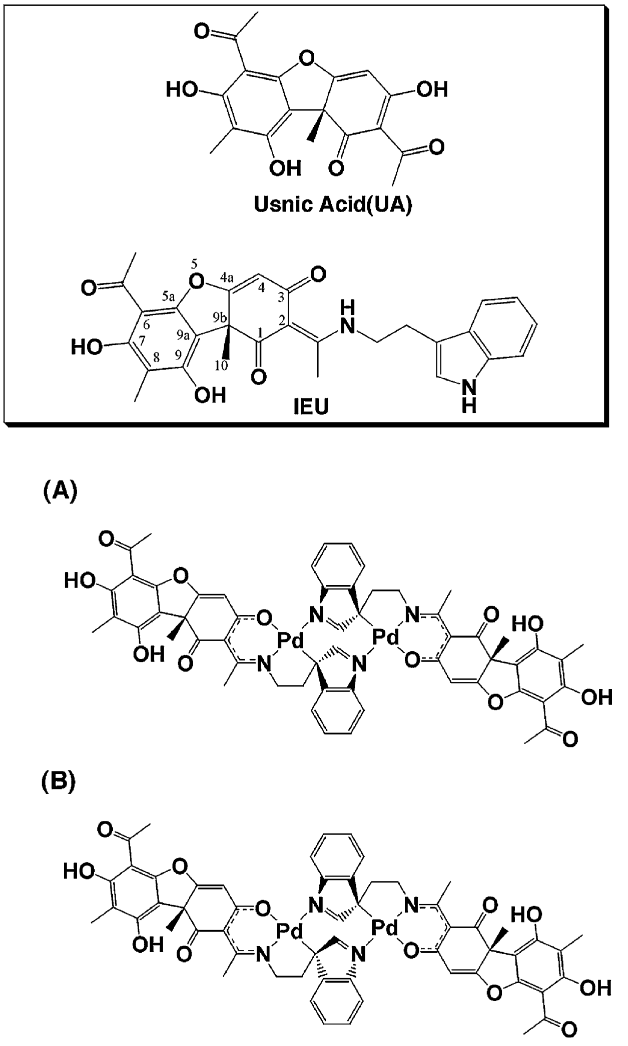


Fig. 5. Structures of D-usnic acid, IEU, and possible isomers of $[\mathrm{Pd(IEUH_{-2})}]_2$ (**9**) [34].

Intramolecular aromatic ring stacking interactions have been studied for ternary Cu(II), Pd(II), and other metal complexes involving aromatic diimine ligands (DA) and various aromatic amino acids (AA) [7,8,48]. For low-molecular-weight ternary Cu(II) complexes, Cu(DA)(AA), the effect of intramolecular stacking may be evaluated by various methods [48–51]. Evaluation of the stability enhancement by the log *K* values,[1] which become positive when complex species Cu(DA)(AA) such as Cu(phen)(Trp) is stabilized by stacking, was made for ternary systems with DA = phen, 2,2′-bipyridine (bpy), 2-pyridylmethylamine (ampy), and histamine (hista) and AA = Trp, 5-hydroxytryptophanate (Htrp), tyrosinate (Tyr), phenylalaninate (Phe), etc. [7,8,49,50,52]. The stability was found to depend on the sizes of DA and AA and the properties of the ring substituents; for

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[1] The stability enhancement due to stacking was evaluated by the following hypothetical equation (charges are omitted for simplicity) [49]:

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

where stacking is possible only in Cu(DA)(AA) while Cu(en)(Ala) (en = ethylenediamine; Ala = alaninate) without any interacting group serves as standard. The equilibrium constant log *K* given by Eq. (2) is considered as a measure of stability enhancement essentially due to stacking:

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

where log *β* refers to the overall stability constant of the complex species indicated by the suffix.

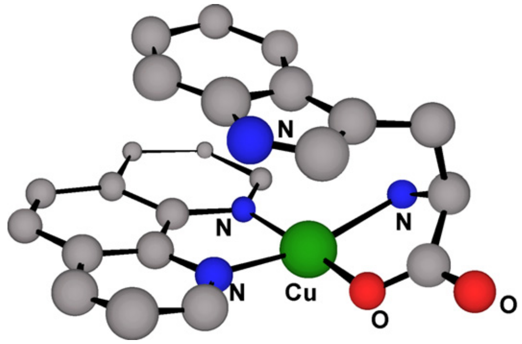
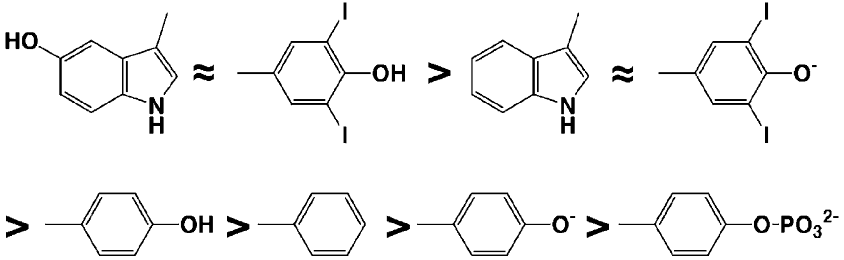


Fig. 6. Structure of $[Cu(phen)(Trp)]^+$ [9,52].

DA the order was phen > bpy > ampy ≈ hista. The highest stability enhancement due to AA was observed for Htrp and Trp both containing a side-chain indole, the order of aromatic rings being as follows:



The existence of intramolecular stacking has been substantiated by the X-ray analyses of $[Cu(phen)(Trp)]^+$ (Fig. 6) [9,53] and $[Cu(bpy)(Trp)]^+$ [10] and a number of other ternary Cu(II) complexes [7,8]. Aromatic ring stacking interaction in aqueous solution is considered to involve various forces such as van der Waals forces, electrostatic interactions, hydrophobic interactions, and interactions between π-electrons [54–58]. Studies on Cu(DA)(AA) with DA = 4,4′-disubstituted bpy and AA = *para*-substituted Phe revealed that the stabilization due to stacking becomes greater with the increase of the electron density difference between DA and the aromatic ring of AA [59]. The results indicate that the electron-rich indole ring stacks with electron-deficient DA more effectively, although electron-withdrawing *p*-halo and *p*-nitro substituents in the aromatic ring of Phe also caused stabilization [59,60].

In the absence of aromatic N-donor ligands, the aromatic side chain of AA in binary Cu(II) and Pd(II) complexes often occupies the space above the coordination plane with a metal–aromatic ring distance of ca. 3.0–3.3 Å, which is less than van der Waals distance, as seen from the structures of $Cu(Tyr)_2$ [61], $Pd(Tyr)_2$ [62], and Cu(Gly-Trp) (Gly-Trp = deprotonated glycyltryptophanate) [63]. Stacking between indole rings was concluded for $Cu(Trp)_2$ [64]. Martin pointed out that the $\log K_2/K_1$ values for binary Cu(II) complexes of aromatic amino acids are larger than those for the complexes of aliphatic amino acids [65] and determined from the ^1H NMR spectra the contribution to the stability by Pd(II)–aromatic ring contact, aromatic ring stacking, and other interactions in the Pd(Gly-Tyr) complex containing a monodentate amine [66]. Our preliminary DFT calculations indicated that in $[Cu(bpy)(Trp)]^+$ there are formed bonding orbitals between Cu^{2+} and the indole ring [67]. In line with the observation of the interaction between the Trp residue of peptides and nucleotides and DNA [11], 9-ethylguanine in $[Pt(dien)(9\text{-ethylguanine})]^{2+}$ (dien = diethylenetriamine) was shown to stack with Trp by fluorescence quenching experiments [68]. Ternary Pt(II) complexes containing A (=Phe, Trp, or Gly) and cyclometalated 2-(2′-thienyl)pyridine coordinated through the thienyl C(3′) and pyridine N atoms exhibited a high binding affinity depending on the side-chain group of A towards human serum albumin (HSA) with enhancement of photoluminescence and cytotoxicities against human carcinoma cell lines, which were in the order Phe > Trp > Gly and corresponded with the HSA binding affinity [69].

2.4. Conformations of the indole-containing side chains in complexes

As seen in the preceding section, the indole-containing side chain is often bent over the coordination plane to be involved in stacking with coordinated pyridine and other aromatic ligands or in the interaction with the metal center. Studies on the behavior of the pendent indole ring in the Pd(II) complexes of 2N1O-donor ligands involving a phenol, a pyridine, and a tertiary amine as metal binding sites [39,40] revealed that the indole ring stacks with the coordinated pyridine ring in preference to the phenolate ring probably due to a larger electron density difference between the indole and coordinated pyridine rings than between the indole and coordinated phenolate rings [39]. Indole-containing tripod-like ligands with two pyridine rings or one pyridine and one phenol ring formed square-planar complexes with Cu(II) and Pd(II) ions. $[Cu_2(impp)_2](ClO_4)_2$ (**10**) [70] and $[Cu_2(iepp)_2](ClO_4)_2$ (**11**) [71], which have the same structure except the side-chain conformation, are dinuclear Cu(II) complexes with each Cu(II) ion situated in a square-planar geometry formed by two bridging phenolate oxygens, a pyridine nitrogen, and a tertiary amine nitrogen (Fig. 7). Each side-chain indole ring of **10** is approximately parallel with the coordination plane to be involved in the intramolecular stacking with the coordinated pyridine ring and is simultaneously in close contact with the Cu(II) center with the shortest Cu(II)–carbon atom distance of 2.98 Å. In contrast to this, complex **11** has no intramolecular interaction with the indole ring. The difference in the side-chain conformation is probably ascribed to the length of the side chain connecting the indole and the tertiary amine nitrogen.

Correspondingly, [Pd(impp)Cl] (**12**) and [Pd(impep)Cl] (**13**) have a mononuclear square-planar structure with a coordination geometry similar to that of the Cu(II) complexes (Fig. 8) [39,70]. Complex **12** has a five-membered chelate ring involving the pyridylmethyl moiety, and the pyridine ring is almost co-planar with the coordination plane, while complex **13** has a six-membered chelate resulting from the pyridylethyl moiety, so that the pyridine ring is tilted from the coordination plane with the angle of 48.9°. The side-chain indole ring is located above the pyridine ring to be involved in the intramolecular π–π stacking in both **12** and **13**. The indole ring in these Pd(II) complexes is positioned above the pyridine ring, but the contact between the indole ring and Pd(II) was negligible in the crystal structure. On the other hand, the complex of tbu-iepp having a coordinated 2,4-di(*tert*-butyl)phenolate moiety in place of the phenolate moiety of iepp showed no intramolecular stacking with the indole ring (*vide infra*). From the structures of these Pd(II) complexes, the observed structural difference is considered to be a consequence of the steric requirements for the side-chain

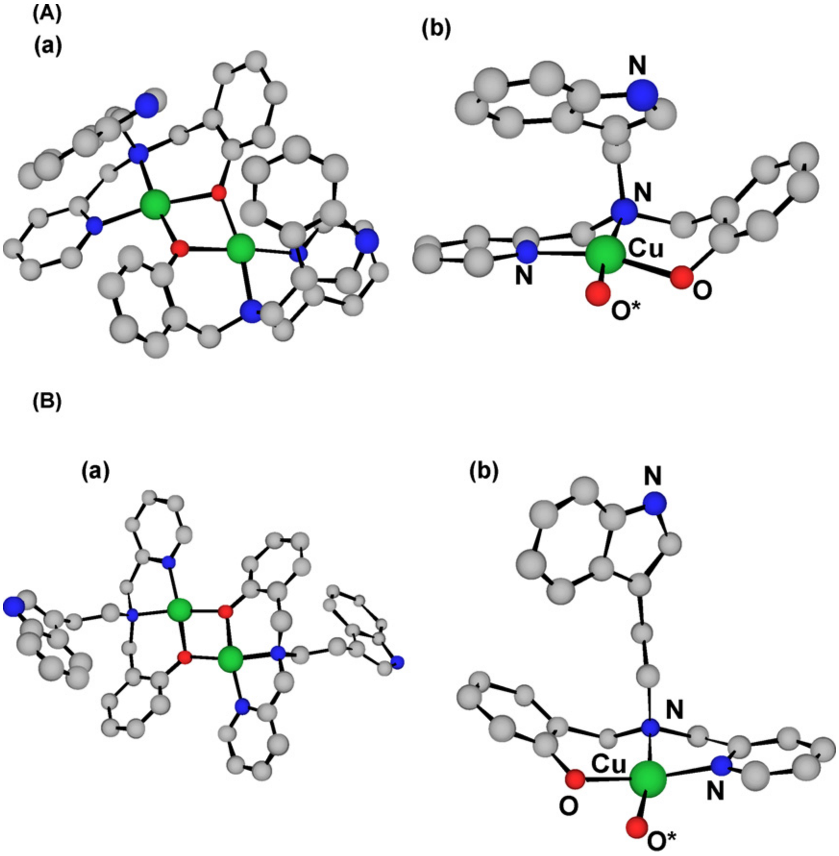


Fig. 7. Structures of (A) $[Cu_2(impp)_2](ClO_4)_2$ (**10**) [70] and (B) $[Cu_2(iepp)_2](ClO_4)_2$ (**11**) [71]: (a) Full view; (b) view of the complex unit.

indole ring to approach the pyridine ring, which is in agreement with the observation about the Cu(II) complexes.

The side-chain conformations in solution are best pursued by ^1H NMR for the Pd(II) complexes. The crystal structures and ^1H NMR spectra demonstrate that the Pd(II) complexes have nearly the same side-chain conformation in solution as in the solid state [39,40,70]. Most of the py protons for the impp and impep complexes having a pendent indole ring showed upfield shifts, reflecting the ring current effect [72] of the side-chain indole ring. The chemical shift differences, $\Delta\delta_{py} = -(\delta - \delta_{alkyl})$, where δ and δ_{alkyl} refer to the py proton chemical shifts for the indole-containing complexes **12** and **13** and for [Pd(etpp)Cl] with an ethyl group in place of the indole ring, respectively, clearly show that the py proton signals for the Pd(II) complexes are shifted upfield by as large as 0.5 ppm, which strongly supports that the pyridine ring is stacked with the indole ring in solution [70]. The largest upfield shift of the py proton signals in **12** was observed for py3 ($\Delta\delta_{py} = 0.67$ ppm) (Fig. 9(A)). This is consistent with the result of the X-ray crystal structure determination, which indicates that py3 is located above the pyrrole moiety of the indole ring with the distance of 3.49 Å, while the other protons are slightly displaced from the indole ring. Similarly the py protons in **13** showed upfield shifts, the largest shift being observed for py6 (Fig. 9(B)). The in4 signals of **12** and **13** (δ) shifted considerably downfield as compared with those for the ligands (δ_{ligand}) with $\Delta\delta_{indole} = \delta - \delta_{ligand} = 0.70$ and 0.64 ppm, respectively, indicating that they are deshielded by the Pd(II) ion.

The Cu(II) complexes also showed a similar tendency. While complex **11** lacking the indole–coordinated pyridine stacking in the solid state exhibited a normal X-band ESR spectrum which is similar to that of the Cu(II)–etpp system, complex **10** showing the intramolecular stacking in the solid state gave a spectrum with different $|A_{//}|$ values, which suggests a greater structural perturbation in **10** due to the close contact between the indole ring and the coordination plane [70].

It is remarkable that the pendent indole ring in the Cu(II) and Pd(II) complexes never approaches the coordinated phenolate moiety, which is present in the same coordination plane, both in the solid sate and in solution. This is most probably due to the higher electron density of the phenolate ring as compared with the pyridine ring. Coordination to a metal ion makes the pyridine ring more electron-deficient, strengthening the stacking with the indole ring [39,70].

3. Structures and reactivities of Cu(I) complexes containing indole rings

3.1. *Cu(I)–indole π-bonding*

In contrast to the indole-binding ability of Pd(II), Cu(II) does not give indole-binding complexes under the conditions used for the Pd(II) complexes, although the indole ring comes close above the Cu(II) coordination plane as a result of stacking with the coordinated pyridine ring. This may reflect the reactivity difference between Cu(II) and Pd(II), the latter of which performs cyclopalladation reactions with various aromatic rings. On the other hand, Cu(I) was revealed to react with a ligand having a pendent indole ring to form a Cu–indole η^2-bond [73]. Since Cu(I) complexes have been extensively studied for their reactivities with dioxygen [74–82], such a Cu(I)–indole π-bonding species is expected to show oxygenation and/or decomposition reactions with dioxygen. In this connection Itoh and co-workers reported d–π interactions in Cu(I) complexes and the reactivities of the complexes toward dioxygen [83,84].

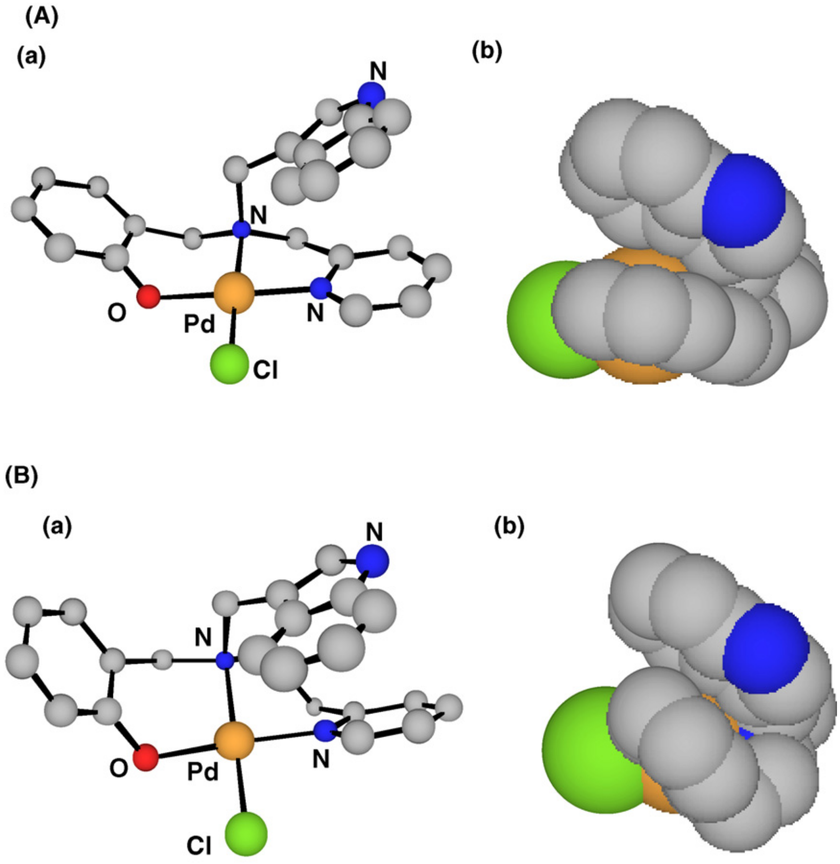


Fig. 8. Structures of (A) [Pd(impp)Cl] (**12**) and (B) [Pd(impep)Cl] (**13**) [39]: (a) full view and (b) side view shown in a space-filling model.

3.1.1. *Structures of Cu(I) complexes*

A tripodal ligand containing an indole ring in place of one of the pyridine rings, Me$_2$-IEP, reacted with Cu(I) to give [Cu(Me$_2$-IEP)]$^+$ (**14**), which was disclosed to have a structure with the Cu(I) ion binding with the C(2)–C(3) moiety of the indole ring through an η^2-type bond with the Cu–C distances of 2.228(5) and 2.270(5) Å (Fig. 10(A)) [73]. In this connection a Cu(I)–naphthyl ring π-bond was reported for a Cu(I)–macrocyclic NS$_2$-donor ligand complex [85,86]. The observed Cu(I)–indole interaction is very different from the Cu(II)–indole weak interaction and Pd(II)–C σ-bonds. The X-ray crystal structure analyses of **14** and [Cu(Me$_2$-IMP)(CH$_3$CN)]$^+$ (**15**) (Fig. 10(B)), both isolated as hexafluorophosphates **14·PF$_6$** and **15·PF$_6$**, respectively, showed that they have structures with different conformations of the indole side chain depending on the length of the 3-indolylalkyl chain [73]. The Cu(I) ion in **14·PF$_6$** has a distorted tetrahedral geometry with three nitrogen atoms and the π-bonded C(2)–C(3) moiety of the indole ring. On the other hand, the tetrahedral geometry around the Cu(I) ion of **15·PF$_6$** is formed by two pyridine nitrogen atoms, a tertiary nitrogen atom, and an acetonitrile nitrogen atom, and the side-chain indole ring is uncoordinated and not involved in stacking or Cu–aromatic ring interactions. The C(2)–C(3) bond length in **14·PF$_6$** (1.379(7) Å) is only slightly longer than that of the uncoordinated indole ring in **15·PF$_6$** (1.365(9) Å), which is in line with the observation that the C–C bond length of coordinated ethylene (1.329–1.360 Å) in several Cu(I)–alkene complexes [87–89] is virtually unchanged from that of free ethylene (1.337 Å) [90,91]. We see from the structures of **14** and **15** that the observed structural difference may be considered as a consequence of the steric requirements for the side-chain indole ring to approach the Cu(I) center and coordination by the solvent molecule.

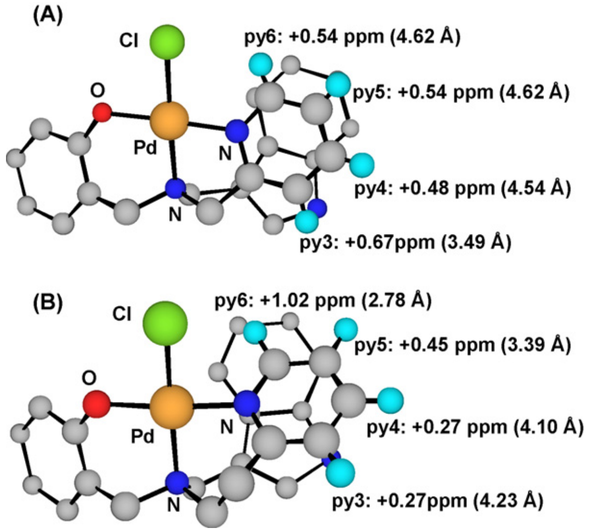


Fig. 9. Schematic views of the stacked structures of (A) complex **12** and (B) complex **13** with the ^{1}H NMR upfield shift values and the indole–pyridine proton distances [70].

Very recently a periplasmic protein, CusF, which is thought to serve as copper chaperone or regulator, has been revealed to bind Cu(I) by two methionine sulfur atoms, an imidazole nitrogen atom, and in addition the C(4)–C(5) moiety of the indole ring from a proximal Trp residue with the Cu(I)–C distances of 2.67 and 2.86 Å [92], which are longer than those observed between the Cu(I) and C(2)–C(3) bond in **14·PF$_6$**. The interaction was described as a

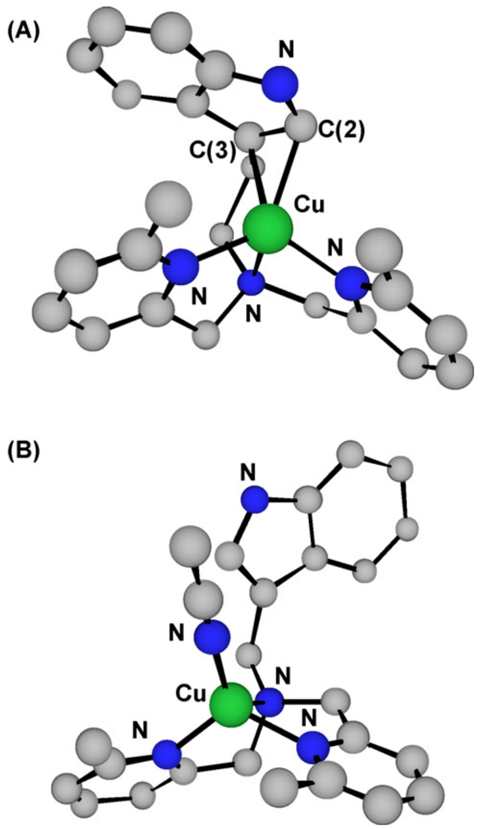
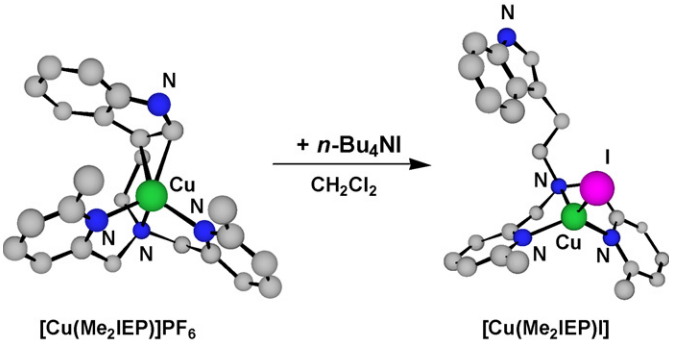


Fig. 10. Structures of (A) $[Cu(Me_2\text{-IEP})]^+$ (**14**) and (B) $[Cu(Me_2\text{-IMP})(CH_3CN)]^+$ (**15**) [73].

cation–π interaction because of the rather long Cu–C distances and lack of spectroscopic information, but it may be taken as an interaction lying somewhere in the continuum between an η^2-bond as seen for **14** and an electrostatic cation–π interaction [93]. This is the first observation of transition metal–indole interactions in biological systems.

3.1.2. *Characterization of Cu(I)–indole bonding*

The absorption spectrum of **14** in CH_2Cl_2 exhibited a characteristic band centered at 308 nm (ε = 18,000), which is assigned to the metal-to-ligand charge transfer (MLCT) [73]. The Cu(I)–Me-IEP system in CH_2Cl_2 also gave the MLCT band centered at 305 nm. This band disappeared when **14** was dissolved in CH_3CN, and the resulting spectrum was similar to that of **15** which has no Cu(I)–indole bonding. The MLCT band disappeared upon addition of one equivalent of iodide ion to **14·PF₆** in CH_2Cl_2, and a complex, **14·I**, was isolated (Scheme 1). These results indicate that the indole ring in **14·PF₆** is weakly bound to Cu(I) and easily replaced by exogenous ligands such as I^-. The difference between the ^1H NMR chemical shifts of the indole ring in **14·PF₆** and those in **14·I** was found to be rather small, which is in contrast with the finding that Cu(I)–coordinated styrene exhibited upfield shifts of 0.1–0.5 ppm as a result of π back donation [87–89]. On the other hand, while the spectrum of **14·I** in CD_2Cl_2 showed the signals of the bridging ethylene group ($-CH_2CH_2-$) at δ = 3.15 as a singlet, they were observed for **14·PF₆** as two separate triplets at δ = 3.03 and 3.17 ppm, which demonstrates that the two methylene groups of $-CH_2CH_2-$ in **14·PF₆** are not equivalent as a result of the coordination of the indole ring. ^1H NMR spectra of the Cu(I) complexes containing a naphthylmethyl, a benzyl, or an indolylmethyl side chain did not exhibit the splitting of the methylene proton signals in CH_2Cl_2, suggesting that the aromatic side chain in these complexes does not undergo noncovalent interactions with the Cu(I)–coordinated ligands in CH_2Cl_2.



Scheme 1. Reaction of complex $[Cu(Me_2\text{-IEP})]PF_6$ (**14·PF₆**) with iodide anion [73].

3.2. *Reactions of Cu(I) complexes with O_2*

Indoles are redox active compounds [94], and recent reports show that the Trp residue in the Cu(II) complex of the model peptide of the octarepeat region of prion proteins is hydrogen-bonded to the axially coordinated water molecule [95–99] and that it is essential for the reduction of Cu(II) to Cu(I) [100,101].

3.2.1. *Reaction intermediates*

The cyclic voltammograms of **14** and **15** recorded in CH_2Cl_2 gave a quasi-reversible redox wave with $E_{1/2}$ = 0.01 and −0.06 V (vs. Fc/Fc^+), respectively. The finding that **14** has a higher redox potential than that of **15** may be interpreted as a result of π back donation from the Cu(I) ion to the coordinated indole ring [73]. The reaction of **15** with O_2 in THF at −90 °C caused a color change from yellow to dark blue, giving an ESR-inactive species [71]. This species exhibited new absorption bands centered at 350 and 561 nm (Fig. 11; the 350-nm peak not shown), which are characteristic of a (μ-η^2:η^2-peroxo)dicopper(II) species [74,102–108]. Upon O_2-binding in THF at −90 °C the Cu(I)–Me-IMP system, which is an analog of the Cu(I)–Me_2-IMP system, gave absorption bands at 379 and 510 nm [109], which are assigned to the

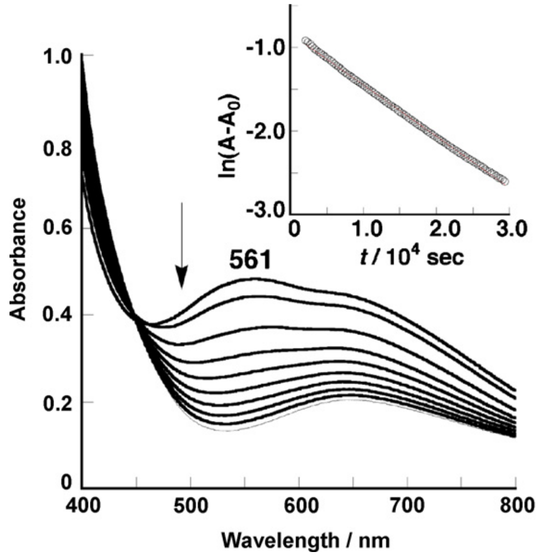


Fig. 11. Decay of the reaction intermediate of $[Cu(Me_2\text{-IMP})(CH_3CN)]^+$ (**15**) with O_2. *Inset*: Plot of $\ln(A_{561})$ vs. time.

bis(μ-oxo)dicopper(III) species by comparison with the system containing a pyridylmethyl side chain in place of an indolylmethyl moiety [105]. However, no intermediate was observed for the reaction of complex **14** with O_2 at temperatures below −80 °C. The decay constant, k_{obs}, of the O_2-adduct of **15** is $6.14 \times 10^{-5}\,s^{-1}$ at −40 °C in THF [71], which is longer than the values for the Cu(I)–pyphe complex containing a phenylethyl moiety (pyphe = *N*,*N*-bis[2-(2-pyridyl)ethyl]-2-phenylethylamine) [106–108]. Although the bis(μ-oxo)dicopper(III) species from the Cu(I)–Me-IMP system is relatively unstable with $k_{obs} = 1.5 \times 10^{-3}\,s^{-1}$ at −80 °C in THF, formation of this intermediate species could not be observed for the complexes of the same 3N-donor ligands containing a phenyl or a naphthyl moiety in place of the indole ring [109]. These observations indicate that the non-coordinating pendent indole ring stabilizes the (μ-η²:η²-peroxo)dicopper(II) and bis(μ-oxo)dicopper(III) intermediates.

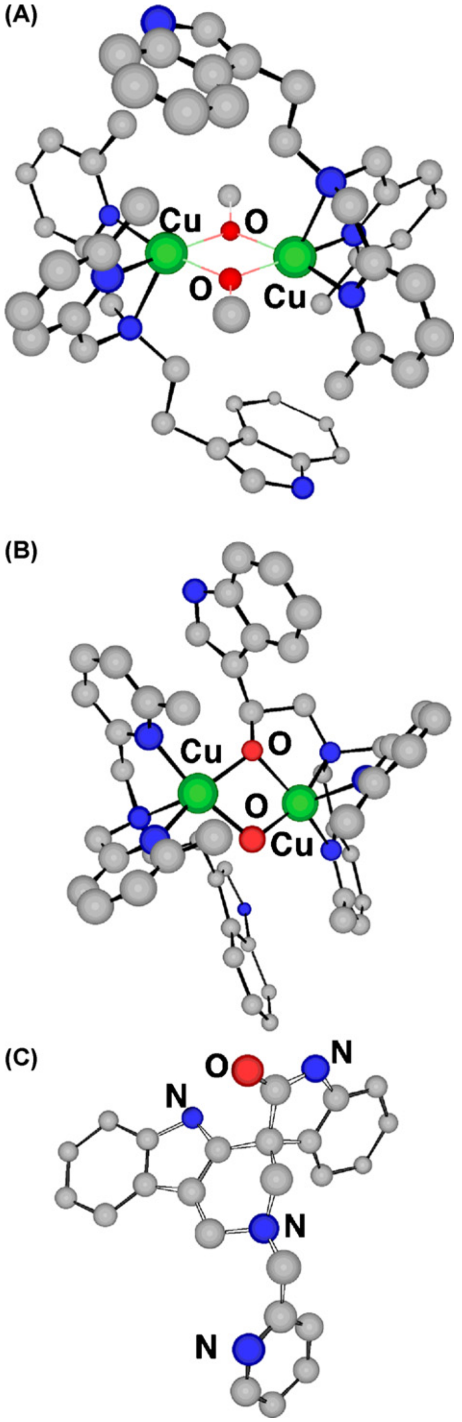
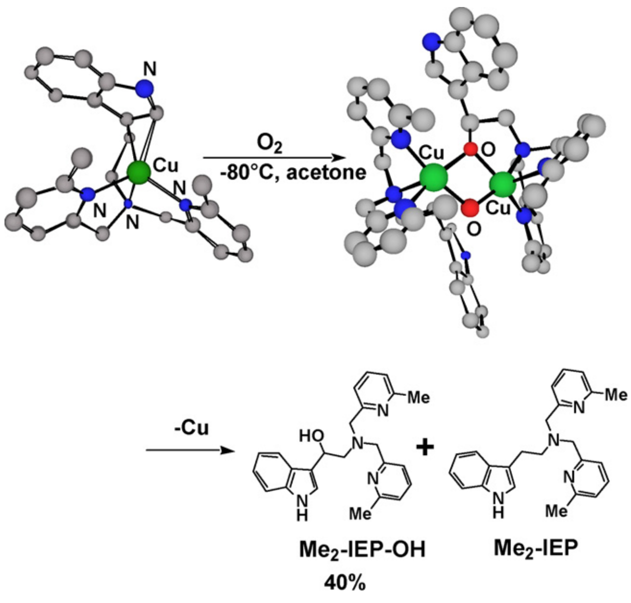


Fig. 12. Structures of the decay products of **15**–O_2 intermediate: (A) $[Cu_2(Me_2\text{-}IEP)_2(\mu\text{-}OMe)_2](ClO_4)_2$ (**16**); (B) $[Cu(Me_2\text{-}IEP)(\mu\text{-}Me_2\text{-}IEP\text{-}ox)(\mu\text{-}OH)_2](ClO_4)_2$ (**17**); (C) indole coupling species (**18**) [109].

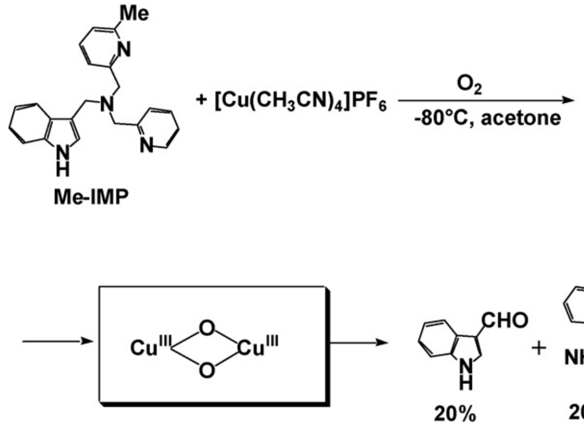
The reaction of **14** with O_2 led to ligand oxygenation (*vide infra*), whose the reaction intermediate is inferred to be a (μ-η²:η²-peroxo)dicopper(II) species, although it was not detected. The **14**–O_2 intermediate may have a structure similar to that of bis(μ-OCH_3)dicopper(II) species, $[Cu_2(Me_2\text{-}IEP)_2(\mu\text{-}OMe)_2](ClO_4)_2$ (**16**), without indole ring–copper ion interactions (Fig. 12(A)). Stabilization of the O_2 adduct of the complexes containing an indole moiety may suggest the presence of the indole–copper center interaction, which protects the intermediate species depending on the side-chain length of the alkyl group connecting the indole ring.

3.2.2. *Decay products*

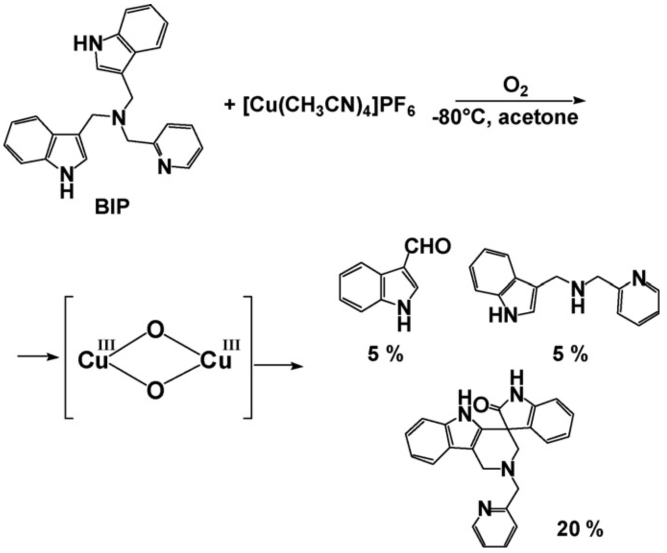
The reaction of complex **14** with O_2 in THF at low temperature gave a new complex, $[Cu(Me_2\text{-}IEP)(\mu\text{-}OH)_2](ClO_4)_2$ (**17**) with Me_2-IEP oxygenated at the β-carbon of the tryptamine moiety without decomposition of the indole ring (Fig. 12(B) and Scheme 2). The ligand oxygenation was not specific for a ligand containing an indole ring, since such reactions have been known for complexes involving a side-chain phenyl group [74,102–104]. Decomposition of the relatively stable (μ-η²:η²-peroxo)dicopper(II) and bis(μ-oxo)dicopper(III) species described above gave indole-3-carboxaldehyde and a secondary amine in same yields (20%), respectively (Scheme 3) [109]. On the other hand, the Cu(I)–BIP system containing two indole moieties reacted with O_2 in THF to give a unique bis(indolyl) species (**18**) in 20% yield, which probably resulted from intramolecular radical coupling between two indole rings (Fig. 12(C) and Scheme 4) [109]. A bis(μ-oxo)dicopper(III) species was detected as an intermediate in the course of the reaction, the C–C bond being formed between the C(2) position of one indole ring and the C(3) position of the other. Isolation of the indole coupling species **18** revealed that the indole rings were in close proximity to the bis(μ-oxo)dicopper(III) site which would abstract



Scheme 2. Reaction scheme of $[Cu(Me_2\text{-}IEP)]PF_6$ (**14·PF₆**) with O_2.



Scheme 3. Reaction scheme of Cu(I)–Me-IMP system with O_2 [109].



Scheme 4. Reaction scheme of Cu(I)–BIP system with O_2 [109].

a hydrogen atom from the proximal C–H bond, but in this case the C–H bond scission at the C(2) position of the proximal indole ring may have caused an indole radical formation, giving a *spiro*-ring composed of two indole rings [109]. Although one of the indole rings was oxidized to a ketone at the C(2) position, this oxygen atom was found to originate from the water molecule in aqueous ammonia solution by an isotope experiment. This position of indole was reported to be easily oxidized to a ketone under basic conditions by hydrolytic reactions [110].

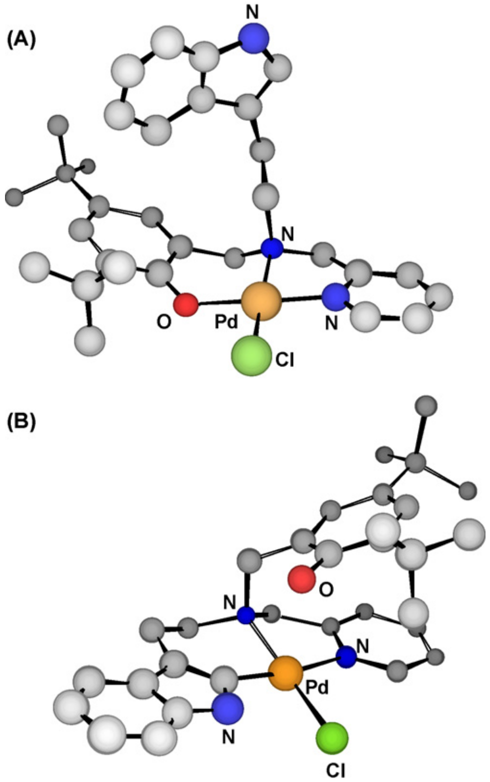


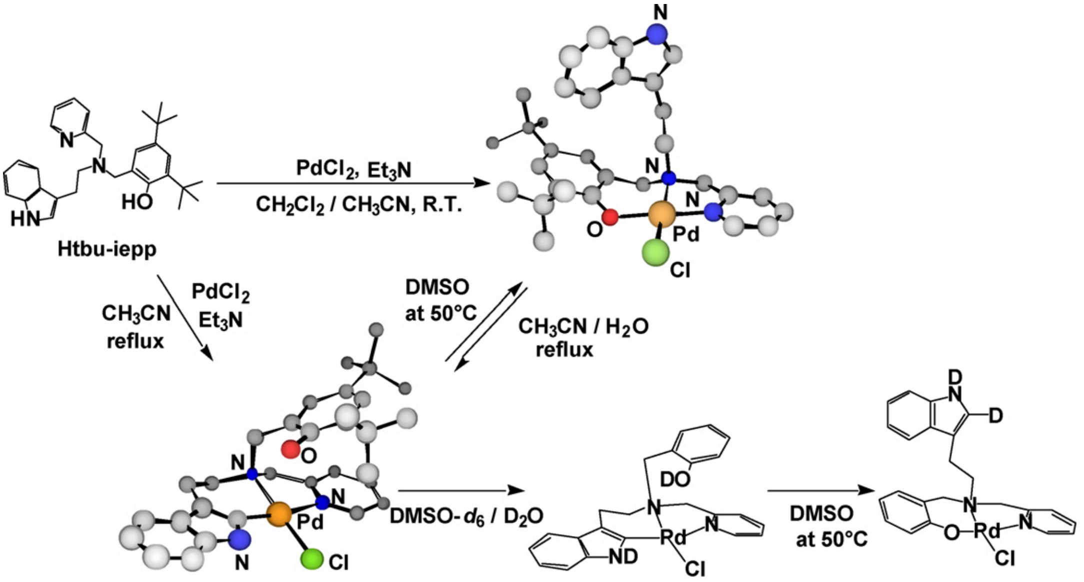
Fig. 13. Structures of (A) phenolate-binding complex [Pd(tbu-iepp-*O*)Cl] (**19**) and (B) indole-binding complex [Pd(tbu-iepp-*C*)Cl] (**20**) [39].

4. Reactivities of Pd(II) and Pt(II) complexes containing indole rings

4.1. Intramolecular phenol–indole ligand exchange reactions

4.1.1. Structures of indole-binding mononuclear Pd(II) and Pt(II) complexes

Reaction of $PdCl_2$ with Htbu-iepp and triethylamine in CH_2Cl_2/CH_3CN at room temperature gave a phenolate-binding orange complex, [Pd(tbu-iepp-*O*)Cl] (**19**), where the indolylethyl side chain assumes a stretched conformation and does not show the stacking interaction with the coordinated pyridine (Fig. 13(A)) [39] (see Section 2.4). However, when the reaction was carried out in CH_3CN at 80 °C or when the orange complex **19** was refluxed in CH_3CN for 12 h, [Pd(tbu-iepp-*C*)Cl] (**20**), which has the same molecular formula as that of **19**, was obtained as yellow crystals. Complex **20** was revealed to have a structure with Pd(II) bound in a square-planar geometry to two nitrogen atoms, a chloride anion, and the C(2) atom of the indole ring (Fig. 13(B)) [39,40]. As compared with **19**, **20** has a longer Pd–N(py) distance, which may be ascribed to the trans effect of the Pd–C(2) bond. The C(2)–C(3) bond length (1.379(3) Å) is the same as that of η^2-coordinated indole in Cu(I) complex **14**·$\mathbf{PF_6}$ (1.379(7) Å) [73] and that of the uncoordinated indole ring [27,40,70,73,109]. The Pd(II)–indole-C(2) bond (1.973(2) Å) in **20** is much shorter than that of the other metal–indole complexes [17,27,73] but is within the normal range reported for other cyclopalladated complexes [111–117]. The side-chain phenol ring of **20** is located above the pyridine ring and involved in intramolecular π–π stacking. On the other hand, [Pd(tbu-impp)Cl] was not converted to the indole-binding complex by refluxing in CH_3CN for 12 h, which indicates that formation of the indole-binding complex depends on the side-chain length [39]. A six-membered chelate ring may be favorable for this cyclopalladation, since the precursor phenolate complex also has a six-membered ring involving the aminomethylphenolate moiety. In this connection, reaction of K_2PtCl_4 with Htbu-iepp gave the indole-C(2)-binding Pt(II) complex, [Pt(tbu-iepp-*C*)Cl], as pale yellow crystals [118]. This complex has a structure very similar to that of **20** with the Pt–C(2) bond length of 1.981(3) Å, which is comparable with the Pd(II)–C(2) distances for the indole-binding Pd(II) complexes of the ligand series [39] and the Pt(II)–C(2) distances for the indole-binding Pt(II) complexes [27]. However, the corresponding Pt(II)-phenolate complex could not be isolated under the conditions employed for the Pd(II) complex **19** [118].



Scheme 5. Interconversion between [Pd(tbu-iepp)Cl] isomers **19** and **20** and indole ring deuteration (*tert*-butyl groups are omitted for clarity in the complexes) [39].

4.1.2. Spectral and mechanistic characterization of conversion between the phenolate- and indole-binding Pd(II) complexes

The absorption spectrum of **20** in DMF in the range 250–1000 nm exhibited a strong peak at 290 nm ($\varepsilon = 14{,}000$), whereas **19** exhibited peaks at 340 (sh, 4100) and 450 nm (sh, 940). The spectral feature of **19** is similar to that of [Pd(tbu-impp)Cl], which has bands at 340 (sh, 900) and 450 nm (3900) [39]. Lack of the 450-nm peak assigned to the phenolate-to-Pd(II) LMCT shows that **20** is not a phenolate complex.

Formation of **19** and interconversion between **19** and **20** are dependent on both the solvent and the temperature (Scheme 5). Conversion of **20-*d*$_{\text{phenol}}$** containing the deuterated phenol OH group to **19** at 50 °C in DMSO-d_6 resulted in >85% deuterium incorporation into the indole C(2) position of **19**, which was not attained by using non-deuterated **20** under the same conditions. On the other hand, the reaction of **19** in 2:1 (v/v) CD$_3$CN–D$_2$O gave non-deuterated **20**. These results indicate that the OH group of the phenol moiety takes part in the conversion between **19** and **20**. It is generally agreed that cyclopalladation reactions of aryl compounds proceed by an electrophilic substitution mechanism [119–121]. The rate-determining step in such processes is usually the C–H bond scission, which is regarded as an irreversible process. In the reversible cyclopalladation reactions of aromatic ligands, the kinetically controlled isomers are different from the thermodynamically controlled ones [122,123]. For the present complex formation, the phenolate complex **19** is kinetically controlled, while the cyclopalladated complex **20** is thermodynamically more stable. The energy gap ΔE between them was estimated to be 15 kJ/mol in DMSO from the van't Hoff plot of the ^{1}H NMR data [39], which is in contrast with the rather small enthalpy of formation of Pd(II)–C bonds in cyclopalladation reactions [119,121,124].

The interconversion between **19** and **20** was found to depend on the donor ability of the phenolate oxygen in the complexes [40]. The plot of the activation energy E vs. pK_a value of the ligand OH group [125,126] clearly indicated that the energy barrier of the conversion is correlated with the oxygen donor ability and hence with the Pd(II)–O bond strength, the order being MeO-phenolate > NO$_2$-phenolate > COO$^-$ (Fig. 14). These conversion properties appear to be peculiar to Pd(II) complexes, since [Pt(tbu-iepp-*C*)Cl] showed no conversion from the indole-C(2)-binding Pt(II) complex to the Pt(II)–phenolate species under the conditions employed for the Pd(II) complexes [118]. The difference in behavior in solution may be in line with the general properties of the Pd(II) and Pt(II) complexes in ligand exchange reactions [127].

4.2. Pd(II)–indole-π-cation and Pt(II)–indole-π-cation radical complexes

The cyclic voltammogram of **19** gave two irreversible oxidation peaks at 0.97 and 1.08 V (vs. Ag/AgCl), which are assigned to the oxidation of the Pd(II)-bound phenolate moiety and the indole ring, respectively [39]. On the other hand, the oxidation peaks of **20** at 0.68 and 0.80 V are assigned to the coordinated indole ring and the free phenol ring, respectively, because the latter peak agrees well with that of a weakly coordinated phenol ring in a Cu(II) complex [128]. Formation of indolyl radicals is known in the catalytic cycle

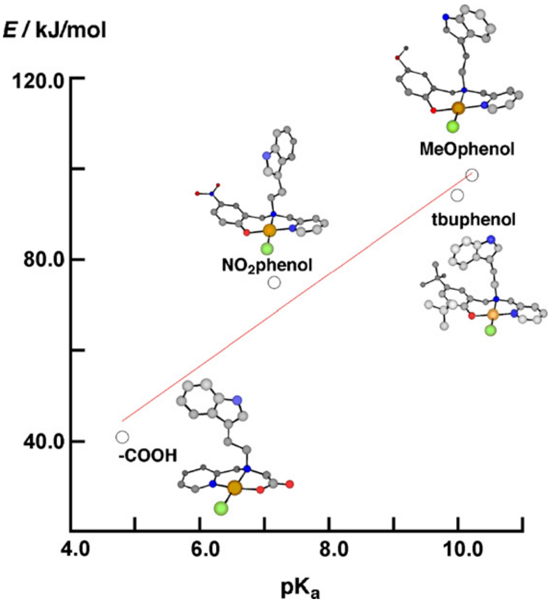


Fig. 14. Activation energies as a function of the pK_a values of the ligand OH groups [40].

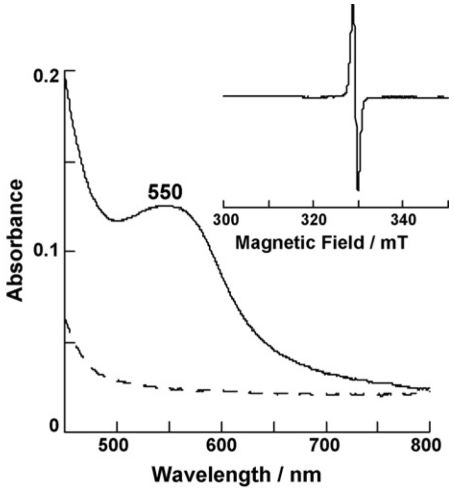


Fig. 15. Absorption and ESR spectra of one-electron oxidized [Pd(tbu-iepp-*C*)Cl] (**20**): Dotted line, **20**; solid line, one-electron oxidized **20**. *Inset*: ESR spectrum of one-electron oxidized **20** [39].

of CcP and other biological systems [129]. In chemical systems, they were generated by pulse radiolysis; the indole radicals from tryptophan and *N*-methylindole were reported to give an absorption band at 510–560 nm, where the π-cation radical and the neutral radical have a band centered at 560 and 510 nm, respectively [129–131]. Oxidation of **20** by one equivalent of Ce(IV) in DMF at −60 °C caused a color change from yellow to green, giving a new peak at 550 nm in the absorption spectrum (Fig. 15) and a new sharp signal at $g = 2.00$ in the ESR spectrum, where the amount of unpaired electron was calculated to be more than 0.90 from the integrated spectrum (Fig. 15, inset) [39]. From the spectral properties, the oxidized species was concluded to be the indole-π-cation radical complex of Pd(II), whose unpaired electron was considered to be localized in the indole ring [39], and the oxidized species of indole-C(2)-binding Pt(II) complex, [Pt(tbu-iepp-*C*)Cl] showing very similar spectral properties, was also assigned as a Pt(II)–indole-π-cation radical species [118]. The stability of the phenoxyl radical–metal complexes is dependent on phenol ring substituents, the di(*tert*-butyl)phenoxyl radical species being expected to have a longer half-life than that for the phenoxyl radical without protecting groups [132]. While the half-life, $t_{1/2}$, of oxidized **20** was calculated to be 20 s ($k_{obs} = 3.5 \times 10^{-2}\ s^{-1}$), the Pt(II)–indole-π-cation radical species was slightly more stable than that of **20** with the $t_{1/2}$ value estimated to be 43 s ($k_{obs} = 1.6 \times 10^{-2}\ s^{-1}$) [118], which is probably due to the inertness of Pt(II) in ligand exchange [127]. The relatively short half-life indicates that the Pd(II)–indole-π-cation and Pt(II)–indole-π-cation radical species are less stable than the metal–phenoxyl and other metal–organic radical species [128,133–135].

5. Conclusion

The indole-containing essential amino acid, Trp, has unique properties, serving as a hydrophobic residue in proteins, an electron-transfer pathway, and a possible Cu(II) reductant in the Cu(II)-bound octarepeat region of the prion protein. The indole ring shows a versatile metal binding ability by the σ-bond with the nitrogen and carbon atoms and the η^2-bond with the C(2) = C(3) bond. The Pd(II) complex of a ligand with a pendent indole ring, impp, was revealed to have a square-planar coordination structure, where the indole ring is stacked with the coordinated pyridine ring but is not in close contact with the Pd(II) ion. On the other hand, the molecular structure of the Cu(II) complex of the same ligand indicated that the indole ring is close not only to the pyridine ring but also to the Cu(II) center. These structures also demonstrated that the indole ring stacks preferentially with the coordinated pyridine ring and not with the coordinated phenolate moiety. The metal-bound indole ring is relatively easily displaced by other ligands; an acetonitrile molecule replaced the η^2-bonded indole in a Cu(I) complex upon dissolution in acetonitrile, and a Pd(II) complex having both a phenol and an indole ring showed the interconversion between the phenolate- and indole-binding species.

A point of interest in this review is that the close contact of the indole moiety with the metal center stabilizes the (μ-η^2:η^2-peroxo)dicopper(II) and bis(μ-oxo)dicopper(III) intermediate species. The reaction of a Cu(I) complex having two indole moieties with O_2 gave an unsymmetrical indole–indole coupling species *via* indole C–H activation, which may support that both indoles could have been in close proximity to the reaction center. In this connection, the Trp indole ring is often seen to occupy a position neighboring the active site of metalloenzymes such as GO, which is probably necessary for subtle control of their activity [6]. These observations may indicate a molecular environmental effect of the indole ring, which could be described as an "aromatic field effect." Although the indole radical formation has not been detected in Cu–indole systems, oxidation of the indole-binding Pd(II) complex gave a relatively stable indole-π-cation radical species.

Indoles often form cyclometalated compounds such as palladacycles which are important in organic and organometallic syntheses and homogeneous catalysis [136–139], for which the behavior of metal–indole complexes as seen in this review may provide useful information. Although the information on the metal–indole complexes is still limited, versatile metal binding properties as well as the redox activities of the indole ring suggest that it is a useful reactant in organic synthesis and that the tryptophyl residue can be a functional unit at or near the metal sites in biological systems. It should be mentioned in this connection that the recent finding on the unique Cu(I)–indole interaction in copper protein CusF [92] points to very interesting possibilities of transition metal–indole interactions and their functions in biological systems.

Acknowledgments

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