*Inorganica Chimica Acta*, 46 (1980) 205–210



# Copper(III) and Nickel(III) Complexes of Tripeptides, Dipeptide Schiff Bases and Related Ligands

TAKESHI SAKURAI, JUN-ICHI HONGO, AKITSUGU NAKAHARA
*Institute of Chemistry, College of General Education, Osaka University, Toyonaka, Osaka 560, Japan*
and YASUO NAKAO
*Chemical Laboratory, Faculty of Education, Okayama University, Okayama 700, Japan*

Received February 27, 1980

*Trivalent copper and nickel complexes of tripeptides, dipeptide Schiff bases and related ligands were comparatively studied by cyclic voltammetry. Depending upon the nature of the coordinated groups and the structure of fused ring systems the electrode potentials of Cu(III)–Cu(II) and Ni(III)–Ni(II) couples vary in the range 0.7–1.4 V. The stronger donating groups such as amino and deprotonated amide nitrogens assist the stabilizing of metal ions in the higher oxidation state, although aromatic nitrogen and oxygen do not contribute effectively for this. The trivalent copper and nickel with smaller ionic radii are stabilized by the 5-5-5 but not by the 5-6-5 or 6-5-6 fused ring structure as in bivalent copper and nickel. These redox characters were related with ESR and the absorption spectral feature of parent and trivalent metal complexes.*

## Introduction

It is known that the type I copper ions behave as electron carriers by transforming their oxidation state either into bivalent or monovalent, whereas most type II copper ions have been believed to be exclusively bivalent even in the course of the catalytic cycles [1]. However, Hamilton *et al.* [2] recently suggested that the copper ion in galactose oxidase is in trivalent state in the oxidized form. This proposal seems enchanting in comparison with the idea that type II copper merely participates as an electron carrier in the living systems. Pioneering works on copper(III) [3] and nickel(III) [4] by Margerum *et al.* presented the stabilization of the central metal ions in the high oxidation state by various peptides. However, chemistry of trivalent copper and nickel ions remains unfamiliar yet and awaits much wider and profound research. This paper deals with redox chemistry of copper and nickel complexes of tripeptides, dipeptide Schiff bases and related compounds. Oxidation–reduction property of copper and nickel complexes is comparatively discussed in view of ligating groups and the structure of fused chelate ring systems.

## Experimental

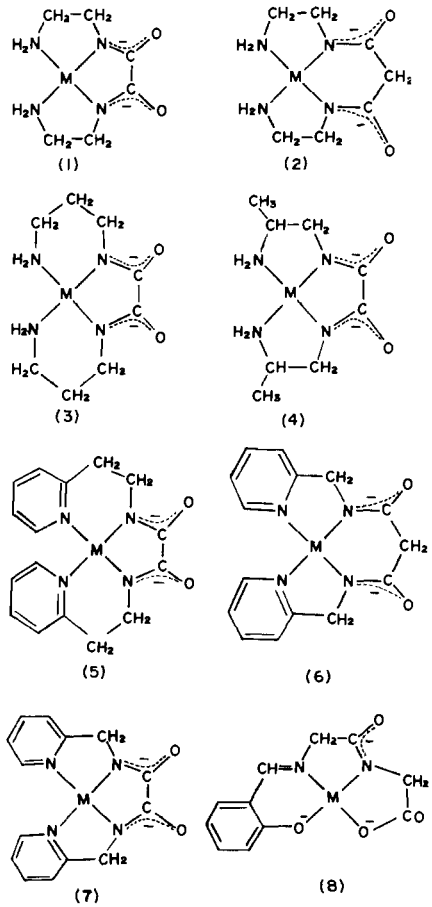
### *Materials*

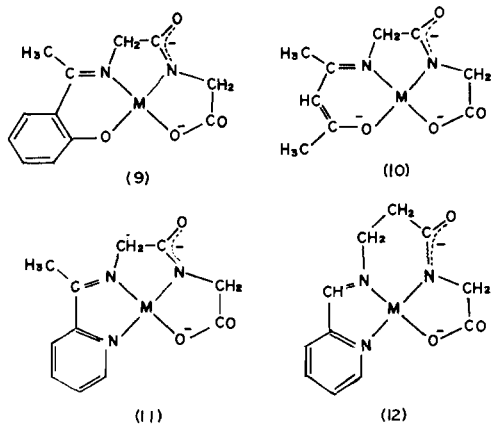
Glycylglycine(GG), glycylglycylglycine(GGG) and glycylglycyl-L-histidine(GGH) were purchased from the Protein Research Foundation. Following compounds were prepared by the methods reported in previous papers [5]: Glycylglycyl-L-alanine(GGA), glycyl-L-alanylglycine(GAG), L-alanylglycylglycine(AGG), glycylglycyl-β-alanine(GGβ-A), β-alanylglycylglycine(β-AGG), glycyl-L-alanine(GA), L-alanylglycine(AG), glycyl-β-alanine(Gβ-A), glycyl-L-asparagine(GAsn), α-aminoisobutyrylglycine(α-AibG). Glycylglycyl-L-valine(GGV) were purchased from Sigma Chemical Co. All other reagents used were of the highest grade available.

### *Preparation of Complexes*

Tripeptide complexes of bivalent metals, Cu(GGG), Cu(GGA), Cu(GAG), Cu(AGG), Cu(GGV), Cu(GGβ-A), Cu(β-AGG), Ni(GGG), Ni(GGA), Ni(GAG), Ni(AGG), Ni(GGV), Ni(GGβ-A) and Ni(β-AGG) were isolated as potassium salt according to the previous method [5]. N,N′-bis(aminoethyl)oxamidato-copper(II) and -nickel(II)-(Cu(AEOA), Ni(AEOA)) (structure 1), N,N′-bis(aminoethyl)malonamidato-copper(II) and -nickel(II) (Cu(AEMA), Ni(AEMA)) (2), N,N′-bis(3-aminopropyl)oxamidato-copper(II) and -nickel(II)(Cu((3-APOA), Ni(3-APOA)) (3), N,N′-bis(2-aminopropyl)-oxamidato-copper(II) and nickel(II) (Cu(2-APOA), Ni(2-APOA)) (4), N,N′-bis(pyridylethyl)oxamidato-copper(II) (Cu(PyEOA) (5), N,N′-bis(pyridylmethyl) malonamidato-copper(II) and -nickel(II) (Cu-(PyMMA)Ni(PyMMA)) (6) and N,N′-bis(pyridylmethyl)oxamidato-copper(II) (Cu(PyMOA)) (7) were

prepared by the reactions of freshly precipitated copper(II) or nickel(II) hydroxide with the condensation products of appropriate amines and diethyloxalate or diethylmalonate according to the method of Ojima *et al.* [6]. The following Schiff base complexes were synthesized as potassium salts by the method in the previous papers [5]: Salicylideneglycylglycinato-cuprate(II) and -nickelate(II) (Cu(Sal = GG), Ni(Sal = GG)) (8), salicylideneglycyl-L-alanininato-cuprate(II) and -nickelate(II) (Cu(Sal = GA), Ni(Sal = GA)), salicylidene-L-alanylglycinato-cuprate(II) and -nickelate(II)(Cu(Sal = AG), Ni(Sal = AG)), salicylideneglycyl-β-alaninatonickelate(II) (Ni (Sal = Gβ-A)), salicylideneglycyl-L-asparaginato-nickelate(II) (Ni(Sal = GAsn)), copper(II) complex of the Schiff base derived from *o*-hydroxyacetophenone and GG, (Cu(acph = GG)) (9), copper(II) complex of the Schiff base from acetylacetone and GG, (Cu(acac = GG)) (10), copper(II) and nickel(II) complexes of the Schiff base from 2-acetylpyridine and GG, (Cu(acpy = GG), Ni(acpy = GG)) (11), nickel(II) complex of the Schiff base from 2-pyridinecarbaldehyde and β-alanylglycine, (Ni(pyal = β-AG)) (12) and nickel(II) complex of the Schiff base from 2-pyridinecarbaldehyde and α-AibG, (Ni(pyal = α-AibG)).




*Measurements*

Cyclic voltammetry was performed at 20 °C with a three-electrode system consisting a glassy carbon electrode, a platinum auxiliary electrode and a standard caromel reference electrode. Voltammograms were generated using a Yanagimoto P-1000 voltammetric analyzer and an NF FG-121B function generator and recorded on a National VP-6421U X–Y recorder for solutions of complexes ($5 \times 10^{-3}$ *M*, $I = 0.1$ ($NaClO_4$)) at pHs *ca.* 8 and 11. $E^0$ values were determined as the midpoints between the peak potentials.

The ESR spectra of the Cu(II) complexes and Ni(III) complexes were measured at 77 K using a JEOL-FX-1 X-band ESR spectrometer modulated at 100 kHz. Nickel(III) species were prepared by oxidation of the corresponding nickel(II) complexes with $Na_2S_2O_8$ or $Na_2IrCl_6$ and the solutions were immediately frozen in liquid nitrogen. The *g* values were determined by taking Li·TCNQ ($g = 2.0025$) as a standard, and the magnetic fields were calculated by the splitting of Mn(II) in MnO ($\Delta H_{3-4} = 86.9$ G).

Visible measurements were obtained on a Union Giken SM-401 spectrometer. A Hitachi-Horiba pH meter F-7 was used for pH measurements.

## Results and Discussion

Figure 1 shows the cyclic voltammogram of Cu(AEOA) as an example for the copper complexes. The separation of the anodic and cathodic peaks was 90 mV, indicating that the reaction is quasi-reversible. The other copper complexes except those of the Schiff bases exhibited the separation of anodic and cathodic peaks of 70–140 mV and ratios of the anodic to cathodic peak of near unity. Table I lists the standard electrode potentials, $E^0$ (*vs.* NHE) determined for a series of Cu(III)–Cu(II) couples. Since the Schiff base complexes exhibit rather ambiguous reduction waves (positive currents), only

TABLE I. Properties of the Copper Complexes.

| Complex | $E^0$ (NHE), V | Cu(II) Parent Species | | | |
|---|---|---|---|---|---|
| | | $\lambda_{max}$, nm | $g_{\parallel}$ | $g_{\perp}$ | $\|A_{\parallel}\|$, G |
| Cu(AEMA) | 0.95 | 520 | 2.18 | 2.06 | 205 |
| Cu(AEOA) | 0.72 | 525 | 2.18 | 2.06 | 200 |
| Cu(3-APOA) | 0.97 | 538 | 2.19 | 2.06 | 200 |
| Cu(2-APOA) | 0.77 | 523 | 2.18 | 2.06 | 200 |
| Cu(PyEOA) | 1.24 | 557 | 2.20 | 2.07 | 194 |
| Cu(PyMMA) | 1.34 | 572 | 2.20 | 2.05 | 199 |
| Cu(Sal=GG) | (1.10)[a] | 576 | 2.21 | 2.06 | 186 |
| Cu(Sal=GA) | (1.05)[a] | 574 | 2.21 | 2.06 | 188 |
| Cu(Sal=AG) | (1.08)[a] | 576 | 2.20 | 2.05 | 183 |
| Cu(acph=GG) | (1.10)[a] | 565 | 2.23 | 2.06 | 184 |
| Cu(acac=GG) | (1.21)[a] | 560 | 2.20 | 2.06 | 196 |
| Cu(acpy=GG) | (1.4)[a] | 580 | 2.21 | 2.07 | 195 |
| Cu(acpy=Gβ-A) | (1.4)[a] | 580 | 2.22 | 2.06 | 194 |
| Cu(acpy=β-AG) | | 567 | 2.21 | 2.07 | 200 |
| Cu(GGG) | 0.91 | 555 | 2.21 | 2.06 | 196 |
| Cu(GGA) | 0.88 | 551 | 2.20 | 2.05 | 196 |
| Cu(GAG) | 0.88 | 548 | 2.20 | 2.05 | 195 |
| Cu(AGG) | 0.87 | 546 | 2.21 | 2.05 | 194 |
| Cu(GGV) | 0.86 | 543 | 2.19 | 2.06 | 205 |
| Cu(GGH) | 0.98 | 525 | 2.17 | 2.06 | 205 |
| Cu(GGβ-A) | 0.94 | 555 | 2.20 | 2.05 | 205 |
| Cu(β-AGG) | 1.02 | 561 | 2.20 | 2.05 | 180 |

[a]Oxidation wave potential.

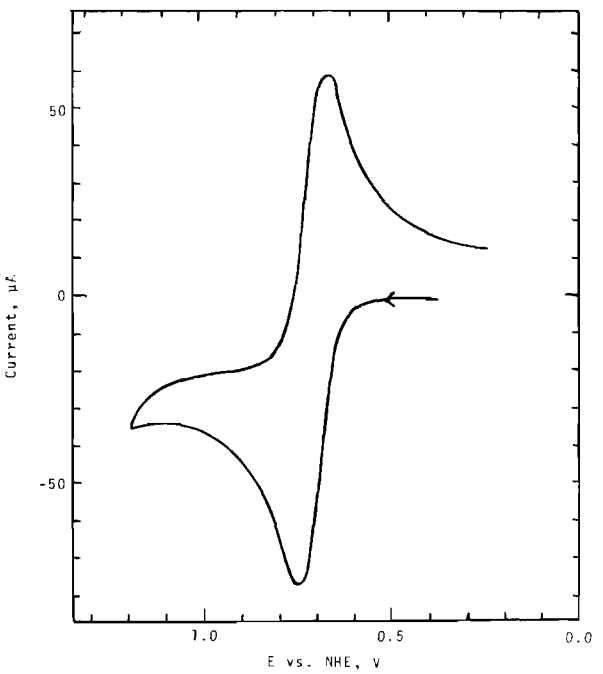



Fig. 1. Cyclic voltammogram of Cu(AEOA) at $5 \times 10^{-3}$ *M* ($I = 0.1$ ($NaClO_4$)), pH 8, 40 mV $s^{-1}$ scan.

oxidation wave potentials are given in Table I. Inspection of Table I reveals that AEOA and 2-APOA, which produce with copper(II) the complexes of 5-5-5 fused chelate ring structure, give much more readily the corresponding Cu(III) complexes comparing with AEMA and 3-APOA, which produce with copper(II) the complexes of 5-6-5 and 6-5-6 fused chelate ring structure, respectively, in spite of the fact that all these ligands contain the same set of donor atoms, two amino and two deprotonated amide nitrogens. The reason why Cu(III) complexes are most stabilized by 5-5-5 fused ring systems can be interpreted on the basis of smaller ionic radius of Cu(III); Cu(II) is stabilized by the greater fused ring systems, such as 5-6-5 or 6-5-6 [5]. The prominent lowering of $E^0$ value by peptides containing α-amino acids [3] might be mostly due to the similar ring size-effect. Copper complexes of GGH, PyEOA and PyMMA which contain aromatic nitrogens are oxidized at rather high potentials, suggesting that aromatic nitrogens do not contribute prominently to stabilize the higher oxidation state of the metal ions on account of the metal to ligand π-back bonding [3]. Incorporation of alanine or valine in place of glycine residue lowers $E^0$ value to some extent through the electron-donating trend due to the C-substituent [3]. Copper(II) ions surrounded by Schiff bases were oxidized at voltages higher than *ca.* 1.05 V. Reduction waves of these complexes did not appear clearly, indicating the occurrence of some rapid fragmentation of ligands by the trivalent copper with potent oxidizing power [7] or of decomposition of

TABLE II. Properties of the Nickel Complexes.

| Complex | $E^0$ (NHE), V | $\lambda_{max}$, nm of Cu(II) Complex | ESR Parameters of Ni(III) Species | | | |
|---|---|---|---|---|---|---|
| | | | $g_{xx}$ | $g_{yy}$ | $g_{zz}$ | $A^N$, G |
| Ni(AEMA) | 0.79 | 454 | 2.21 | 2.23 | 2.01 | |
| Ni(AEOA) | 0.77 | 415 | 2.24 | | 2.01 | |
| | | | 2.23 | 2.18 | 2.02 | 22(t)[d] |
| Ni(3-APOA) | 0.82 | 459 | 2.25 | | 2.01 | |
| Ni(2-APOA) | 0.80 | 414 | 2.24 | | 2.01 | |
| Ni(PyMMA) | 1.08 | 478 | 2.17 | | 2.02 | 22(t) |
| Ni(Sal=GG) | (1.13)[a] 0.75[b] | (430)[c] | 2.23 | | 2.01 | |
| Ni(Sal=GA) | (1.10)[a] 0.75[b] | (430)[c] | 2.24 | | 2.01 | |
| Ni(Sal=AG) | (1.13)[a] 0.70[b] | (440)[c] | 2.23 | | 2.01 | |
| Ni(Sal=Gβ-A) | (0.97)[a] | (420)[c] | 2.25 | | 2.01 | |
| Ni(Sal=GAsn) | (1.03)[a] | (430)[c] | 2.23 | 2.24 | 2.01 | |
| Ni(pyal=β-AG) | (1.24)[a] | (420)[c] | 2.24 | | 2.01 | |
| | | | 2.17 | | 2.02 | 23(t) |
| Ni(pyal=AibG) | (1.19)[a] | (420)[c] | 2.26 | | 2.02 | |
| Ni(acpy=GG) | | (420)[c] | 2.29 | 2.23 | 2.02 | |
| Ni(acpy=GA) | 1.07 | (420)[c] | 2.27 | 2.23 | 2.02 | |
| Ni(GGG) | 0.84 0.66[b] | 430 | 2.24 | 2.29 | 2.01 | |
| | | | 2.17 | | 2.02 | 22(t) |
| | | | 2.14 | | 2.02 | 20(q)[e] |
| Ni(GGA) | 0.85 0.64[b] | 430 | 2.23 | 2.29 | 2.01 | |
| | | | 2.18 | | 2.02 | 22(t) |
| Ni(GAG) | 0.85 0.63[b] | 430 | 2.23 | 2.28 | 2.01 | |
| | | | 2.18 | | 2.02 | 21(t) |
| Ni(AGG) | 0.85 0.64[b] | 430 | 2.24 | 2.30 | 2.01 | |
| | | | 2.17 | | 2.01 | 21(t) |
| | | | 2.14 | | 2.02 | 20(q) |
| Ni(GGV) | 0.89 | 430 | 2.25 | 2.27 | 2.02 | |
| Ni(GGH) | 0.94 0.62[b] | 425 | 2.24 | | 2.01 | |
| Ni(GGβ-A) | 0.95 0.68[b] | 441 | 2.24 | | 2.01 | |
| Ni(β-AGG) | 1.04 0.70[b] | 446 | 2.28 | 2.21 | 2.02 | |

[a]Oxidation wave potential. [b]$E^0$ value of the species appeared only at high pH. [c]Shoulder. [d]Triplet. [e]Quintet.

Schiff bases owing to the inadaptability to the smaller Cu(III) ion.

The $\lambda_{max}$ values for d–d transitions and ESR spectral parameters, $g_{\parallel}$ and $|A_{\parallel}|$, for Cu(II) complexes are also included in Table I. Comparing these values and the corresponding $E^0$ values, it is considered that bivalent copper complexes with smaller $\lambda_{max}$ values, smaller $g_{\parallel}$ and larger $|A_{\parallel}|$ values exhibit greater tendency for affording trivalent copper complexes. The important reason for this is probably the increase of the crystal field stabilization energy accompanied by the oxidation of $d^9$ Cu(II) to $d^8$ Cu(III), which corresponds to the electronic configuration of the planar Ni(II) [3].

Standard electrode potentials of Ni(III)–Ni(II) couples in aqueous solution at pH *ca.* 8 range from 0.8–1.2 V (Table II). The ligand effect on the $E^0$ value is smaller, being well contrasted with that of the corresponding copper complexes. This may be due to the structural rearrangement from the square planar to the tetragonally distorted octahedral geometry as clearly indicated in the ESR spectra (Fig. 2a, Table II). Nevertheless, the $E^0$ values exhibit a correlation with fused ring structure and the kinds of ligating groups similarly to the copper complexes. The AEOA, which has donor groups of two amino and two deprotonated amide nitrogens, most readily gives trivalent Ni complexes with the 5-5-5 fused chelate rings. Aromatic nitrogens and oxygens are unfavorable for stabilizing the Ni(III) state as in the copper complexes. The ease in giving Ni(III) complexes appears to be related to $\lambda_{max}$ values of the d–d transition band of the corresponding Ni(II) complexes, thus the greater the extent of the crystal field stabilization is, the lower the $E^0$ value is.

Most of the Ni(III) complexes except Ni(III) (acpy = GG), Ni(III) (acpy = GA) and Ni(III) (β-AGG) exhibited near axially symmetrical ESR spectra. ESR parameters for the Ni(III) complexes are nearly the same regardless of the kinds of ligands, again suggesting that the tetragonally distorted octa-

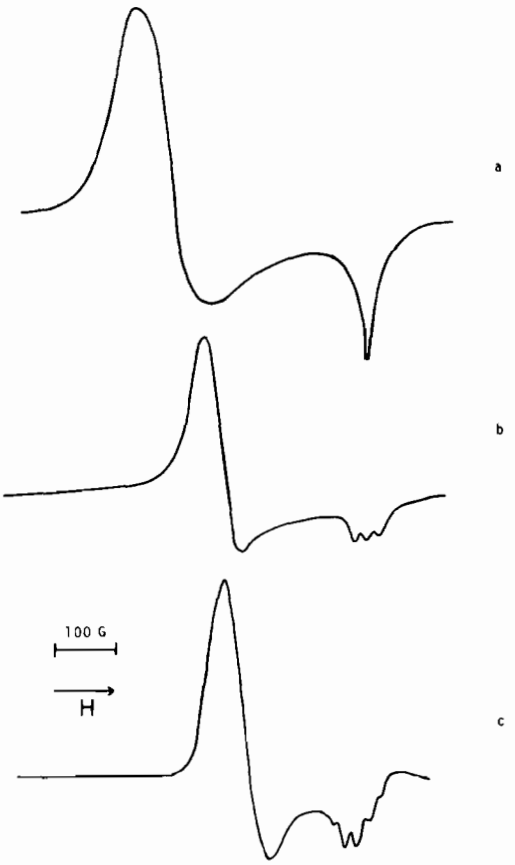



Fig. 2. ESR spectra for Ni(III)(AGG) (a) and peptide fragment adducts (b and c) at 77 K and 9.252 GHz (a), 9.254 GHz (b), 9.254 GHz (c), respectively.

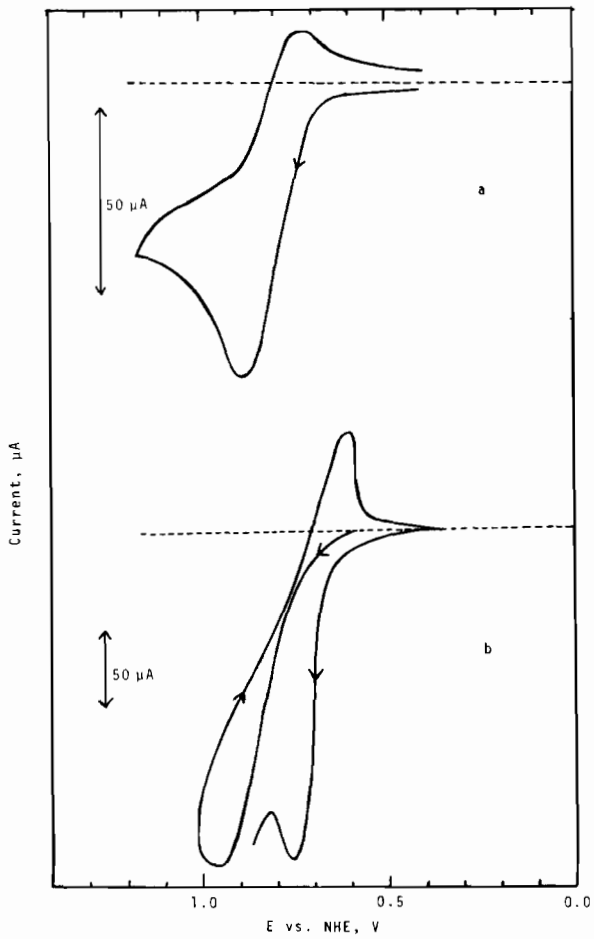



Fig. 3. Cyclic voltammograms of Ni(AGG) at $5 \times 10^{-3}$ *M* (*I* = 0.1($NaClO_4$)), pH 8(a) and pH 12(b), 30 mV $s^{-1}$ scan.

hedral geometry is affected lesser by ligand groups in the equatorial sites. Being accompanied by the oxidation of Ni(II) to Ni(III), most ligands are destroyed [8], and one nitrogen atom ($^{14}N$, I = 1) of the fragment comes in coordination at one of the axial positions, exhibiting three superhyperfine splittings of 1:1:1 intensity in the $g_{zz}$ region and simultaneously a shifting of $g_{\perp}(g_{xx} \cong g_{yy})$ signal in the higher magnetic field region (Fig. 2b) [9]. Succeedingly, another nitrogen atom comes to be coordinated at the other axial position to give $g_{zz}$ peaks with 1:2:3:2:1 intensity and the $g_{\perp}$ values become even smaller (Fig. 2c). The $g_{zz}$ and $g_{average}$ values for the cases with two, one and no axial nitrogens were similar to those reported [10].

It is interesting that in the course of the voltammetric research other reversible oxidation–reduction waves sometimes appeared after the first oxidation of the Ni(II) complexes at high pHs (Fig. 3). The concerned species with lower redox potentials might be compared to those having dimeric or even higher structures, as has sometimes been discovered the formation through the potentiometric titrations [11].

The copper in galactose oxidase was considered to have a donor set of two nitrogens, two oxygens and an axial sulfur atom [12]. However, the ligation of aromatic nitrogen and oxygen does not seem to be favorable for stabilizing Cu(III) state. In addition, axial ligation will weaken the donation of equatorial groups. The above view suggests the difficulty of the copper ions to be in trivalent state. Nevertheless, the $E^0$ values of copper ions in protein might be lowered by the peculiar environment. Hamilton *et al.* [2] indicated that the $E^0$ values of the Cu(III)–Cu(II) couple in galactose oxidase is only 0.44 V, which is the value that cannot be attained in aqueous solution by ligands in this work. Further studies will be required to shed light on this problem. Successful activation of apo galactose oxidase by copper but not by nickel [13] might suggest the presentation of the highly specific environment for Cu(III)–Cu(II) couple in this enzyme.

## Acknowledgements

This work was supported by a grant from the Ministry of Education. The financial support of Takeda Science Foundation is also gratefully acknowledged.

## References

1 B. Reinhammar, in 'Advances in Inorganic Biochemistry', Vol. 1, eds. by G. L. Eichhorn and L. G. Marzilli, Elsevier, North Holland (1979), p. 91.
2 G. A. Hamilton, P. K. Adolf, J. de Jersey, G. C. DuBois, G. R. Dyrkacz and R. D. Libby, *J. Am. Chem. Soc., 100,* 1899 (1978).
3 F. P. Bossu, K. L. Chellappa and D. W. Margerum, *ibid., 99,* 2195 (1977).
4 F. P. Bossu and D. W. Margerum, *Inorg. Chem., 16,* 1210 (1977).
5 (a) Y. Nakao and A. Nakahara, *Bull. Chem. Soc. Jpn., 46,* 187 (1973);
(b) O. Yamauchi, Y. Nakao and A. Nakahara, *ibid., 46,* 2119 (1973) and papers cited therein.
6 (a) H. Ojima and K. Yamada, *Nippon Kagaku Kaishi, 89,* 490 (1968).
(b) *ibid., 91,* 49 (1970).
7 J. L. Kurtz, G. L. Burce and D. W. Margerum, *Inorg. Chem., 17,* 2454 (1978).
8 (a) F. P. Bossu, E. B. Paniago, D. W. Margerum, S. T. Kirksey, Jr. and J. L. Kurtz, *ibid., 17,* 1034 (1978); (b) T. Sakurai and A. Nakahara, *Inorg. Chim. Acta, 34,* L243 (1979).
9 A. G. Lappin, C. K. Murray and D. W. Margerum, *Inorg. Chem., 17,* 1630 (1978).
10 Y. Sugiura and Y. Mino, *ibid., 18,* 1336 (1979).
11 A. Kaneda and A. E. Martell, *J. Coord. Chem., 4,* 137 (1975).
12 A. R. Amundsen, J. Whelan and B. Bosnich, *J. Am. Chem. Soc., 99,* 6730 (1977).
13 D. Amaral, L. Bernstein, D. Morse and B. L. Horecher, *J. Biol. Chem., 238,* 2281 (1963).