

Study of the probable reason why Ni(II) is excluded from metalloenzymes

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Abstract. The formation constants of the complexes of the type $[\text{NiAL}]$, where $A = 2,2'$ -bipyridyl, 1,10-phenanthroline, 2-(2'-pyridyl) benzimidazole, or 2-(2'-pyridyl) imidazoline and $L =$ ethylenediamine, 1,2-diaminopropane, N -methyl-ethylenediamine, glycine, α -alanine, β -alanine, malonate, histidine, or histamine have been determined in dioxan-water (1:1 v/v) medium and $\mu = 0.2 \text{ mol dm}^{-3} \text{ NaClO}_4$ at 30°C . The values of $\Delta \log K_M$ ($\log K_{MAL}^M - \log K_{ML}^M$) in Ni(II) complexes have been compared with corresponding Cu(II) complexes. It is observed that for $[\text{NiAL}]$ complexes, where $L = L^1$ to L^7 , $\Delta \log K$ is more negative than for the corresponding $[\text{CuAL}]$ complexes whereas in cases where $L = L^8$, or L^9 , $\Delta \log K$ for Ni(II) complexes is less negative than for the corresponding Cu(II) complexes. The reason has been discussed.

Keywords. Mixed-ligand complexes with histidine; mixed-ligand complexes with histamine; complexes with heteroaromatic N-bases; mixed-ligand complexes of Ni(II).

1. Introduction

It has been observed (Sigel 1967; Bhattacharya and Chidambaram 1970; Griesser and Sigel 1970) that in the complexes $[\text{CuA}]$, where $A = 2,2'$ -bipyridyl or 1,10-phenanthroline, there is $\text{Cu} \rightarrow A$ π interaction, resulting in the increase in class A character of Cu(II) in $[\text{CuA}]$, with consequent discriminating behaviour of $[\text{CuA}]$ for the ligands with $\text{N}-\text{N}$, $\text{O}^- - \text{N}$ and $\text{O}^- - \text{O}^-$ coordination (Griesser and Sigel 1970; Sigel 1980; Prijs and Sigel 1975; Bhattacharya *et al* 1982a). There is maximum stabilization of $[\text{CuA O}^- - \text{O}^-]$ complexes. This has been ascribed to the increase in class A character of $[\text{CuA}]$ (Griesser and Sigel 1970) in the ternary complexes, with consequent release of repulsion between metal ion $d\pi$ electrons and the lone pairs of electrons over the O^- of the ligands (Bhattacharya *et al* 1982b).

Kruck and Sarkar (1973) and Bhattacharya and Patel (1984) observed that Cu(II) forms two types of complexes with histidine in aqueous medium, $[\text{Cu}(\text{H. Hist})]$ with coordination from the amino carboxylate end, the imidazole nitrogen being free and protonated, and $[\text{Cu}(\text{Hist})]$, with coordination from the amino nitrogen, the imidazole nitrogen and carboxylate. At very low pH i.e. $1.8 \sim 3.2$, there is formation of a $[\text{Cu}(\text{H. Hist})]$ species involving glycine-like coordination and the imidazole nitrogen remains protonated. At pH 4.1–6.0, there is coordination of the second histidinate moiety Hist or H. Hist respectively, resulting in the formation of $[\text{Cu}(\text{Hist})(\text{H. Hist})]$, where one tridentate histidine molecule binds to Cu(II) through

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the imidazole nitrogen, amine nitrogen and carboxylate, and another histidine molecule binds like glycine i.e. through the amino nitrogen and carboxyl oxygen, the imidazole nitrogen remaining free and protonated. At still higher pH there is formation of $[\text{Cu}(\text{Hist})_2]$ with two tridentate histidines.

In ternary complexes of Cu(II) containing aromatic tertiary amines A and histidine, both $[\text{CuA}(\text{H.Hist})]$ and $[\text{CuA}(\text{Hist})]$ species are formed in aqueous medium (Bhattacharya *et al* 1984), and $\Delta \log K$ is less negative for $\text{O}^- - \text{N}$ coordinating $[\text{CuA}(\text{H.Hist})]$ species and more negative for $\text{N} - \text{N}$ coordinating $[\text{CuA}(\text{Hist})]$ species.

Histidine is known to coordinate with Ni(II) only as a tridentate ligand through the imidazole nitrogen, amino nitrogen and carboxylate, forming $[\text{NiL}]$ and $[\text{NiL}_2]$ species (Fraser and Harding 1967; Grant and Led 1977).

It is interesting to study the formation constants of mixed-ligand complexes $[\text{MAL}]$, where $\text{M} = \text{Ni(II)}$, $\text{A} = 2,2'$ -bipyridyl (A^1), 1,10-phenanthroline (A^2), 2-(2'-pyridyl)-benzimidazole (A^3), 2-(2'-pyridyl)imidazoline (A^4) and $\text{L} =$ ethylenediamine (L^1), 1,2-diaminopropane (L^2), *N*-methylethylenediamine (L^3), glycine (L^4), α -alanine (L^5), β -alanine (L^6), malonate (L^7), histidine (L^8), or histamine (L^9). In order to compare the stabilities of the ternary complexes with those of Cu(II), the formation constants of the mixed-ligand complexes $[\text{CuAL}]$, where $\text{L} = \text{L}^1$ to L^7 , have been taken from our earlier work (Bhattacharya *et al* 1982a). For $[\text{CuAL}]$ complexes where $\text{L} = \text{L}^8$, or L^9 , the formation constants are known in aqueous medium (Bhattacharya *et al* 1984) but the values were redetermined in 50% dioxan-water (1:1 v/v) medium, for comparison with Ni(II) complexes under identical conditions.

2. Experimental

All reagents used were of AR grade, except 2-(2'-pyridyl)-benzimidazole and 2-(2'-pyridyl)imidazoline, which were prepared by known methods (Freiser and Walter 1954).

The proton-ligand and metal-ligand formation constants were determined by normal Irving-Rossotti titration techniques (Irving and Rossotti 1953, 1954). The titrations were carried out on solutions containing Ni(II):A:L in 1:1:1 and 1:1:10 ratio, for mixed-ligand complexes $[\text{NiAL}]$ where, $\text{L} = \text{L}^1 - \text{L}^7$, to determine formation constants $\log K_{\text{NiAL}}^{\text{NiA}}$ and $\log K_{\text{NiAL}_2}^{\text{NiA}}$ by using an extension of the Irving-Rossotti technique (Bhattacharya and Chidambaram 1970). In mixed-ligand complexes $[\text{NiAL}]$, where $\text{L} = \text{L}^8$, or L^9 , only the species $[\text{NiAL}]$ is formed with coordination through imidazole and the amino nitrogen and hence, the formation constant of the species $[\text{NiAL}]$ was determined.

The values of proto-ligand and binary metal-ligand formation constants were subjected to refinement by using the computer program scogs (Sayce 1968, 1971; Sayce and Sharma 1972) as discussed earlier (Bhattacharya *et al* 1982a), and the values are given in table 1. The refinement was carried out in two ways by considering

(i) species present in the solution to be LH_2 , LH , L , $[\text{NiA}]$ and $[\text{NiAL}]$ and $[\text{NiAL}_2]$, where $\text{L} = \text{L}^1$ to L^7 ,

(ii) all possible species present in the solution i.e. LH_2 , LH , L , AH_2 , AH , A , $[\text{NiL}]$, $[\text{NiL}_2]$, $[\text{NiL}_3]$, $[\text{NiA}]$, $[\text{NiA}_2]$, $[\text{NiAL}]$ and $[\text{NiAL}_2]$, where $\text{L} = \text{L}^1$ to L^7 .

In $[\text{NiAL}]$ complexes, where $\text{L} = \text{L}^8$, or L^9 , formation of $[\text{NiAL}_2]$ species was not

Table 1. Proton-ligand and binary-complex formation constants of nickel (II) in 50% dioxan-water (1:1 v/v) medium, with 0.2 M NaClO₄, and at 30°C, refined by computer method, with standard deviation $\sigma\beta$ in parentheses.

Ligand	Proton-ligand formation constants			Binary complex formation constants		
	K_1^H	K_2^H	K_3^H	$\log K_{NiL}^{Ni}$	$\log K_{NiL_2}^{NiL}$	$\log K_{NiL_3}^{NiL_2}$
L ¹	9.72 (0.03)	6.98 (0.04)	—	8.83 (0.08)	7.34 (0.13)	7.26 (0.18)
L ²	9.26 (0.03)	6.35 (0.03)	—	8.94 (0.12)	7.03 (0.11)	5.92 (0.15)
L ³	9.64 (0.03)	6.89 (0.04)	—	7.58 (0.10)	6.23 (0.09)	4.38 (0.16)
L ⁴	9.71 (0.01)	3.29 (0.01)	—	7.27 (0.07)	5.70 (0.08)	4.57 (0.10)
L ⁵	9.43 (0.01)	3.38 (0.01)	—	6.28 (0.08)	5.14 (0.08)	4.58 (0.10)
L ⁶	9.81 (0.04)	4.48 (0.00)	—	5.90 (0.10)	4.21 (0.10)	2.36 (0.26)
L ⁷	7.09 (0.07)	4.20 (0.10)	—	7.27 (0.11)	6.60 (0.10)	3.29 (0.20)
L ⁸	9.14 (0.07)	5.90 (0.10)	2.93 (0.10)	10.19 (0.06)	7.93 (0.09)	—
L ⁹	9.47 (0.06)	5.62 (0.08)	—	6.99 (0.08)	4.76 (0.20)	3.48 (0.30)

considered, because this did not lead to convergence in computer calculations. This is probably because of steric hindrance, and hence the species considered were LH₃, LH₂, LH, L, [NiA] and [NiAL] in the first computer method and LH₃, LH₂, LH, L, AH₂, AH, A, [NiA], [NiA₂], [NiL], [NiL₂] and [NiAL] in the second.

In binary Cu(II)-histidine complexes, in 50% dioxan-water (1:1 v/v) medium, the species [CuL], [CuLH], [CuL(LH)] and [CuL₂] were considered to be formed and convergence was obtained. However, in the ternary system, in 50% dioxan-water (1:1 v/v) medium, no protonated mixed-ligand species [CuA(LH)] was considered unlike in aqueous medium (Bhattacharya *et al* 1984), because protonated species do not lead to convergence. The non-existence of the species [CuA(LH)] may be because in dioxan-water medium, the protonation of the imidazole nitrogen is weak and hence the proton dissociates in the lower pH range. Hence, histidine coordinates with [CuA] through the imidazole nitrogen and the amino nitrogen resulting in the formation of [CuAL]. The formation constant of [CuAL] was determined by the two computer methods considering the same species as in Ni(II) complexes. The values are reported in table 2.

3. Results and discussion

It is interesting to observe that in ternary complexes of Ni(II), the value of the mixed-ligand formation constant $\log K_{NiAL}^{NiA}$ obtained by the first computer method, assuming

Table 2. Binary complex formation constants of copper(II) in 50% dioxan-water (1:1 v/v) medium, with 0.2 M NaClO₄ and at 30°C, refined by the computer method, with standard deviation 6β in parentheses.

Binary complex formation constants of Cu(II)				
Ligand	$\log K_{\text{CuLH}}^{\text{Cu}}$	$\log K_{\text{CuL}}^{\text{Cu}}$	$\log K_{\text{CuL(LH)}}^{\text{CuL}}$	$\log K_{\text{CuL}_2}^{\text{CuL}}$
L ⁸	9.94 (0.10)	11.43 (0.04)	8.28 (0.20)	8.15 (0.03)
L ⁹	—	9.97 (0.30)	—	8.54 (0.50)

Note: For ligand L = L¹ to L⁷ see Bhattacharya *et al* (1982a).

the formation of the complex in steps, $\text{Ni} + \text{A} \rightleftharpoons [\text{NiA}]$ and $[\text{NiA}] + \text{L} \rightleftharpoons [\text{NiAL}]$, and the value obtained by the second computer method, assuming simultaneous coordination of A and L, are nearly equal. This shows that $[\text{NiA}]$ formation is almost complete in the lower pH range and in the higher pH range L combines with $[\text{NiA}]$ forming $[\text{NiAL}]$.

This is further confirmed by observing the concentrations of various species (as percentages of the total Ni(II) present) against pH in the second computer method. In the system $[\text{NiA}^1\text{L}^1]$, at the lower pH, Ni(II) and $[\text{NiA}^1]$ are the major species. After this the formation of $[\text{NiA}^1\text{L}^1]$ starts, which is maximum at pH 6.0 (61.0%), after which it decreases and the formation of $[\text{NiA}^1\text{L}^1_2]$ increases and reaches maximum (46.0%) at pH 6.7. In $[\text{NiA}^1\text{L}^4]$, the maximum percentage of the mixed-ligand complex is 62.0% at pH 6.9, after which formation of $[\text{NiA}^1\text{L}^4_2]$ increases and reaches a maximum (21.0%) at pH 8.2. In $[\text{NiA}^1\text{L}^7]$, the maximum percentage of mixed-ligand is 61.0% at pH 5.6. In $[\text{NiA}^1\text{L}^8]$, the maximum percentage of the mixed-ligand complex is 67.0% at pH 6.5, $[\text{NiA}^1]$ is 14.0%, $[\text{NiL}]$ 6.0%, and $[\text{NiL}_2]$ 13.0% at the same pH, the total being almost 100%. In $[\text{NiA}^1\text{L}^9]$, the maximum percentage of the mixed-ligand complex is 88.0% at pH 9.5.

The value of $\log K_{\text{NiAL}_2}^{\text{NiA}}$ obtained from the data of the 1:1:10 solution using the first computer method does not agree with that obtained by the second method. This is because $[\text{NiAL}_2]$ is formed at higher pH and formation of $[\text{NiL}_3]$ starts in this range. Thus, the reaction mixture does not only contain the complex species $[\text{NiA}^1]$, $[\text{NiAL}]$ and $[\text{NiAL}_2]$ as considered by the first method. A reliable value of $\log K_{\text{NiAL}_2}^{\text{NiA}}$ is obtained by the second method which considers all the possible species formed i.e. $[\text{NiA}]$, $[\text{NiA}_2]$, $[\text{NiL}]$, $[\text{NiL}_2]$, $[\text{NiL}_3]$, $[\text{NiAL}]$ and $[\text{NiAL}_2]$.

Since values obtained by the second method are more precise, they have been presented in table 4 for $\log K_{\text{NiAL}}^{\text{NiA}}$ (L = L¹ to L⁹) and $\log K_{\text{NiAL}_2}^{\text{NiA}}$ (L = L¹ to L⁷) and these have been used to interpret the data. This table also includes $\Delta \log K_{\text{M}}$ ($\log K_{\text{MAL}}^{\text{MA}} - \log K_{\text{ML}}^{\text{M}}$) for Ni(II) complexes. $\Delta \log K_{\text{M}}$ for Cu(II) complexes are also included from our earlier work (Bhattacharya *et al* 1982a) for ligands L = L¹ to L⁷, and from the present work for L = L⁸, or L⁹, for comparison.

The formation constant values show that in the complex $[\text{NiAL}]$, where L coordinates through two nitrogen atoms (L¹, L², and L³) or one nitrogen and one O⁻ (L⁴, L⁵, and L⁶), $\Delta \log K_{\text{Ni}} (\log K_{\text{NiAL}}^{\text{NiA}} - \log K_{\text{NiL}}^{\text{Ni}})$ has a negative value. In cases where L

Table 3. Ternary complex formation constants of copper(II) in 50% dioxan-water (1:1 v/v) medium with 0.2 M NaClO₄ and at 30°C refined by computer method, with standard deviation $\sigma\beta$ in parentheses.

Ligand	$\log K_{\text{CuAL}}^{\text{CuA}}$			
	A ¹	A ²	A ³	A ⁴
L ⁸	8.80 (0.10)	8.89 (0.10)	9.33 (0.20)	9.10 (0.20)
L ⁹	8.79 (0.01)	7.99 (0.01)	9.09 (0.08)	7.38 (0.07)

Note: For L = L¹ to L⁷ see Bhattacharya *et al* (1982a).

has two O⁻ as coordinating sites like malonate (L⁷), and A = A¹, A², or A⁴, $\Delta \log K_{\text{Ni}}$ is negative, though less than N-N or O⁻-N coordinating ligands in [NiAL] complexes. In the [NiA³L⁷] complex, $\Delta \log K$ is positive. Thus, there is a statistical stabilization of ternary Ni(II) complex though not to the same extent as that in Cu(II) complexes (Bhattacharya *et al* 1982a). This can be explained as in Cu(II) complexes, by considering M → Aπ interaction. The stabilization of ternary complexes is in the increasing order of M → Aπ interaction as observed in Cu(II) complexes. The order of formation constants of ternary complexes is



It is interesting to observe that in [NiA³O⁻-O⁻] complexes $\Delta \log K$ is positive, because the Ni → A³π interaction is maximum. This is perhaps the first case of a positive $\Delta \log K$ observed in Ni(II) complexes.

[NiA] complexes also discriminate the ligand L in the order O⁻-O⁻ > O⁻-N > N-N, though not to the same extent as in [CuA]. This can be explained as in Cu(II) complexes, in terms of release of electron repulsion in the ternary complex. The release in repulsion is maximum in a O⁻-O⁻ ligand with lone pairs of electrons over the two O⁻. The release in repulsion is less in O⁻-N with the lone pair electrons only over O⁻. The effect is absent in N-N coordinating ligand with no lone pair electrons over the N atoms.

In [MAL] complexes, where M = Cu(II), or Ni(II) and L = L⁸, or L⁹, $\Delta \log K$ is negative as expected for a N-N coordinating ligand.

It is generally observed that $\Delta \log K_{\text{M}} (\log K_{\text{MAL}}^{\text{MA}} - \log K_{\text{ML}}^{\text{M}})$ for Cu(II) complexes is less negative than that for Ni(II) complexes for the same ligand L (table 4). This has been explained as due to the Jahn-Teller distortion (Griesser and Sigel 1970). This is true when L = aliphatic ligands L¹ to L⁷. But in cases of [NiAL] complexes, where L = L⁸, or L⁹, coordinating through two tertiary nitrogens, $\Delta \log K$ for Ni(II) complexes is less negative than Cu(II) complexes (table 4). This leads us to the conclusion that in [M(Hist)] with tridentate histidine, the tridentate ligand is in an equatorial plane. In [MA(Hist)] complexes however, A occupies two equatorial positions and hence histidine has to occupy two equatorial and one axial position. In [CuA(Hist)] complexes axial coordination will be weak due to the Jahn-Teller effect and hence the ternary complex is less stable. In Ni(II) complex, there is no destabilization in occupying

L ⁶ a	5.25 (0.04)	-0.65	-0.71	4.95 (0.03)	-0.95	-0.83	5.34 (0.10)	-0.56	-0.23	4.70 (0.01)	-1.20	-1.01
b	3.62 (0.05)	—	—	2.79 (0.04)	—	—	—	—	—	—	—	—
L ⁷ a	6.64 (0.18)	-0.63	+0.48	6.55 (0.09)	-0.72	+0.48	7.38 (0.12)	+0.11	+0.72	6.15 (0.08)	-1.12	-0.34
b	4.71 (0.11)	—	—	4.73 (0.06)	—	—	—	—	—	—	—	—
L ⁸ a	8.35 (0.10)	-1.84	-2.63	7.93 (0.10)	-2.26	-2.54	8.61 (0.10)	-1.58	-2.10	7.23 (0.20)	-2.96	-2.33
b	—	—	—	—	—	—	—	—	—	—	—	—
L ⁹ a	5.87 (0.10)	-1.12	-1.18	6.03 (0.10)	-0.96	-1.98	6.20 (0.40)	-0.79	-0.88	5.65 (0.40)	-1.34	-2.59
b	—	—	—	—	—	—	—	—	—	—	—	—

* For L = L¹ to L⁷ refer Bhattacharya *et al* (1982) and for L = L⁸ or L⁹ see text.

the axial position and hence $\Delta \log K$ for Ni(II) complexes is less negative than that of Cu(II) complexes (Bhattacharya *et al* 1973, 1977).

However, in [MA (histamine)] system also $\Delta \log K$ for Ni(II) is less negative than the corresponding Cu(II) complexes, though histamine is bidentate and can occupy two equatorial positions in both $[\text{Cu}(\text{histamine})]^{2+}$ and $[\text{CuA}(\text{histamine})]^{2+}$. The probable reason could be that as in $[\text{Cu}(\text{bipy})_2(\text{H}_2\text{O})_2]$, complexes with *cis* distorted structure (Sigel 1972), and the $[\text{Cu}(\text{Hist})_2]$ complex with one ligand having a histidine type of coordination in an equatorial plane and another having a histidine type N-N coordination, one in the equatorial and the other in the axial position, $[\text{Cu}(\text{bipy})\text{L}(\text{H}_2\text{O})_2]$ (L = histidine or histamine coordinating through two tertiary nitrogens as in bipyridyl), also has a *cis* distorted structure. Hence, in the formation of $[\text{Cu}(\text{bipy})(\text{Hist})]$ from $[\text{Cu}(\text{bipy})(\text{H}_2\text{O})_2]$, histidine gets coordinated at two equatorial positions (O-N) and one axial position through the imidazole N. In $[\text{CuA}(\text{histamine})]$ also the histamine nitrogens occupy one equatorial and one axial position. Due to Jahn-Teller effect, the ligand L is strained and the value of $\log K_{\text{CuA}/\text{CuAL}}$ is lowered, resulting in more negative $\Delta \log K$ values. In Ni(II) complexes, there is no Jahn-Teller distortion and hence L is not strained in the formation of *cis* $[\text{Ni}(\text{bipy})\text{L}]$ and $\Delta \log K$ is less negative than in Cu(II) complexes.

Thus, Cu(II) bound to a tertiary amine does not prefer to coordinate with another tertiary amine molecule, but prefers to coordinate with $\text{O}^- - \text{N}$ or $\text{O}^- - \text{O}^-$ ligands. However, Ni(II) bound to a tertiary amine molecule does not resist combination with another tertiary amine molecule. Further, $[\text{Ni}(\text{tertiary amine})]$ also has a lesser tendency to coordinate with $\text{O}^- - \text{N}$ or $\text{O}^- - \text{O}^-$ ligands.

This may be extended as the probable reason for Cu(II) occurring in biological systems forming ternary complexes involving coordination of tertiary amine (imidazole, histidine, or histamine) and amino or peptide ($\text{O}^- - \text{N}$) or phenolate ($\text{O}^- - \text{O}^-$). But Ni(II) prefers to form $[\text{Ni}(\text{tertiary amine})_2]$ and hence has a lesser tendency to form $[\text{Ni}(\text{tertiary amine})\text{O}^- - \text{N}]$ or $[\text{Ni}(\text{tertiary amine})\text{O}^- - \text{O}^-]$ type of complexes. Hence, Ni(II) has a lesser probability of occurring in metalloenzymes involving imidazole type ligands and $\text{O}^- - \text{N}$ or $\text{O}^- - \text{O}^-$ coordinating ligands.

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