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Noncovalent interactions in biocomplexes

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1 Introduction

Noncovalent interactions perform essential roles in biological systems such as molecular recognition, protein stabilisation, and specificity and efficiency of enzymatic reactions [1–4]. They are formed and cleaved instantaneously and are dependent on such factors as the properties of the interacting groups or atoms, the distances between them, and the media in which they are present. The interactions, which are often called weak interactions, are also important for metal complex systems involving nucleotides and DNA [5, 6] and supramolecular architecture [7, 8].

Essential transition metal ions such as copper and zinc are bound to proteins mainly by the side chain groups of the amino acid residues such as the histidine (His) imidazole, cysteine (Cys) thiol, and tyrosine (Tyr) phenol moieties. The ligands forming the metal site may be in contact with the amino acid residues forming the molecular environment through weak interactions, and therefore the metal centre is under conditions which are different from bulk water. Such interactions protect the metal centre from the attack of solvent molecules and have subtle effects on the properties of the metal ion. The function of metalloproteins therefore depends on the active site structure and the noncovalent interactions with the molecular environment. As seen in cytochrome *c* peroxidase [9, 10] and type 1 copper sites [11], interactions between the coordinating groups such as the imidazole and thiolate moieties and the protein side chain groups surrounding the metal site can influence the structure and electron density and thus the reactivity of the metal centre.

However, various metal ions and complexes are known to be enzyme inhibitors [12], and new steps toward metallodrugs [13–16] and functional complexes considering the second coordination sphere [17] have been made, which indicate that noncovalent interactions and structural fitness are important for the activity.

DNA is well known as the target of the anticancer drugs such as cisplatin and its analogues and metallointercalators, the latter of which bind with DNA by noncovalent interactions, especially aromatic ring stacking and electrostatic interactions. Studies have been carried out for developing effective and specific metallointercalators and metallo-insertors and clarifying their binding modes [5, 18]. Zinc finger proteins are a class of proteins that bind with Zn(II) to form finger structures with basic, polar, and aromatic amino acids such as arginine (Arg) and His at the finger domains, whose noncovalent interactions with DNA have attracted much attention [19, 20].

In view of the importance of noncovalent interactions in biological systems, this chapter is intended to give a perspective of noncovalent interactions in and around the metal centre and their relevance to the metal site of proteins, focusing on ligand− ligand interactions in metal−amino acid and related complexes and interactions involving metal complexes and proteins.

2 Noncovalent interactions in metal complexes

In the past 50 years there has been growing interest in noncovalent interactions in metal complexes of biological ligands. This section will give an overview of the backgrounds and basic findings related to metal−ligand systems.

2.1 Some historical backgrounds

An early indication of intramolecular ligand–ligand interactions was provided by the solution studies on ternary (mixed ligand) complexes of Cu(II) etc. Preferential formation of ternary complexes depending on

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certain combinations of ligands has been shown by Sigel and his collaborators by evaluation of the stability enhancement relative to the complexes without such a ligand set [21–23]. Studies have been reported for the intramolecular ligand−ligand stacking interactions in ternary Cu(II) complexes with aromatic diimines (DA) and nucleotides such as Adenosine 5′-monophosphate (AMP) [22, 24–26], and complexes containing amino acids with aromatic, aliphatic, charged, or polar side chains capable of various interactions have been studied [27–29].

Metal transport in biological systems has been an important and interesting subject from the view point of bioinorganic chemistry. Most of the Cu ions (ca. 95 %) in blood serum are bound to ceruloplasmin and are not exchangeable, and the rest are present mainly as Cu(II)−serum albumin and to a smaller extent as mixed amino acid complexes containing His, both of which are considered to be involved in copper transport [30, 31]. A ternary complex containing His and threonine (Thr), Cu(His)(Thr), was detected in human blood serum [32], while the tracer studies using ^{64}Cu showed that the amino acids Thr, glutamine (Gln), and asparagine (Asn) effectively formed ternary complexes with His, Cu(His)(L) (L = Thr, Gln, and Asn) [33]. The structure of Cu(His)(Thr) was established by X-ray analysis to have His bound to Cu(II) through the amine and imidazole nitrogens with the carboxylate oxygen at an axial position [34]. Later the structure of Cu(His)(Asn) (Figure 1(a)) was revealed to have the same coordination structure as that of Cu(His)(Thr) [35].

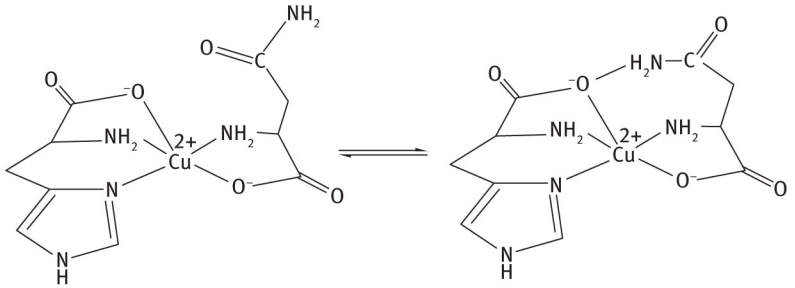

Figure 1: Structures of Cu(His)(Asn) (a) and its possible conformational isomer with ligand−ligand interaction (b) [35, 37].

Preferential formation of certain ternary amino acid Cu(II) complexes was also indicated by computer simulation of Cu(II)-amino acid systems in solution. Some discrepancies between the tracer experiment and computer simulation regarding the preferred formation of the above mentioned mixed amino acid complexes have been carefully reinvestigated, and the conclusions from both approaches are now in satisfactory agreement [36].

Since the side chains of all the above amino acids L have a polar group, the structure of Cu(His)(Asn) suggested the possibility of hydrogen bonding between the axially coordinated His carboxylate oxygen and the amide group of Asn. They are located on the same side of the coordination plane, and the amide NH_2 moiety may then approach the coordinated oxygen atom by rotation around the C_β-C_{amide} bond and a slight deformation of the chelate ring (Figure 1(b)) [37]. The situation is considered to be similar for Thr and Gln in place of Asn, and formation of His-containing ternary Cu(II) complexes in blood plasma as shown by tracer studies and isolation of Cu(His) (Thr) may be due to such intramolecular hydrogen bonding.

The structures of metalloenzymes were first reported for a zinc-containing enzyme carboxypeptidase A (CPA) and its complex with a substrate model peptide glycyltyrosine (GlyTyr) by Lipscomb and his collaborators [38, 39]. The active site structure of the CPA−GlyTyr complex revealed the coordination of GlyTyr to Zn(II) to form a complex, and in addition it showed weak interactions between the carboxylate and phenol moieties of GlyTyr and the guanidinium group of an arginine (Arg) residue (Arg145) and a hydrophobic pocket of the enzyme, respectively (Figure 2(a)) [38]. This enzyme-substrate complex is considered as a ternary Zn(II) complex, and these interactions can be regarded as ligand−ligand interactions, which may be partly mimicked by ternary amino acid complexes as shown in Figure 2(b) [28]. These and other features of the enzyme−substrate complex prompted studies on ligand−ligand interactions and ligand reactivities in ternary metal complexes containing amino acids [40–43].

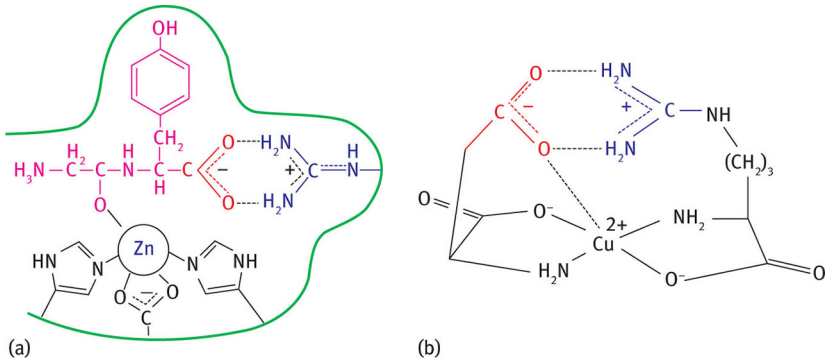

Figure 2: (a) Schematic presentation of the CPA−GlyTyr complex based on Lipscomb et al. [38, 39]. (b) A ternary complex mimicking the CPA−substrate complex [28].

2.2 Types of interactions in and around metal complexes

Noncovalent interactions are bonding interactions that are not covalent and with rather long interatomic distances (2−5 Å) and energies usually less than 1/10 of covalent bonds (<100 kJ/mol). Typical noncovalent interactions and their characteristics are summarised in Table 1 [44–46]. Hydrogen bonds, electrostatic interactions, aromatic ring stacking (p−p) interactions, and interactions between hydrophobic groups are among the interactions observed in biological systems. It is worth mentioning that although the energy of a single interaction is small, combination of multiple weak interactions can result in a bonding that is comparable with a covalent bond.

Table 1 Noncovalent interactions [44–46].

Interactions	Energy/kJ mol^{-1}	Distance dependence	Angular dependence
Ion−ion	40–380	1/r	No
Hydrogen bond (X, Y: electronegative atoms)		X···Y (Å)	
Strong hydrogen bond X−H···Y	20–40	2.5–3.2	Yes
Weak hydrogen bond X−H···π (X = C, N, O), C−H···O, C−H···N, etc.	2–20	3.0–4.0	Yes
Ion−dipole			
Fixed	40–200	$1/r^2$	No
Freely rotating		$1/r^4$	
Cation-π			
Positive charge-dipole	4–160	$1/r^2$	Yes
Positive charge-induced dipole		$1/r^4$	
π-π stacking			
Fixed	4–20	$1/r^3$	Yes
Freely rotating		$1/r^6$	
Dipole-induced dipole	4–20	$1/r^6$	Yes
Induced dipole-induced dipole	4–20	$1/r^6$	No
Nonpolar molecule-nonpolar molecule			

2.3 Characterisation of interactions

The intermolecular interaction energy E is expressed by the sum of the energies of Coulomb attraction E^C, induction E^I, dispersion E^D, charge transfer E^{CT}, and exchange repulsion E^{ER} [44]:

$$E=E^C+E^I+E^D+E^{CT}+E^{ER} \quad (1)$$

where E^{CT} is important for charge transfer complexes and E^{ER} is the energy of repulsion between the electron shells of molecules and important only when the distance between the interacting molecules is very short. Therefore, contribution of the first three terms of eq. (1) is important for usual intermolecular interactions, whose energy E is in the order of the interactions, ion−ion > ion−dipole > dipole−dipole > dipole−quadrupole [44].

In metal complexes there are metal−ligand coordinate covalent bonds forming the coordination structure, and in addition there can be various weak interactions between the ligands and between the metal ion and ligands. Metal−ligand systems may involve the following interactions in addition to the metal−ligand coordinate bonds:

i. Through-metal ligand−ligand interactions

ii. Through-space ligand−ligand interactions

   a. Hydrogen bonds and electrostatic interactions

   b. Aromatic ring stacking interactions

   c. CH− π and other interactions

iii. Metal−aromatic and metal−alkyl interactions

iv. Intermolecular interactions between a metal complex and neighbouring molecules

Interactions (i)–(iii) as well as factors such as the statistical factor and neutralisation of charges are considered to contribute to mixed ligand metal complex formation. Complexes with interacting groups may undergo intermolecular interactions (iv) with neighboring molecules to form molecular adducts, where selective binding may lead to molecular recognition.

2.4 Interactions within complex molecules

2.4.1 Through-metal ligand–ligand interactions

Through-metal ligand–ligand interactions are regarded as electronic interactions between ligands mediated by the central metal ion. These interactions have been concluded for ternary Cu(II) complexes containing DA (= 2,2′-bipyridine (bpy), 1,10 phenanthroline (phen), etc.) and a negatively charged oxygen ligand such as catecholate (cat), Cu(DA)(cat), where the combination of an electron-deficient DA with an electron-rich oxygen ligand, cat, in the Cu(II) coordination plane is favoured [21–23] (cf. 2.5.1.). The stabilising effect of such a ligand combination is explained by electron donation from ligands such as $-O^-$ and Cl^- with filled π orbitals to the metal ion (π-donation) and from the metal ion to ligands such as pyridine and CN^-, which have empty π^* orbitals at a relatively low energy level (π-back donation). The former ligands are called π-donors or π-bases and the latter are called π-acceptors or π-acids.

Tanaka presented an equation for estimating the stability constants of ternary Ni(II) and Cu(II) complexes of nitrogen-and/or oxygen-donor ligands from mechanistic considerations by introducing the ligand interaction terms, δ_{ij}, which were calculated from the reported stability constants and allow for the effect of the donor atom X_i of a ligand on the donor atom Y_j of the other ligand [47, 48]. The δ_{ij} values may be considered to reflect the through-metal ligand-ligand interactions, and the equation gave estimates of the stability constants for mixed ligand complexes such as His-containing ternary Cu(II) complexes, which were in excellent agreement with the experimental values [49].

2.4.2 Through-space ligand ligand and metal ligand interactions

In ternary (mixed ligand) complexes there can be steric repulsion between the coordinated ligands due to bulky side chain groups, but here we will consider attractive ligand−ligand interactions, such as hydrogen bonds, electrostatic interactions, and interactions involving aromatic rings, which favour ternary complex formation. Most L-a-amino acids are effective biological N,O-donor ligands, and those with a metal binding side chain group, especially His, Cys, methionine (Met), aspartate (Asp), glutamate (Glu), and Tyr, are important metal binding sites in proteins. α-Amino acids with the side chain group (X) at neutral pH as shown below are capable of interaction and thus of interest for their possible interactions in and around metal complexes:

i. Negatively charged group: Asp, Glu (X = $-COO^-$)

ii. Positively charged groups: Arg (X = $-NHC(NH_2)_2^+$); lysine (Lys) (X = $-NH_3^+$)

iii. Polar groups: serine (Ser), Thr (X = −OH); Asn, Gln (X = $-CONH_2$)

iv. Aromatic rings: phenylalanine (Phe) (X = phenyl); Tyr (X = *p*-hydroxyphenyl); tryptophan (Trp) (X = 3-indolyl); His (X = 4(5)-imidazolyl)

At higher pH or at the metal site, some X groups and Cys (X = −SH) dissociate to give a negative charge and may be involved in noncovalent interactions and/or metal binding. In addition, the derivatives such as phosphotyrosine (PTyr) and phosphoserine (PSer) (X = $-OPO_3^-$) may be involved in hydrogen bonds or electrostatic interactions, and biological amino acids such as cysteic acid ($CySO_3H$; X = $-SO_3^-$), ornithine (Orn; X = $-NH_3^+$), and citrulline (Cit; X = $-CONH_2$) also have interacting side chains. Bulky alkyl side chain groups may be involved in CH−π and hydrophobic interactions in and around the metal centre [27, 43, 50].

2.5 Detection and evaluation of ligand ligand interactions in solution

Preferential formation of ternary complexes due to ligand−ligand interactions may be concluded on the basis of the information most commonly from stability constants and spectral data, while X-ray crystal structure analysis provides detailed information on the mode and strength of interactions in the solid state and serves as a basis for their existence.

2.5.1 Stability constants

The existence of intramolecular ligand−ligand interactions has been concluded for various complexes in solution by stability constant measurements. The stability enhancement of ternary complexes can be evaluated by using the values such as log K_m, Δlog K, and log K calculated from the relevant stability constants [22, 29, 51]. Here the constants will be expressed as the stepwise stability constants (K values) for 1:1 complexes and as the overall stability constants (β values) for complexes with more than one ligand. The equilibrium constant, K_m, is defined as follows (charges are omitted for simplicity) [22, 51]:

$$\begin{gathered} MA_2 + MB_2 \overset{K_m}{\rightleftharpoons} 2MAB \\ \log K_m = 2\log \beta_{MAB} - (\log \beta_{MA_2} + \log \beta_{MB_2}) \end{gathered} \quad 2$$

where M is a metal ion and A and B are bidentate ligands such as α-amino acids. The statistical value of log K_m is 0.6 for square-planar complexes, and therefore the log K_m value greater than 0.6 indicates that the ternary complex MAB is favoured over the binary complexes MA_2 and MB_2. The Δlog K value corresponds to the logarithm of the equilibrium constant K' for eq. (3) and indicates the preference for binding of A to MB or binding of B to MA rather than binding of A or B to the solvated metal ion M [22, 51]:

$$\begin{gathered} MA + MB \overset{K'}{\rightleftharpoons} MAB + M \\ \log K' = \log \beta_{MAB} - (\log K_{MA} + \log K_{MB}) = \Delta\log K \end{gathered} \quad 3$$

However, the constant K is defined for the following equilibrium [29]:

$$\begin{gathered} MA'B + MAB' \overset{K}{\rightleftharpoons} MAB + MA'B' \\ \log K = \log \beta_{MAB} + \log \beta_{MA'B'} - (\log \beta_{MA'B} + \log \beta_{MAB'}) \end{gathered} \quad 4$$

where A and B are ligands with an interacting group and A′ and B′ are corresponding ligands without it. This is an equilibrium showing preferred formation of complex MAB with ligand−ligand interactions, with MA′B′ serving as the standard. While the log K_m and Δlog K values indicate the preferential formation of ternary complexes due to various factors, the log K value reflects the stability increase of MAB relative to MA′B′ mainly due to ligand−ligand interactions [29, 40].

Stabilisation of ternary complexes by through-metal ligand−ligand interactions has been known for complexes with DA and a phenolate ligand such as cat (L) as seen in 2.4.1. The log K_m and Δlog K values for Cu(DA)(L) with DA = bpy or phen and L = cat or oxalate are greater than those for Cu(en)(L) and Cu(DA)(en) (en = ethylenediamine) due to the above mentioned electron flow, which does not occur with en [21–23].

2.5.2 Spectral data

NMR spectra provide information on ligand−ligand interactions. The interactions expected for ternary M−amino acid complexes such as those containing an acidic and a basic amino acid [28] and those containing His and a polar amino acid [37] can affect the side chain conformation of amino acids, which may be studied by ^{1}H NMR spectral measurements of Pd(II) and low-spin Ni(II) complexes with a coordination structure similar to that of Cu(II) complexes. Changes in the side chain conformations of coordinated amino acids due to the intramolecular interactions in complexes can be detected by the changes in the populations (P) of their staggered rotamers (Figure 3(a)) calculated from the coupling constants, J, of the ^{1}H NMR spectra according to the following equations [52, 53]:

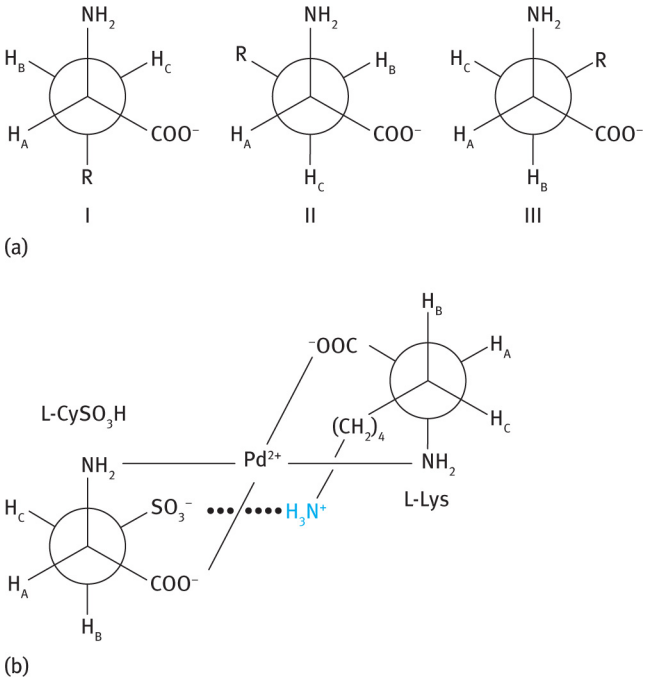

Figure 3: (a) Staggered rotamers of α-amino acids. (b) Structure of [Pd(L-CySO$_3$H)(L-Lys)] showing that rotamers III of the amino acids are necessary for intramolecular interactions [54].

$$P_{\mathrm{I}} = \frac{(J_{\mathrm{AC}} - J_{\mathrm{g}})}{(J_{\mathrm{t}} - J_{\mathrm{g}})}$$
$$P_{\mathrm{II}} = \frac{(J_{\mathrm{AB}} - J_{\mathrm{g}})}{(J_{\mathrm{t}} - J_{\mathrm{g}})} \qquad 5$$
$$P_{\mathrm{III}} = \frac{(J_{\mathrm{t}} + J_{\mathrm{g}}) - (J_{\mathrm{AB}} + J_{\mathrm{AC}})}{(J_{\mathrm{t}} - J_{\mathrm{g}})}$$

where J_{AB} and J_{AC} are coupling constants between the protons shown in Figure 3(a) and J_{t} = 13.56 Hz and J_{g} = 2,60 Hz [52]. The population of rotamer III (P_{III}), which enables the intramolecular interactions in complexes as shown for Pd(Lys)(CySO$_3$H) in Figure 3(b)), increases with the temperature decrease and the solvent polarity decrease as compared with rotamers I and II, indicating the effect of the electrostatic side chain interactions [54]. Use of rotamer populations for determining the side chain conformations has been reported, for example, for metal−peptide systems such as Ni(II)−TyrGlyGly and Pd(II)−AlaTyr (Gly = glycine; Ala = alanine), which exhibited the P_{III} increase due to the metal ion−side chain aromatic ring interaction [55–57].

Aromatic ring stacking in complexes may be detected by the upfield shifts of the proton NMR signals due to the ring current effect [58]. The upfield shifts have been used for evaluating the stacking interactions in ternary complexes involving DA (= bpy, phen, etc.) and nucleotides, amino acids, or peptides [27, 59, 60]. The adduct formation between Pt(II) complexes such as Pt(phen)(en) and nucleotides such as AMP caused upfield shifts of the ^{1}H NMR signals and downfield shifts of the ^{195}Pt NMR signals, $\Delta\delta_{\mathrm{n}}$, which have been shown to increase with the increase of the enthalpy changes, $-\Sigma\Delta H_{\mathrm{n}}^{\circ}$ (n = 1, 2), for the 1:1 and 1:2 adduct formations (Figure 4) [61]. The downfield shifts indicate that the electron density of Pt(II) decreases with the increasing stability of the stacked form probably due to delocalisation of the electrons over the stacked structure.

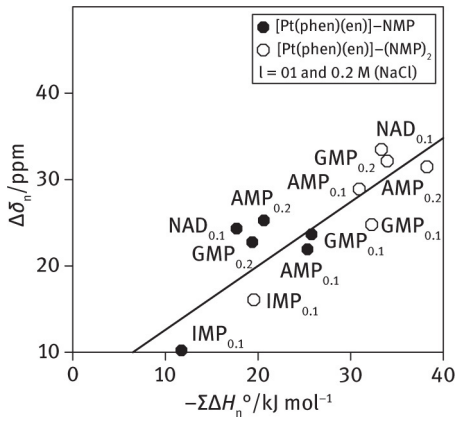

Figure 4: ^{195}Pt NMR downfield shifts ($\Delta\delta_n$/ppm) plotted against enthalpy changes ($-\Sigma\Delta H_n°$/kJ mol^{-1}; n = 1 (●) and 2 (○)). The ionic strength (*I*) is indicated for each nucleotide as a suffix [61].

Absorption and CD spectra are important sources of information on ligand−ligand interactions. Stacking interactions give rise to charge transfer (CT) bands in the near ultraviolet region as observed, for example, for ternary Cu(II)−bpy−nucleotide systems involving bpy−purine base stacking [62]. CT bands were also observed for Cu(II)−DA−amino acid complexes; a Trp-containing complex Cu(bpy) (Trp), which has an average bpy···indole distance of 3.67 Å, exhibited a broad band centred at 320 nm in the difference spectrum [63], and similarly Cu(phen)(XPhe) (XPhe = Phe, Tyr, or *p*-aminophenylalanine (NH_2Phe)) and related complexes gave weak peaks assigned to CT at 320–400 nm [64, 65].

Optically active ligands such as L-α-amino acids and their peptides coordinated to transition metal ions give CD bands in the d-d region due to the vicinal effect of the asymmetric carbon. The CD magnitude ($\Delta\epsilon$) of the Cu(II) complexes of oligopeptides are known to be an additive function of the magnitudes due to the component amino acid residues [66]. In the absence of ligand−ligand interactions the CD magnitudes of ternary amino acid−Cu(II) complexes have also been found to be an additive function of the contributions from each amino acid. The magnitude for M(A)(B) (M = Cu(II), Pd(II); A and B = amino acids), $\Delta\epsilon_{calcd}$, can be estimated from the magnitudes $\Delta\epsilon_{Cu(A)2}$ and $\Delta\epsilon_{Cu(B)2}$ observed for the binary complexes $M(A)_2$ and $M(B)_2$, respectively, by the following equation [28]:

$$\Delta\varepsilon_{calcd} = \frac{1}{2}\left(\Delta\varepsilon_{MA_2} + \Delta\varepsilon_{MB_2}\right) \qquad 6$$

When there exist interactions between the side chains of A and B in M(A)(B), the observed magnitude, $\Delta\epsilon$, deviates from the additivity, i.e. $\Delta\epsilon/\Delta\epsilon_{calcd} \neq 1$, due to increased asymmetry. The magnitude anomaly was first observed for ternary complexes containing an acidic and a basic amino acid such as Cu(edma)(Arg) (edma = ethylenediamine-*N*-monoacetate) and Cu(Asp)(Arg) and the corresponding Pd(II) complexes (Table 2) [28, 67, 68] and has been assigned to the intramolecular electrostatic ligand−ligand interactions between the oppositely charged side chains as shown in Figure 2(b). For the complexes with stacking interaction such as Cu(phen)(AA) (AA = aromatic amino acids), the CD magnitude has been found to be much larger than that for Cu(en)(AA) and depend on the aromatic ring of AA in the order Phe < TyrO < Tyr < Trp (TyrO = Tyr with the deprotonated phenol moiety) [29].

Table 2 CD spectral magnitude anomaly observed for ternary metal(II)-L-α-amino acid systems[1] [54, 67, 68, 71].

System	pH	λmax	D	D /D $_{calcd}$
Cu(Ala)(Arg)	9.4	600	-0.10	1.0
Cu(Ala)(Asp)	9.3	630	-0.06	1.0
Cu(Val)(Arg)	7.2	590	-0.19	1.0
Cu(Val)(Glu)	7.4	600	-0.19	1.0
Cu(Asp)(Arg)	7.2	630	-0.09	1.4
Cu(Asp)(Lys)	7.2	640	-0.08	1.2
Cu(Glu)(Arg)	7.3	600	-0.14	1.4
Cu(Glu)(Lys)	7.3	600	-0.13	1.2
Cu(Ala)(PTyr)	10.0	603	-0.177	1.15
Cu(Ala)(Pser)	7.5	630	-0.128	0.96[2]
Cu(PTyr)(Arg)	10.0	585	-0.411	2.54
Cu(PSer)(Arg)	7.8	616	-0.214	1.57

Cu(PTyr)(Lys)	9.7	591	-0.382	2.27
Pd(Asp)(Arg)	6.4	327	0.41	0.86
Pd(Asp)(Lys)	6.4	328	0.41	0.70
Pd(Ala)($CySO_3H$)	6.6	304	0.32	1.00
Pd($CySO_3H$)(Lys)	6.4	304	0.20	0.87
Pd(His)(Ala)	7.1	324	-0.10	0.93
Pd(His)(Val)	7.0	319	-0.47	0.96
Pd(His)(Ser)	6.9	321	-0.11	0.58
Pd(His)(Thr)	7.1	315	-0.29	0.90
Pd(His)(Asn)	6.8	307	-0.12	0.64

Various other methods such as ESR and resonance Raman spectroscopies are also useful for dectection of structural changes due to interactions.

2.6 Ligand ligand interactions in ternary metal complexes involving amino acids

The formations and properties of the complexes with intramolecular ligand−ligand interactions have been studied by various methods. Stability increase due to through-metal ligand−ligand interactions as observed for Cu(bpy)(cat) etc. was briefly mentioned in 2.5.1. Here we will see some typical examples of through-space noncovalent interactions in amino acid-containing complexes.

2.6.1 Stability enhancement

In ternary complexes such as Cu(DA)(AA) the side chain group of aromatic amino acids (AA = Phe, Tyr, Trp) can be involved in intramolecular stacking interactions with coordinated DA (DA = bpy, phen, histamine (hista), etc.), and the observed stability enhancement has indicated the existence of such interactions. Table 3 shows a comparison of the log *K* values calculated for Cu(DA)(AA) by eq. (7) based on eq. (4),

$$\log K = \log\beta_{Cu(DA)(AA)} + \log\beta_{Cu(en)(Ala)} - (\log\beta_{Cu(en)(AA)} + \log\beta_{Cu(DA)(Ala)}) \quad 7$$

Table 3 Structure dependence of log K values for Cu(DA)(AA) calculated according to eq. (7) (25 ±C; I = 0.1 M (KNO3)) [29, 69, 71, 158].

	AA									
DA	**Val**	**Phe**	**Tyr**	**TyrO**	**PTyr**	**I_2Tyr**	**I_2TyrO**	**Trp**	**MTryp**	**HTrp**
bpy	0.02	0.60	0.90	0.25	−0.14	1.88	1.20	1.19		1.80
phen	0.08	0.64		1.05	−0.02	2.18	1.38	1.39	1.86	2.22
hista	0.06	0.26	0.51	0.11	−0.15	0.84	0.28	0.60	0.83	0.87

which revealed the stability sequences due to DA and the side chain groups of AA as follows:
DA: phen > bpy > hista
Side chain aromatic group of AA:

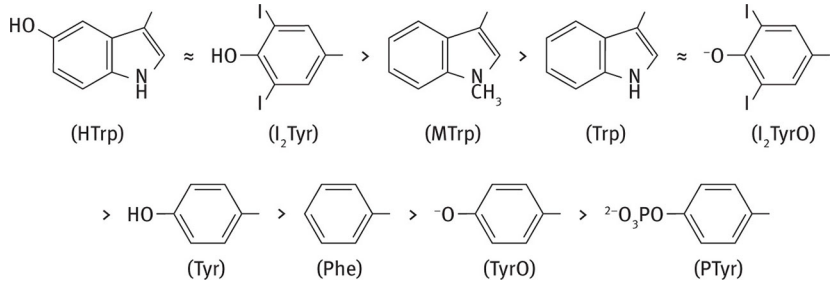

Figure 5:

The sequences (Figure 5) clearly show that the stabilisation due to ligand−ligand stacking interactions depends on the size and electron density of the aromatic rings of DA and AA involved. The enhanced stability observed for I_2Tyr (= 3,5-diiodotyrosine) and I_2TyrO (I_2Tyr deprotonated from the phenol moiety) suggests the stabilising effect of the interaction between the iodine atom and the aromatic ring [69, 70]. In contrast to this, phosphorylation of Tyr to PTyr reduced the log K values by ca. 1 log unit for DA = bpy or phen (Table 3), which indicates that the stacking interaction is virtually lost [71]. The dependence of the complex stabilisation on the Hammett σ values (σ_p) of various p-substituents of Phe for the complexes Cu(DA)(XPhe) (DA = 4,4′-disubstituted-2,2′-bipyridines; XPhe = Phe, NH_2Phe, Tyr, NO_2Phe, FPhe) indicated that the stability enhancement due to stacking is larger for the systems with a larger electron density difference between the stacked rings [70]. For example, for DA = $(NEt_2)_2$bpy with two diethylamino groups, the ternary complex with NO_2Phe containing an electron-deficient ring showed a larger log K value than that for the complex with NH_2Phe with an electron-rich ring, while for DA = $(COOEt)_2$bpy with two electron-attracting ester substituents the log K value was larger for NH_2Phe than for NO_2Phe.

A small stability difference was previously reported for the D-and L-His-containing ternary Cu(II) complexes with basic amino acids (B) such as L-Lys and L-Arg with a protonated side chain at neutral pH. In Cu(D/L-His)(L-B), L-B is considered to be coordinated as seen for L-Asn in Figure 1(a), and thus its side chain can interact with the axially bound carboxylate oxygen of L-His but not of D-His, resulting in stabilisation of Cu(L-His)(L-B); this stability difference disappeared upon deprotonation from the side chain of B, indicating that the interaction is electrostatic [72, 73]. The difference in the equilibrium constants due to the interactions in ternary complexes with an acidic amino acid (A) and B, Cu(A)(B), was detected in the deprotonation process of the protonated side chain group of B, whose pK_a value was 0.57–0.87 log units higher for Cu(A)(B) as compared with Cu(Ala)(B), which is devoid of the interacting group [74]. The result indicates that the proton of the side chain group of B is necessary for the interaction with A as shown in Figure 2(b). For the ternary Cu(II) complexes with A = PTyr, PSer, etc. and B = Lys, Arg, etc., the log K values calculated from eq. (4) with A′ = B′ = Ala were found to be larger at I = 0.1 M (KNO_3) than at 1 M (KNO_3), which supports that the stabilising effect is due to the intramolecular electrostatic interactions involving the phosphorylated phenol moiety [71]. As compared with the low stability of stacking in Cu(DA)(PTyr) described above, the phosphoester moiety is effectively involved in electrostatic interactions with Arg and Lys. The result may suggest a possible conversion of the Tyr phenol moiety from stacking to electrostatic interactions upon protein phosphorylation [29].

Stabilisation due to noncovalent interactions may occur in binary complexes when ligands have a set of side chain groups as in peptides. The reactions of Cu(II) with a pentapeptide, NSFRY (= AsnSerPheArgTyr-NH_2), which is a fragment from the 28-peptide atrial natriuretic factor, and its analogs have been studied by pH titrations and spectroscopic methods, and this particular peptide was revealed to form an exceptionally stable 4N-donor complex with Cu(II) compared with the analogs [75, 76]. From comparative studies of the stability constants, the stabilisation has been attributed to various interactions between the side chain groups; the Asn side chain is considered to interact with the amino group to lower its pKa and make it react easily with Cu(II) and further form a fence with Phe. In the 4N-donor complex, hydrogen bonding between the polar atoms of Asn and Tyr is considered to be formed. An interesting stabilising effect comes from the Arg and Tyr residues, which is explained to be due to formation of an additional fence over the one formed by Asn and Phe [75–79]. The results suggest that non-coordinating side chain groups located close together in the coordination sphere interact with each other and cover the space around the metal centre, thus protecting it from the attack of solvent molecules, etc. The observations suggest a situation that is comparable to that at the metal site in proteins.

2.6.2 Structure and selectivity

As described in the foregoing sections, noncovalent ligand−ligand interactions in complexes M(DA)(AA) and M(A)(B) (M = Cu(II), Pd(II)) have been concluded from solution and spectral studies. The X-ray structures of the complexes isolated as crystals have provided the details of the interactions, although the mode of interactions in the solid state may not always be the same as that in solution. Crystal growth requires interactions between molecules, and intramolecular interactions may be converted to intermolecular interactions to form a polymeric chain. The electrostatic ligand−ligand interactions concluded for Cu(edma)(Arg) in solution [28] were found to be intermolecular in the solid state as shown in Figure 6 [80].

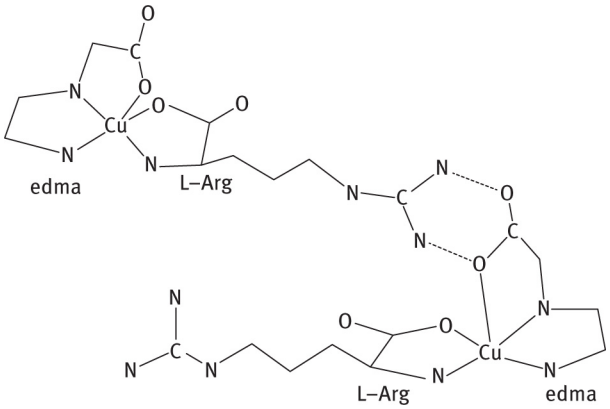

Figure 6: Schematic presentation of intermolecular guanidinium−carboxylate interactions in $[Cu(edma)(L\text{-}Arg)]^+$ in the solid state [80].

While stacking within complexes such as M(DA)(AA) often remains localised, association of complexes or adducts with a stacked structure can occur, forming an infinite pile of stacked rings. In the crystal structure of [Pt(phen)(L-Ala)](AQS) (AQS = anthra-quinone-2-sulfonate), $[Pt(phen)(L\text{-}Ala)]^+$ stacks with AQS^- (Figure 7(a)), and this adduct unit stacks with the other units, resulting in an alternate pile of the coordinated phen and AQS rings (Figure 7(b)) [81]. A similar solid state structure was disclosed, e.g. for [Pt(bpm)(L-Ala)](IA) (bpm = 2,2′-bipyrimidine; IA = indole-3-acetate) [82]. In contrast, the adduct of $[Pt(bpm)(L\text{-}Arg)]^{2+}$ with a nucleotide (GMP^{2-}) exhibited an interesting structure (Figure 8), which is formed as a discrete unit by intramolecular interactions, a stacking interaction between coordinated bpm and the guanine ring of GMP and hydrogen bonds between the guanidinium and amino groups of Arg and the phosphate oxygen atoms of GMP [82]. This structural unit is connected to the neighbouring units through unique guanine−guanine hydrogen bonds with the distances of 2.82−2.86 Å.

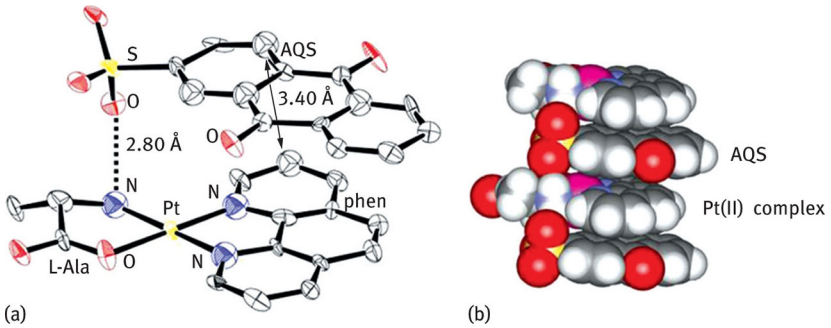

Figure 7: [Pt(phen)(L-Ala)]···AQS adduct. (a) Molecular structure and (b) stacking between the adducts [81].

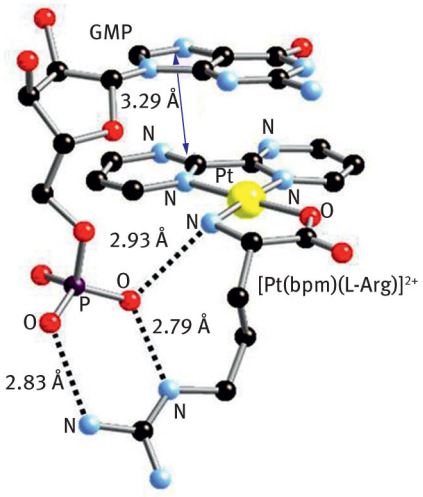

Figure 8: Structure of $[Pt(bpm)(Arg)]^{2+}$···GMP^{2-} adduct [82].

A number of structures with π−π stacking interactions have been reported for ternary complexes containing an aromatic amino acid (AA) or its peptide and DA, such as Cu(phen)(Trp) [83], Cu(bpy)(Trp) [63],

Cu((CONH$_2$)$_2$bpy)(Phe) (Figure 9(a)) [70], Cu(hista)(I$_2$TyrO) (hista = histamine) [84], Cu(phen)(TyrGlyH$_{-1}$) (Figure 9(b)) [85], and Pd(bpy)(TyrGlyH$_{-1}$) [85], where the aromatic side chain of AA is involved in intramolecular stacking with coordinated DA. Figure 9 shows that stacking takes place between the Tyr phenol ring and phen bound perpendicular to the Cu(II) plane, which is different from the parallel stacking in Pd(bpy)(TyrGlyH$_{-1}$) on the Pd(II) plane. The interaction in M(DA)(AA) usually remains localised in the complex molecule with the shortest atomic distances of 3.0–3.5 Å. The stability sequence due to intramolecular stacking of Phe shows that Cu(DA)(Phe) is rather weakly stabilised by stacking compared with Tyr and Trp (cf. 2.6.1. and Table 3). Probably because of this, the side chain of Phe in [Cu(phen)(Phe)Cl] has been found to be both in the stacked structure and the extended structure without stacking [64], and other examples such as [Cu(bpy)(Phe)(H$_2$O)]$^+$ [64] and [Cu(phen)(Phe)]ClO$_4$·H$_2$O [86] were also without intramolecular stacking.

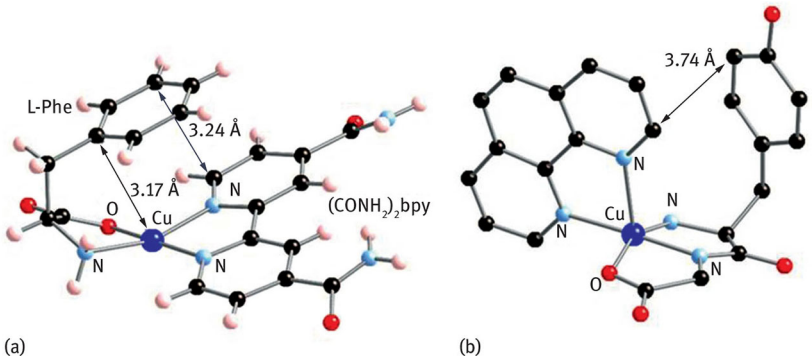

Figure 9: Structures of Cu(CONH$_2$)$_2$bpy)(L-Phe) (a) [70] and Cu(phen)(L-TyrGlyH$_{-1}$) (b) [85].

Stacking interactions in proteins are well known to contribute to the stability of proteins [3], where the modes of stacking are often edge-to-face and offset or parallel-displaced to avoid π−π repulsion [87, 88] and possibly for steric reasons. In metal complexes with aromatic nitrogen donors such as M(DA)(AA), stacking is usually offset, showing limited overlapping due to the steric requirements of the coordination structure and the ligand side chain length. However, the distortion of the coordination plane observed in X-ray structures suggests that the aromatic rings involved in stacking tend to be close to each other to be in a parallel position. This may reflect the weakening of π−π repulsion due to the electron density decrease of coordinated aromatic nitrogen heterocycles, which are already with a low π-electron density [89].

The stacking in M(DA)(AA) may be expressed as MLπ −L′π interactions shown in Figure 10, where ML and L′ denote a metal-bound aromatic ligand and a pendent aromatic ring, respectively [70]. The stacking also implies MLπ −L′π or d−π interactions and other interactions when there are ring substituents X and Y. Preference for stacking partners is seen from the structures of the Cu(II) and Pd(II) complexes of tridentate ligands containing a pyridine and a phenolate moiety as donor groups and a side chain indole ring as shown in Figure 11, where the electron-rich indole ring stacks with the pyridine ring but not with the electron-rich phenolate ring [90]. It is interesting to note in this connection that a Trp residue was found to be in contact with the Cu-bound Tyr residue by stacking at the active site of a copper enzyme galactose oxidase; the coordinated Tyr272 phenolate ring with a thioether bridge stacks with the Trp290 indole ring, where the indole ring is considered to play important roles in stabilising the electron-deficient phenoxyl radical formed in the course of the reaction and in the functioning of the enzyme [91, 92].

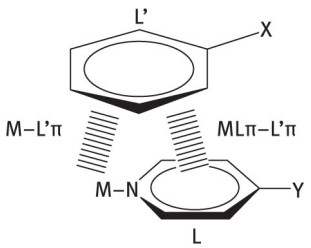

Figure 10: π−π stacking between a metal-coordinated aromatic nitrogen ligand L and a pendent aromatic ring L′ [70]. X and Y are ring substituents.

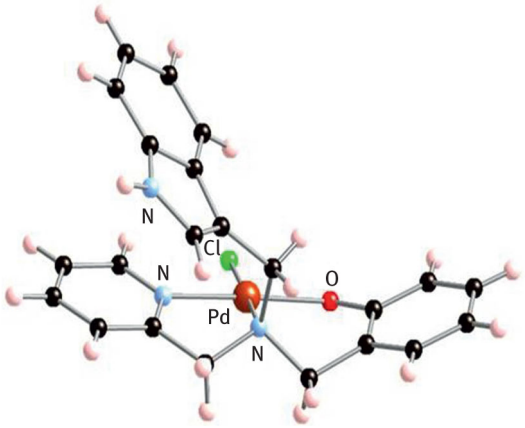

Figure 11: Stacking of the indole ring in a Pd(II) complex involving a pyridine and a phenolate moiety as coordinating groups [90].

The histidine imidazole ring is an important metal binding site in metalloproteins and can be involved in stacking with other aromatic rings. The X-ray analysis of ternary complexes, [Cu(hista)(AA)(ClO_4)] (hista = histamine; AA = Phe, Tyr), revealed intramolecular stacking interactions shown in Figure 12 [93]. From the log *K* values listed in Table 3, the hista-containing ternary complexes are less stabilised by stacking than those containing bpy or phen probably due to the smaller ring size and higher electron density. The structures show that the shortest distances between the stacked rings are 3.45−3.49 Å, which are within the normal range. Although ring overlapping is limited and the dihedral angles between the stacked rings are rather large (38.1−38.5°) in the model complexes, the results suggested the possibility of His−Phe and His−Tyr stacking interactions at the metal sites in proteins. Later the coordinated His−Phe stacking has been actually detected at the Cu site of a plastocyanin from fern (*Dryopteris crassirhizoma*) between coordinated His90 and nearby Phe12 (Figure 13), which is the first observation of stacking interactions involving a coordinated His residue [94].

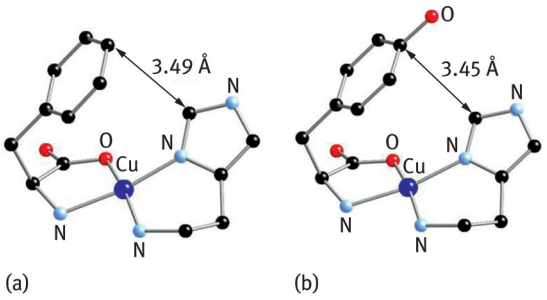

Figure 12: Structures of Cu(hista)(L-Phe) (a) and Cu(hista)(L-Try) (b) [93].

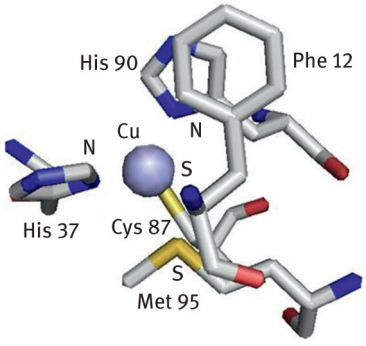

Figure 13: Stacking of coordinated imidazole with Phe in plastocyanin from fern (PDB code: 1KDJ) [94].

While steric hindrance in ternary complex formation is well known as a source of stereoselectivity of ligands, noncovalent interactions are important for chiral and molecular recognition in systems involving complexes and other molecules [4, 43]. Selective incorporation of the L-enantiomer of DL-His via formation and isolation of Cu(His)(L-Asn or L-Cit) is in line with the intramolecular hydrogen bonds inferred from the syntheses and structures of the ternary Cu(II) complexes containing His and an amino acid with a polar side chain (Figure 1(b)) [37, 95] (cf. 2.1 and 2.6.1). Stereoselectivities or chiral recognitions upon complex formation with His-or hista-containing ligands have been reported for complexes, such as Cu(II)−His−amino acid

[96] and Cu(II)−*cyclo*-HisHis−amino acid complexes [97] by stacking, and for Cu(II)−hista-functionalised β-cyclodextrin−amino acid complexes by hydrophobic interactions [98]. Differences in the steric requirements for D-and L-Ala in a chiral Co(III) complex [99] and in the rate of complex formation by a chiral Co(III) complex of a leucine-containing ligand with D-and L-Phe due to π−π stacking [100] and stereoselective binding of α-amino acids by a chiral cyclen−Co(III) complex [101] serve as further examples of enantioselectivity arising from ligand−ligand interactions.

3 Structural and functional characterisation of noncovalent interactions in chemistry and biology

Noncovalent interactions have influences on the properties of complexes, which is seen from the structures in the solid state and the behaviour in solution. Molecular recognition and stereoselectivity are functions typically expected for noncovalent interactions in metal complexes, but various other contributions to structures and functions of complexes have been reported. In this section, examples showing the effects of intra-and intermolecular interactions in systems involving metal ions will be presented, and their relevance to biological systems will be considered.

3.1 Association of oppositely charged ions in Cu(II) arginine complexes

The guanidinium group of Arg has three NH/NH2 moieties positively charged and is known to be involved in the hydrogen bonding called a salt bridge with the carboxylate group of Asp and Glu, which is effective for protein structure stabilisation [1, 3] and substrate binding by enzymes such as in CPA [38, 39] and Cu,Zn-SOD [102]. It is also known to interact with aromatic rings such as indole to undergo cation−π interactions (cf. 3.3.).

The binary Cu(II) complex of Arg, $[Cu(Arg)_2](NO_3)_2$, in the solid state has two Arg molecules coordinated in the *cis* configuration due to the hydrogen bonds between the amino groups and a nitrate ion (Figure 14(a)) [80]. When the nitrate ions are replaced by a dianion, X, with two hydrogen bond acceptors, the $[Cu(Arg)_2]^{2+}$ core unit self-organises with X to give supramolecular structures depending on the structure of X; with X = isophthalate (*m*-benzenedicarboxylate (mbc)) and pyridine-2,6-and -3,5-dicarboxylates (2,6-and 3,5-pdc, respectively) having the acceptors of the hydrogen bonds with the Arg guanidinium groups and the coordinated amino groups in suitable positions, $[Cu(Arg)_2]^{2+}$ forms a double-helical structure reflecting the chirality of Arg (Figure 14 and Figure 14) [103], and a single-helical structure is formed with X = SO_4^{2-} [104]. However, dianions such as terephthalate and benzene-1,3-disulfonate bind with $[Cu(Arg)_2]^{2+}$ having the NH_2 groups coordinated in *trans* positions to give a tape structure, which then associates to form a sheet structure [104].

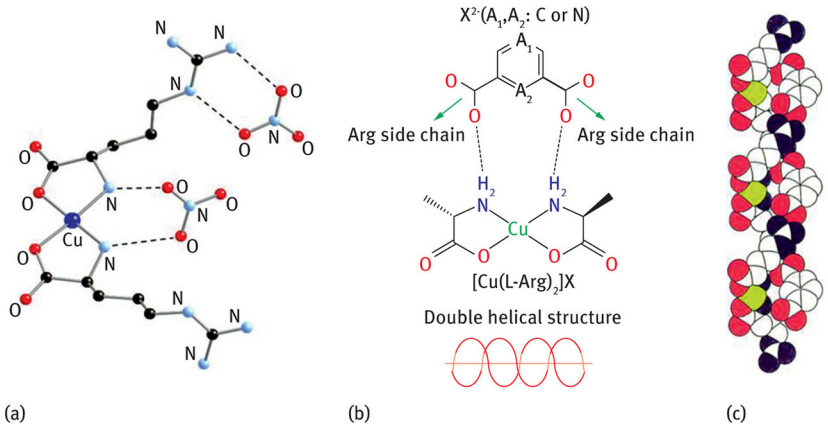

Figure 14: (a) Structure of $[Cu(L\text{-}Arg)_2](NO_3)_2$ (A) [80]; (b) formation of a double helical structure by association of $[Cu(L\text{-}Arg)_2]^{2+}$ with a dicarboxylate by guanidinium-carboxylate interactions; (c) space-filling model of $[Cu(L\text{-}Arg)_2]$(mbc) [103, 104].

The Cu(II)-L-Arg system with a phosphate ion as a counter ion has been reported to give a doubly phosphate-bridged dimer, which is then bound to neighbouring dimers by the guanidinium-carboxylate hydrogen bonds to give a layer [105]. A dipeptide complex, $Cu(ArgGlyH_{-1})$, was found to form hydrogen bonds between the guanidinium group and the Cu(II)-bound β-carboxylate group of a neighbouring complex molecule, resulting in a zigzag chain [106].

These examples suggest that owing to the guanidinium group, Arg-containing metal systems can be prototypes for molecular recognition and constituents or synthons of supramolecules [107].

3.2 Interactions between metal complexes and surrounding groups

Intermolecular interactions between metal complexes and non-coordinated molecules or ions may form adducts, which could be regarded as second-sphere coordination. Such interactions may influence the structures and functions of the complexes and/or the surroundings. The metal site of proteins is in the molecular environment produced by the proteins, and the interactions between them are essential for the activity. For these reasons, there is a growing interest in the effects of the microenvironment of metal complexes in chemical and biological systems [17].

3.2.1 Adduct formation and its effect

Pt(II) complexes such as Pt(phen)(Arg) bind with IA, AQS (Figure 7(a)), GMP (Figure 8), and other aromatic molecules by stacking and hydrogen bonding [81, 82]. FMN (riboflavin 5′-phosphate) is known as the prosthetic group of redox carrier proteins flavodoxins; in the flavodoxin from *Anabaena*, FMN is noncovalently bound to the protein through its isoalloxazine ring sandwiched between the Tyr phenol and Trp indole rings in addition to hydrogen bonds, and the molecular environment is known to control the semiquinone/hydroquinone redox potential of FMN [108, 109]. FMN was reported to form ternary Cu(II) complexes with DA = bpy or phen, where it is bound to Cu(II) through the phosphate moiety and stacking with DA [110]. The Pt(II) complexes were found to interact with FMN to form 1:1 adducts as seen for AQS with a similar three consecutive ring system (Figure 7(a)), and the stability constants (log K values) were determined to be 2.83~3.42 by ^{1}H NMR spectra [81]. Upon adduct formation the redox potential ($E_{1/2}$) for the two-electron redox processes of FMN exhibited anodic shifts due to the electron density decrease, the shift differences indicating the effects of both stacking and hydrogen bonding.

Complex molecules can interact with the other molecules in the second coordination sphere. For example, crown ethers have been shown to surround Ru-ammine complexes in place of solvent molecules [111]; 18-crown-6 and other crown ethers form adducts with the Ru complexes by hydrogen bonds between the oxygen atoms and the coordinated ammine ligands and cause a cathodic shift of the Ru redox potential, which indicates that the electron density of the Ru centre increases due to binding with the oxygen donors. The factors affecting the adduct formation have been studied [112].

In view of the functions of polyamines such as putrescine and spermidine in genetic information transfer processes, Lomozik and collaborators have investigated the complex formations in metal-ligand systems involving polyamines and nucleosides or nucleotides and interactions between metal complexes and non-coordinated molecules or groups. In ternary systems involving amino acids, nucleotides etc., coordinated polyamines have some protonated amine nitrogens, which bind with the other ligand by hydrogen bonds [113, 114] (for details, see Chapter 1.3.3.2).

3.2.2 Protein small molecule interactions

Interactions of metal complexes with biological macromolecules are of current interest in view of the activities of metallodrugs [13–18]. Biological processes of enzyme catalysis and electron transfer require interactions between the enzyme and its substrate and between the electron donor and the acceptor, respectively. Structural studies have been performed, for example, for the enzyme−substrate model complex of CPA (cf. 2.1) and the electron transfer complexes such as cytochrome *c*−cytochrome *c* peroxidase [9] and amicyanin−methylamine dehydrogenase−cytochrome c_{551i} [115], where various interactions, notably electrostatic interactions between basic and acidic amino acid residues and hydrophobic interactions, have been observed within the complexes.

Plastocyanin (PC) is a mobile electron transfer protein involved in photosynthesis and accepts an electron from cytochrome *f* (cyt *f*) of photosystem II and transfers it to photosystem I [116]. Higher plant and green algae PCs have consecutive acidic amino acid residues at the solvent-accessible site near the Tyr residue (negative patch), while cyt *f* has a Lys residue-rich site exposed to solvents (positive patch) [117]. These oppositely charged sites are known to be involved in the recognition process. Subtle effects of the interaction between the proteins on the structural and electrochemical properties of *Silene pratensis* PC [118] have been studied by using positively charged Lys peptides such as tetralysine in place of cyt *f* at neutral pH (Figure 15) [119, 120]. The absorption spectral changes of PC at around 600 nm caused by pentalysine indicated that the Cu site structure or the

Cu−S(Cys) bond was altered, and from the difference resonance Raman spectrum in the 200–600 cm^{-1} region (excitation wave-length, 591.0 nm), several bands at 375–475 cm^{-1} related with the Cu−S bond were found to be slightly shifted to lower frequencies, indicating that the Cu−S(Cys) bond was weakened by addition of pentalysine. The resonance Raman spectral changes of PC caused by lysine peptides were the same as those by cyt *c*, which is positively charged, and the fact that the peptides, especially tetra-and pentalysine peptides, competitively inhibited the electron transfer from reduced cyt *c* to oxidised PC indicates that lysine peptides serve as the PC interacting site models of cyt *c*, cyt *f*, etc. The PC−lysine peptide association constants were found to increase with the peptide length, dilysine < trilysine < tetralysine < pentalysine, showing that PC binds more strongly with longer peptides or peptides with more positive charges. Interestingly, as the Cu−S(Cys) bond became longer due to the PC−lysine peptide interaction, the redox potential shifted to a higher value, facilitating the electron transfer from the redox partner to PC.

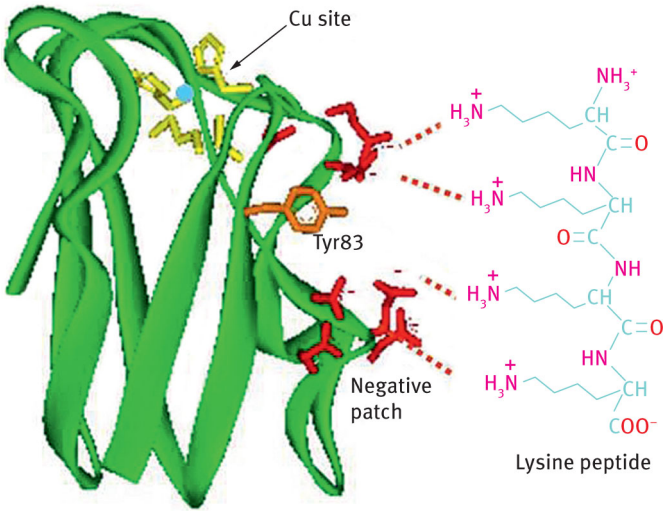

Figure 15: Structure of *Silene pratensis* plastocyanin (PDB code: 1BYO) [118] and schematic presentation of interaction with a lysine peptide [119]. Modified from ref [120].

Recently proteins have become important targets for metal complexes and metal-based pharmaceuticals, both for therapeutic and diagnostic purposes [16, 121]. The specificity of enzymes depends on the structural fitness of the substrate to the active site, where the substrate is bound to the enzyme by noncovalent interactions. Transition metal ions have the possibilities of forming diverse structures by complex formation and may fit into the protein's crucial site, serving as metallodrugs. Interesting studies have been reported by Meggers and collaborators on fitting the structures of inert complexes to the protein kinase active site by mimicking a natural product staurosporine (Figure 16(a)) known as an effective inhibitor of the enzyme [122]. They developed pyridocarbazole ligands resembling staurosporine and synthesised mixed ligand complexes, which were named as octasporines (Figure 16(b)), and tailored them to fit into the ATP binding site of protein kinases, where the pyridocarbazole moiety occupies the adenine binding site. The inhibitory activities of the complexes thus prepared were studied, and the Ru complex shown in Figure 16(b), for example, has been found to be a selective inhibitor of the a-form of glycogen synthase kinase 3 [123]. The structure of a protein kinase, human 8-oxo-dGPTase, with a bound Ru complex is shown in Figure 17(a), where the complex (Figure 17(b)) interacts with the Lys, Asn, and Asp residues of the kinase by hydrogen bonds in a hydrophobic environment with Phe, Trp, etc. [124]. The studies indicate the importance of steric fitness of the complex to the active site and noncovalent interactions between them.

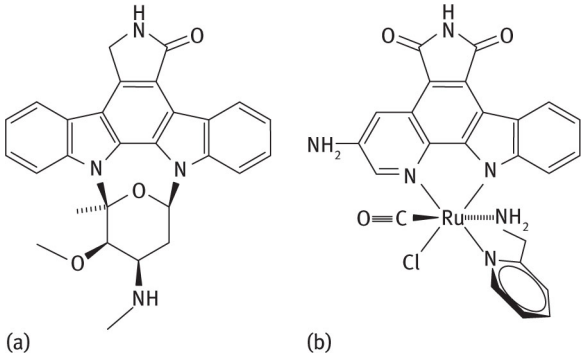

Figure 16: Structures of staurosporine (a) and an octasporine (b) [122].

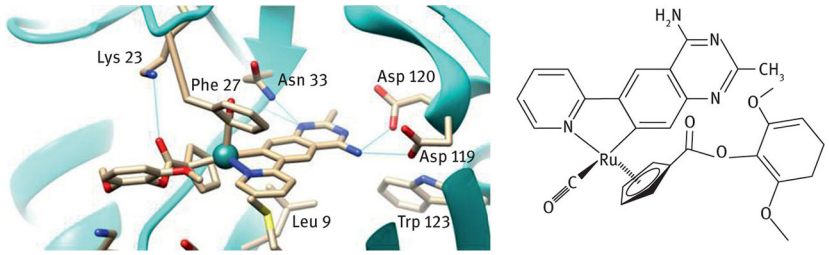

Figure 17: Structures of protein kinase−inhibitor complex (PDB code: 3WHW) (a) and the inhibitor (b) [124].

The approach toward site specific binding of small complexes to proteins will be important for the elucidation of the active site structures and functions and developing new metallodrugs and other functional complexes that can pinpoint the target.

3.2.3 Interactions involving coordinated ligands at the metal site of proteins

Functions of metalloproteins depend on the coordination structure and properties of the central metal ion, donor atoms, and the effect of the molecular environment. Hydrogen bonds and stacking interactions of the donor groups with the second-sphere groups such as the peptide -NHCO-and the side chain groups of amino acid residues can affect the electron density of the coordinating groups and thus the redox properties of the central metal ion. We will see some examples of non-covalent interactions in blue copper proteins and iron-sulfur proteins and their models.

Blue copper proteins such as PC [116] (cf. 3.2.2.) have a unique Cu coordination structure with two His imidazole nitrogens and Cys thiolate and Met thioether sulfurs. As shown in Figure 13, PC from fern has a Phe residue stacked with the coordinated imidazole and exhibits a higher redox potential than the other PCs from higher plants [94]. Further studies have been reported on the spectroscopic and electrochemical effects of mutation of *Achromobacter cycloclastes* pseudoazurin at Met16 located close to coordinated His81 to aromatic and aliphatic amino acids [125, 126]. Mutation to Tyr, Trp, and Phe caused shifts of the Cu−S(Cys) stretching modes to a higher frequency region, indicating that a structural perturbation has occurred to make the Cu−S(Cys) bond stronger. Comparison of the CysS-to-Cu(II) CT bands and ESR spectra indicated a trigonal disposition of the Cu site. The redox potentials were found to be higher for the mutants with the aromatic amino acids than the wild type and the mutants with aliphatic amino acids [125, 126].

At the metal centre of proteins, hydrogen bonds between the donor groups and the peptide bonds and/or side chain groups of the protein are known to modulate the redox activities of the metal centre. The Cu sites of a blue copper protein azurin and its mutant are shown in Figure 18 [127, 128]. Wild type azurin has two hydrogen bonds involving coordinated Cys thiolate sulfur and two peptide groups [127], but upon mutation of Phe114 to Pro114 one of the NH moieties was lost, leaving a hydrogen bond with the peptide NH of Asn47 only [128]. This caused a redox potential lowering from 297 mV to 211 mV. A similar shift has been reported for amicyanin, where a hydrogen bond added at the Cu site by mutation caused an anodic shift of the redox potential [130]. Hydrogen bonds around the metal centre have also been known for iron-sulfur [131] and nonheme-iron proteins such as shown in Figure 19 for superoxide reductase (SOR) [132]. Recent detailed ENDOR and DFT studies on a heme enzyme cd_1 nitrite reductase indicated dynamic formation of hydrogen bonds between the reduction product nitric oxide bound to the heme and the distal His and Tyr residues [133]. Among the approaches to the iron-sulfur proteins, the iron-sulfur clusters were synthesised by using a Cys-containing peptide ligand incorporating the characteristic CysGlyAla sequence of the metal site and related ligands [134]. $Fe_4S_4(ZCysGlyAlaOMe)_4]^{2-}$, which is capable of N−H···S hydrogen bonding when bound through $-S^-$, exhibited a higher redox potential than $[Fe_4S_4(ZCysGlyOMe)_4]^{2-}$ where hydrogen bonding is not possible. The result was supported by further studies [135, 136].

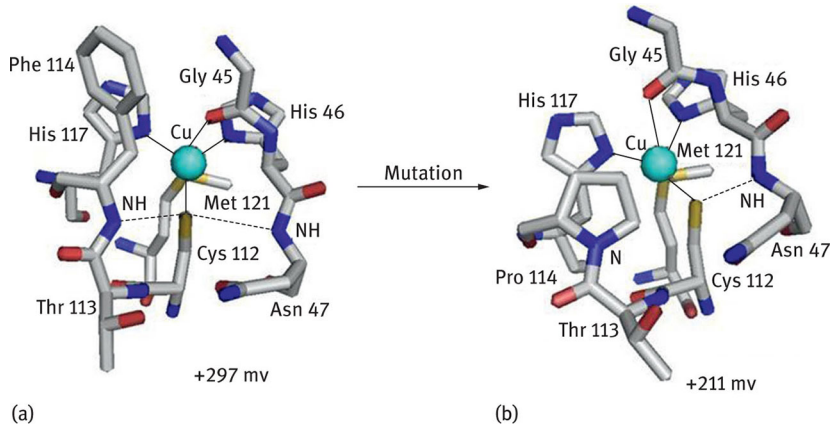

Figure 18: Shift of the redox potential (midpoint potential E_m) due to loss of a N−H···S hydrogen bond at the copper site in a blue copper protein azurin. (a) *Pseudomonas aeruginosa* azurin (PDB code: 4AZU) [127]; (b) Phe114Pro mutant of azurin (PDB code: 2GHZ) [128]. Hydrogen bonds are indicated by broken lines. Reproduced from ref [129] by the courtesy of Asakura Publishing, Tokyo, Japan.

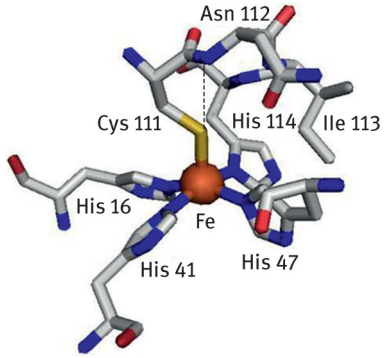

Figure 19: NH···S hydrogen bonding in a non-heme iron enzyme superoxide reductase (SOR) from *Pyrococcus furiosus* (PDB code: 1DQI) [132]. Hydrogen bonds are indicated by broken lines. Reproduced from ref. [129] by the courtesy of Asakura Publishing, Tokyo, Japan.

3.3 Close contact between the metal centre and the side chain groups

3.3.1 Metal aromatic ring interactions

Aromatic rings are known to contribute to the protein structure stabilisation [1, 3, 137] and molecular recognition [138–140] and are often located close to the coordination sphere. This is well known for Cu(II) complexes, where the side chain aromatic ring of amino acids and peptides have been shown to be bent over the Cu(II) coordination plane. As shown earlier (cf. 2.6.2), the aromatic rings of AA and DA in Cu(DA)(AA) undergo stacking interactions within the complex molecule, but at the same time the side chain aromatic ring is located close above the Cu(II) centre to be within the sum of the van der Waals radii, suggesting electronic interactions between them. Aromatic rings tend to occupy a space above the Cu(II) coordination plane even in the absence of aromatic−aromatic stacking. In the solid state structure of Cu(II)−GlyTrp complex [141], deprotonated GlyTrp ($GlyTrpH_{-1}$) coordinates to Cu(II) as a tridentate ligand in the planar positions with the side chain indole ring of Trp bent over Cu(II) with a rather large dihedral angle of 50°, which is probably due to the planarity of the dipeptide coordination with a deprotonated peptide nitrogen; on the other side of the Cu(II) plane, however, there is the indole ring from a neighbouring molecule at the distance of 3.12 Å and with an angle of 13°. The aromatic ring−metal ion interaction was also proposed by NMR studies of the Tyr-containing dipeptide complexes of Pd(II) [56] and tripeptide complexes of Ni(II) and Pd(II) [55], and similar Cu(II)-aromatic ring contact was established by X-ray analysis of complexes such as $Cu(L\text{-}Tyr)_2$ [142]. These observations indicate that aromatic rings have a tendency to be close to the metal centre possibly due to electrostatic, electronic, and/or hydrophobic interactions.

The intramolecular stacking shown in the earlier sections is considered to involve both metal-coordinated ligand−ligand p − p (or *MLp−L′* p) and metal *d−L′* p interactions (Figure 10). The presence of the electronic interaction between the metal ion and the aromatic ring is suggested by the ^{195}Pt NMR shift upon adduct

formation with AMP, etc. (Figure 4) considered to be due to delocalisation of the d electrons, and the relatively large enthalpy changes, -SD*H*o, indicate that the adduct is formed as a result of bonding interactions rather than the entropy effect [61].

Cation–π interactions are of current interest, and indeed they are well recognised in protein structures, ion channels, and enzyme reactions, where the interactions of alkali metal ions, the Arg guanidinium group, and the trimethylammounium group of acetylcholine have been shown to interact with the aromatic rings of Trp, etc. [143–147]. A striking example of transition metal−aromatic ring interactions in proteins has been reported for a copper chaperone CusF, where the Cu(I) ion bound with two Met sulfurs and a His imidazole nitrogen interacts with a Trp indole ring located close to the Cu site (Figure 20(a)) [148]. This is the first example of the interaction of the Trp indole ring with a metal ion in biological systems. Figure 20(a) shows that the indole C(4)-C(5) moiety of Trp44 is in contact with Cu(I) with rather long distances of 2.67 and 2.86 Å, and the interaction has been assigned to a cation−π interaction [148, 149]. Subsequent studies indicated that the Cu(I) binding affinity (log *K*) of CusF is 14.3 ± 0.1 [150] and that the Cu(I)-Trp44 interaction is important for stabilising the complex and protecting Cu(I) from oxidation by water [151, 152].

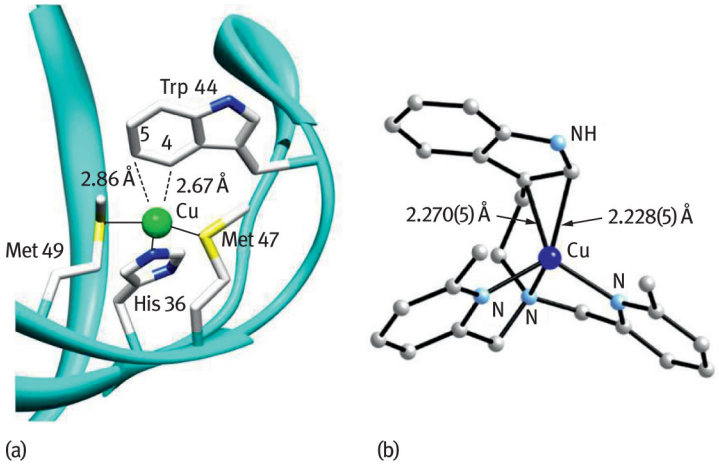

Figure 20: (a) Cu(I)−p interaction in a copper chaperone CusF (PDB code: 2VB2) [148]. Reproduced from ref. [129] by the courtesy of Asakura Publishing, Tokyo, Japan. (b) Cu (I)−indole h^2-bonding with a 3N-donor ligand [154].

On the other hand, Cu(I) is known to form p-type bonds with alkenes [153]. The reaction of Cu(I) with a 3N-donor ligand containing a pendent indole ring has been shown to give a Cu(I) complex, whose X-ray structure revealed that Cu(I) bound to three nitrogen atoms forms an η^2-*bond* with the C(2)−C(3) moiety as shown in Figure 20(b) [154]. The bond distances between Cu(I) and the carbon atoms (2.228 and 2.270 Å) are longer than those of the Cu(I)−alkene complexes (1.943–2.028 Å), indicating that the bonds are rather weak; when acetonitrile is added to the solution of the complex dissolved in CH_2Cl_2, the carbon donors are replaced by acetonitrile with concomitant changes of the Cu(I)-to-indole CT band at 308 nm. In this connection structures and quantitative evaluation of similar η^2-*bond* formation between Cu(I) and a side chain phenyl ring have been reported for ligands containing a *p*-substituted phenyl ring in place of the indole ring such as shown in Figure 21 [155], where the Cu−C bond distances were 2.336 and 2.211 Å and comparable with those for the indole ring. These Cu(I)-arene interactions were concluded to consist mainly of the interaction between the Cu(I) d_z^2 orbital and the phenyl ring π orbital. The cation− π interactions involving transition metal ions are considered to be somewhat different from those of alkali metal ions. A theoretical study on the Cu(I)−benzene systems indicated that the electrostatic interaction is not important and that Cu(I) forms an η^6 cation− p complex with the decrease of the Cu(I) 3d electron density as a result of a 3d→π* electron flow, i.e. back donation from Cu(I) d to π* of the aromatic ring [156]. The study also showed that Cu(I) tends to form η^2 complexes in the presence of counterions.

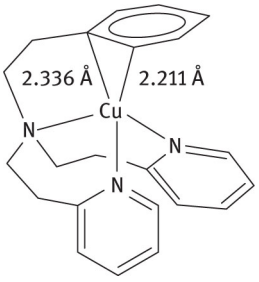

Figure 21: d−π interaction in Cu(I) complexes [155].

As shown in Figure 20, the distances for the Cu-indole interaction in CusF are longer than those for the Cu(I)−indole complex, which suggests that the interaction is a more electrostatic cation−π interaction rather than d− π interactions. Thus, depending on the metal ions involved and the distances between the interacting groups, cation−π interactions may lie somewhere between covalent η-type bonds and electrostatic interactions. A spectroscopic study on Cu(II)−Trp interactions using Gly-AsnHisTrp-NH_2 showed the UV and CD spectral changes which were ascribed to the cation−π interaction, and the most stable structure obtained by molecular mechanics calculations indicated that the Cu(II) ion bound by four nitrogens of the peptide is located above the pyrrole moiety of the indole ring with a distance of 3.85 Å, which supported that the interaction is a cation−π interaction [157]. The pyrrole NH moiety of the indole ring has a very weak acidity which may be compared with the phenol ring [158], and the metal binding ability of indole by the nitrogen or by the carbon atoms has been reviewed recently [159]. These results suggest further possibilities of Trp−metal ion interactions in biological systems, for example, in prion−Cu(II) binding.

3.3.2 Interactions involving a hydrogen atom

A hydrogen atom from a metal-coordinated ligand has attracted attention due to its ability to interact with an aromatic ring in the second coordination sphere. The active site of metalloproteins is often associated with aromatic rings from aromatic amino acid residues such as Trp and Phe. The hydrogen atom bound to a ligand may gain a positive charge from the metal ion and undergo an effective cation−π type interaction. By detailed surveys of the crystallographic data of the Protein Data Bank (PDB), Zaric and collaborators revealed the existence of such interactions in metalloproteins and called them "metal ligand aromatic cation−π (MLACp)" interactions [160]. MLACp interactions will be stronger when the number of bonds from the coordinating atom to the hydrogen atom is smaller. In metalloproteins the distances between the aromatic centroid and the nearest non-hydrogen ligand atom were found to be 3.09–4.41 Å, and the energies of interactions were calculated to be 4–120 kJ/mol [161]. Interestingly the structure of the alcohol dehydrogenase−ethanol complex indicated the MLACp interaction of the CH_2 moiety of ethanol bound to Zn(II) with a Phe residue, which may suggest a possible pathway for the hydride transfer to NAD [160, 161].

Close proximity of an alkyl side chain at the type 1 copper site of laccases and domain 2 of ceruloplasmin may be interesting in view of the influence of the molecular environment on the metal site of proteins. The Cu site of these proteins is formed by two His imidazoles and a Cys thiolate, and a branched alkyl group of Leu occupies the position above the trigonal plane with the Cu···C distance of 3.71 Å for ceruloplasmin (Figure 22) [162]. It has a very high redox potential as compared with that of the blue copper proteins and oxidases with a 2N2S-donor distorted tetrahedral structure. Although the alkyl side chain is not considered as a ligand to the Cu ion, the rather short Cu···alkyl distance suggests certain noncovalent interactions which could affect the properties of the central ion. As structural models for the active site, Cu(II) and Pd(II) complexes of 3N-donor ligands with a branched alkyl side chain have been synthesised and revealed to have a structure as shown for a Pd(II) complex in Figure 23, where the methyl group (C(4)) is located above the coordination plane with the metal−C(4) distances of 3.30–3.35 Å [163]. The ^{1}H NMR spectra indicated that the conformation with the methyl group above the Pd(II) plane is maintained in solution, and the down-field shifts of the signals were larger in solvents with a lower dielectric constant. Considering that the ligand side chain is flexible and can be extended outward in less polar solvents, these observations indicate that the metal−alkyl contact is considered to be a weak bonding interaction of electrostatic nature. A similar Cu−alkyl contact has been reported for the Cu(II) complex of an ephedrine derivative [164]. The M−H−C angles observed for these complexes are greater than 100°, and the interactions may be classified as hydrogen bonds and not agostic bonds [165]. An interesting property probably arising from the interaction is that the Cu redox potentials of the complexes with the Cu−alkyl contact were more positive than those of the complexes without the contact, which suggests that the electron density is decreased due to the Cu···H−C interaction [163]. These observations suggest that the Cu sites of laccase, etc., with an alkyl side chain in close proximity, may also have a decreased electron density.

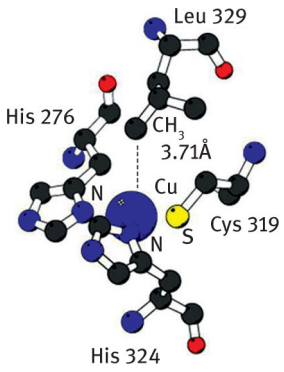

Figure 22: Cu···alkyl close contact at the type I Cu site of ceruloplasmin (PDB code: 2J5W) [162]. Reproduced from ref. [129] by the courtesy of Asakura Publishing, Tokyo, Japan.

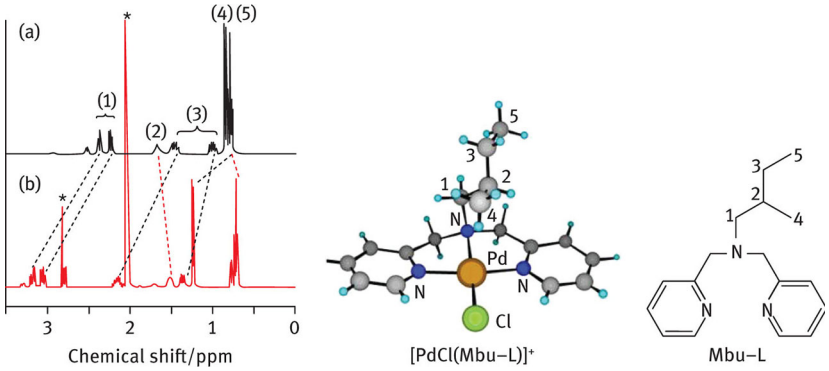

Figure 23: Behaviour of the branched alkyl side chain in a Pd(II) complex [163]. (a) ^{1}H NMR spectra: (a) ligand Mbu-L; (b) Pd(II)−Mbu-L complex. (b) Structures of Mbu-L and its Pd(II) complex.

4 Concluding remarks

Noncovalent interactions have long been recognised in chemistry, but in the past they seem to have been mostly behind the scenes in part due to the difficulty of detection and evaluation. With deeper insights into noncovalent interactions around the metal centre in the field of bioinorganic chemistry, their importance is now well recognised, and without the knowledge of the interactions, it is impossible to fully understand and control chemical and biological reactions. The chemistry of biocomplexes sup-ported by information on noncovalent interactions will play essential roles in elucidation of biological systems involving metal ions.

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Notes

1 The ionic strength (I) of the solutions was not adjusted (I = var.).
2 I = 0.1 M (NaClO4).

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