Transition Metal Chemistry **29**: 722–727, 2004.

Synthesis, spectra and redox behavior of copper(II) complexes of curcumin diketimines as models for blue copper proteins

James P. Annaraj, Kanagasabai M. Ponvel and Periakaruppan Athappan*
Department of Inorganic Chemistry, Madurai Kamaraj University, Madurai 625 021, India

Sankaran Srinivasan
A&B Labs, 10100, East Freeway, Houston, TX 77015, USA

Received 22 December 2003; accepted 10 February 2004

Abstract

Several new Cu^{II} complexes, having positive reduction potentials in an *in situ* manner, were synthesized by reaction of the Knoevenagel condensate, 4-salicylidene-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (from curcumin) with 4-X-anilines and $CuCl_2$. The solution electronic spectra of these complexes show intense absorption around 530 nm with unusual high extinction values (ε, 1600–3600 M^{-1} cm^{-1}) due to the low symmetry Lπ–dπ (Cu) LMCT transition. The e.s.r. spectral features with $g_{||} > g_{\perp} > 2.0$ having four $g_{||}$ values and a broadening of the $g_{\perp}$ component with moderately low $A_{||}$ (110×10^{-4} cm^{-1}) also suggest a lower symmetry around Cu^{II}. The cyclic voltammetric studies of the Cu^{II} complexes in MeCN show a positive reduction potential ($E_{pc} = 502$–138 mV) with high peak-to-peak separation ($\Delta E_p = 87$–335 mV). The higher ε and low $A_{||}$values together with positive reduction potentials for these Cu^{II} complexes suggest that they can mimic the functional properties of blue copper proteins, but have poor redox stability.

Introduction

Investigations on the coordination chemistry of copper(II) complexes continue to be stimulated due to the interest in developing bio-models for copper proteins and in understanding the factors which give rise to the seemingly infinite variety of distortions from regular geometries [1, 2]. The protein structure imparts a distortion in coordination geometry around the metal ion, which is an important factor in controlling the redox properties of the central metal [3, 4]. The properties of many low molecular weight copper complexes have been examined to determine to what extent both the kinetic and thermodynamic properties of the copper(II/I) redox couple are dependant upon geometry and coordinating atoms [5]. The unusual spectral and redox properties of the central copper(II) in naturally occurring blue copper proteins have been of great fascination to inorganic chemists and in most of the synthetic models having one or more S-donor atoms, copper(II) is known to have a distorted square planar configuration. Synthesis of copper(II) complexes and studying their structure, spectral and redox properties as models for metalloproteins are essential in order to further address the structure–redox relationship. It is therefore of interest to carryout investigations on model compounds [6, 7] to understand how a ligand environment could affect the redox properties of the central metal and, thereby, the spectral properties also. Therefore, to develop synthetic models it becomes necessary to design ligands containing nitrogen and/or sulphur atoms.

β-Diketones, a versatile ligand system, have been long known to form complexes with almost every metal ion and metalloid. Curcumin, the naturally occurring coloring pigment of *Curcuma longa*, is known as an antioxidant, food additive and as an anti-inflammatory agent, and has a diketone moiety with a highly conjugated side chain [8]. Condensation of the active methylene group of the β-diketone with an aldehydic group will give a non-enolisable Knoevenagzel condensate, which can effectively react with amines to form Schiff bases [9]. Such Schiff bases can be synthesized from salicylidenecurcumin and primary amines, which are expected to form stable complexes with transition metals. Since such complexes have not been studied elsewhere, and since curcumin is well known for its medicinal value. We report here the synthesis, spectral and electrochemical characterization of several new curcumin-based copper(II) complexes with a high degree of distortion, which can mimic the functional properties of blue copper proteins [10].

Experimental

Curcumin was obtained from E. Merck and salicylaldehyde from SRL. Other chemicals used were of reagent

* Author for correspondence

grade. Solvents were double distilled. N.m.r. measurements were made on a BRUKER 300 MHz spectrometer. Deuteriated organic solvents along with tetramethylsilane (TMS) as the internal standard were used. The u.v.–vis. spectra were recorded on a Shimatzu UV-160 spectrophotometer in MeCN. The i.r. spectra were recorded on a JASCO FT-IR 410 spectrophotometer using KBr pellets. The magnetic moments of the complexes in the solid state were determined on a Gouy balance at room temperature using $Hg[Co(SCN)_4]$ as calibrant. X-band e.s.r. spectra were recorded on a JEOL-JF spectrometer using DMSO, fitted with a quartz Dewar for measurements at the liquid N_2 temperature, and the spectra were calibrated with DPPH ($g = 2.0037$). Cyclic voltammetric measurements were made in MeCN (HPLC grade) using the Bio-Analytical-System (BAS) CV-50W electrochemical analyzer. The three-electrode cell comprised a reference Ag/AgCl, auxiliary Pt and the working Glassy Carbon electrodes, n-Bu_4NClO_4 (TBAP) was used as the supporting electrolyte. All experimental solutions were purged with N_2 for 30 min prior to each set of experiments.

Knoevenagel condensate

The nonenolisable diketone was prepared by employing the modified procedure reported earlier [11]. Curcumin (368 mg, 1 mmol) was mixed with salicylaldehyde (122 cm^3, 1 mmol) and piperidine (0.05 cm^3), and the reaction mixture was stirred thoroughly for *ca.* 5 h with occasional cooling. Gradually a dark brown precipitate separated in small amounts. The reaction mixture was set aside to evaporate to dryness and the residual solid was washed with an excess of petroleum-ether to remove any unreacted reagents. Washing was repeated two to three times and the compound was recrystallized from a $CHCl_3$–petroleum-ether mixture to give a pure dark brown solid Knoevenagel condensate (salicylidenecurcumin). This was used as the starting material for the preparation of Schiff bases (m.p. 98 °C]. [^{1}H-n.m.r. δ 3.88 (s, 6H, OCH_3), 8.46 (s, 1H, —C=CH—), 6.57–6.7 (6H, aromatic, curcumin), 6.75–7.28 (4H, aromatic, salicylaldehyde), 7.06 (2H, 4,4′), 7.66 (2H, 3,3′), 9.68 (s, 1H, —OH)].

Salcimine Schiff base

This Schiff base was prepared by dissolving salicylidenecurcumin (454 mg, 1 mmol) and $C_6H_4NH_2$/substituted aniline (2 mmol) with piperidine (0.05 cm^3) in EtOH (50 cm^3). The reaction mixture was kept stirring for 6 h at room temperature. The dark brown solution was set aside to evaporate and the dark brown solid that separated was filtered off and recrystallized from MeOH. Yield: 80%. [^{1}H-n.m.r. δ 7.35 (s, 10 H, aromatic, two aniline rings)] (Figure. 1).

Complexes

The title complexes were prepared *in situ*. MeOH solutions of salicylidenecurcumin (454 mg, 1 mmol) and $PhNH_2/C_6H_4NH_2$ (2 mmol) were mixed. To the resulting solution piperidine (0.05 cm^3) was added and the solution was kept stirring for 5 h. Then a MeOH solution of $CuCl_2$ (170 mg, 1 mmol) was added. A greenish brown solid complex separated instantly and was filtered, washed with MeOH and air dried. These complexes were recrystallized from MeOH. The preparation of the complexes is shown below in Scheme 1 (yield: 70%).

Results and discussion

The analytical data of the metal complexes, which are consistent with the assigned molecular formulae, and the electronic spectral data are grouped in Table 1. The

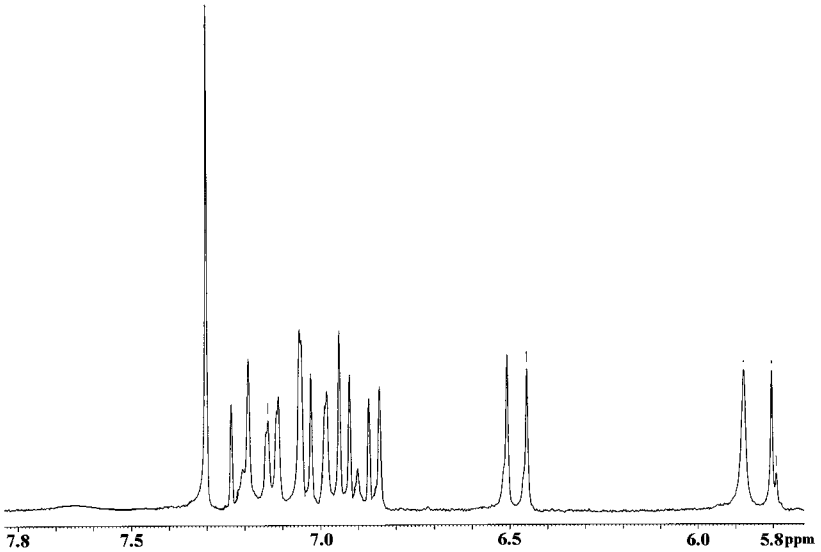
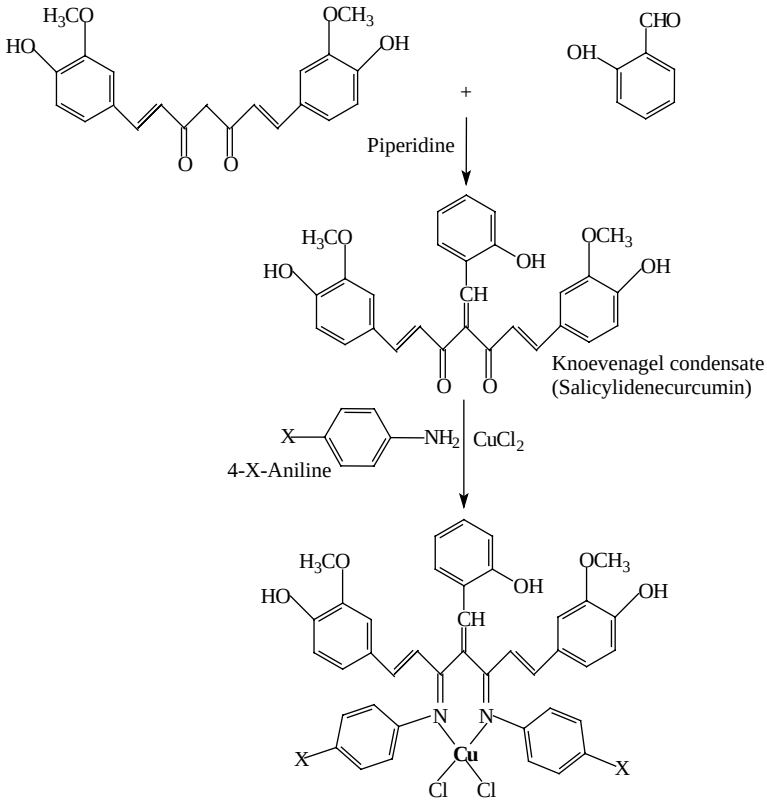


Fig. 1. N.m.r. spectrum of Salcimine-H in DMSO-d6.



[Cu(Salcimine-X)Cl_2]

	X		X
(1) [Cu(Salcimine-H)Cl_2]	H	*(2)* [Cu(Salcimine-CH_3)Cl_2]	CH_3
(3) [Cu(Salcimine-OCH_3)Cl_2]	OCH_3	*(4)* [Cu(Salcimine-Cl)Cl_2]	Cl
(5) [Cu(Salcimine-Br)Cl_2]	Br	*(6)* [Cu(Salcimine-NO_2)Cl_2]	NO_2

Scheme 1.

hyperfine splitting constants of these copper(II) complexes are collected in Table 2. The redox potentials of the metal complexes are listed in Table 3.

I.r. spectra

The i.r. spectra of the complexes were compared with the i.r. spectra of Salcimine-X in order to ascertain the changes that might have taken place. All the complexes show a new strong band in the 1590–1617 cm^{-1} region corresponding to ν(C═N) due to the presence of coordinated azomethine groups [9]. Coupled with this, the absence of a band above 1630 cm^{-1} [12], characteristic of ν(C═O) in salicylidenecurcumin, suggests that the condensation of the keto groups is complete. The free —OH group of the Salcimine-X vibrates at

Table 1. Elemental analysis, magnetic moment and electronic spectral data of copper-salcimine complexes

Complex	Found (calcd., %) C	H	N	Cu	$\mu_{eff.}$ (B.M.)	λ_{max}(nm)	ε (M^{-1}, cm^{-1})
(1)	63.6 (63.6)	4.3 (4.2)	3.7 (4.1)	8.4 (8.3)	1.91	533	1620
						408	4998
(2)	64.0 (64.2)	5.9 (6.1)	3.7 (3.5)	8.0 (7.9)	1.85	530	3400
						389	4820
(3)	61.5 (61.4)	5.2 (5.3)	3.4 (3.3)	7.7 (7.8)	1.91	533	2640
						390	4972
(4)	58.2 (58.2)	3.9 (3.8)	3.4 (3.5)	7.7 (7.8)	2.01	550	1870
						345	3714
(5)	52.5 (52.4)	3.5 (3.6)	3.1 (3.1)	7.0 (6.8)	1.86	517	3400
						433	4998
(6)	56.7 (56.6)	3.8 (3.9)	6.6 (6.5)	7.5 (7.3)	1.90	534	1760
						409	4980

Table 2. E.p.r. spectral parameters of copper–salcimine complexes in DMSO at 77 and 300 K

Complex	g_{iso}	$g_{\|\|}$	$g_{\perp}$	A_{iso} (10^{-4} cm^{-1})	$A_{\|\|}$ (10^{-4} cm^{-1})	$A_{\perp}$ (10^{-4} cm^{-1})	$g_{\|\|}$ $A_{\|\|}$
(1)	2.142	2.132	2.123	74.67	102	18.21	209
(2)	2.133	2.253	2.052	58.28	111	18.21	202
(3)	2.138	2.232	2.024	63.74	120	25.49	186
(4)	2.142	2.264	2.041	65.57	115	20.03	197
(5)	2.147	2.263	2.042	80.13	127	18.21	178
(6)	2.111	2.253	2.041	0.99	126	23.72	179

Table 3. Electrochemical data (in mV) of copper–salcimine complexes in MeCN

Complex	E_{pc}	E_{pa}	ΔE_p	$E_{1/2}$
(1)	247	437	190	342
(2)	502	637	135	570
(3)	180	506	326	343
(4)	138	473	335	305
(5)	502	589	87	546
(6)	444	581	137	513

3445 cm^{-1} [12]. This band does not show any shift in their complexes, and hence the —OH groups are not involved in the complex formation. The band in the 300–350 cm^{-1} region is assigned to the Cu–Cl vibration.

Electronic spectra

The electronic spectra of Salcimine-X and their copper complexes were recorded in acetonitrile. The sharp band, obtained in the 345–390 nm region for all these Salcimine-X species, is assignable to the intraligand (IL) π–π^* transition and to a peak at 265 nm for the σ–π^* band.

All these complexes show a broad d–d band (Table 1) with unusually high intensity at 520–550 nm ($\varepsilon = 1600 - 3600$ M^{-1} cm^{-1}, Figure 2), assigned to the combination of $^2B_{1g} \rightarrow {}^2E_g$ and $^2B_{1g} \rightarrow {}^2B_{2g}$ transitions in a distorted planar geometry. The spectral feature of these complexes is comparable [13] to the natural blue copper proteins. In the absence of a sulphur donor the unusual increase in intensity in the $^2B_{1g} \rightarrow {}^2E_g$ transition may be due to its possible overlap with the conjugated L_π–d_π (Cu) LMCT transition. The ligand π^*-orbitals may function as the empty dπ orbitals of the sulphur in blue copper and, hence, an increase in intensity is observed. The intraligand π–π^* entities in the complexes are observed in the 400 nm range with higher intensities comparable to their free ligands, which may be due to the presence of imine functions [14].

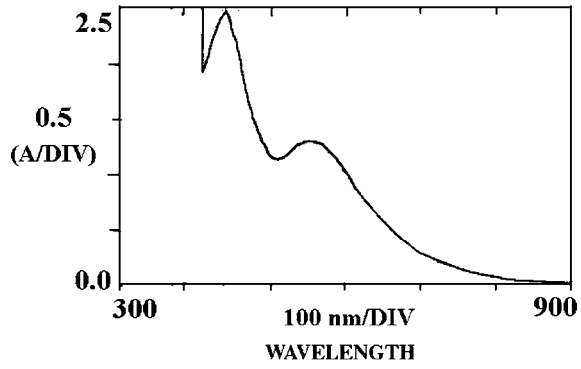


Fig. 2. Electronic spectrum of 10^{-3} M of *(3)* in MeCN.

Room temperature magnetic moments of the copper(II) complexes suggest that they are paramagnetic with μ_{eff} in the 1.85–2.07 B.M. range, corresponding to the presence of one unpaired electron (Table 1).

E.s.r. spectra

The e.s.r. spectra of all of the copper(II) complexes were recorded in DMSO at 300 and 77 K (Figure 3). The spin Hamiltonian parameters calculated for the complexes are given in Table 2. The $g_{||}$ values are greater than the corresponding $g_\perp$ values and therefore the unpaired electron occupies the $d_{x^2-y^2}$ molecular orbital [15]. All the spectra exhibit a typical four-line pattern. The spectral data are consistent with typical monomers but with distorted tetrahedral copper(II) geometry [16]. It is known that as the tetrahedral distortion increases, the $g_{||}$ will increase with a decrease in $A_{||}$ [17]. For blue copper proteins the $A_{||}$ values are in the 15–90 $\times$ 10^{-4} cm^{-1} region due to deviation from planarity, towards a suppressed tetrahedron. The observed $A_{||}$ values (~110 $\times$ 10^{-4} cm^{-1}) reveal that these complexes largely deviate from the regular square planar geometry.

The $A_{||}$ values of these complexes are on the borderline between naturally occurring blue copper proteins and typical planar structures. Often the $g_{||}/A_{||}$ quotient is empirically treated as an index of tetrahedral distortion [16]. The $g_{||}/A_{||}$ values are expected to be in the 105–135 and 150–250 range respectively for square planar and tetrahedral distorted copper(II) complexes. In the present case the $g_{||}/A_{||}$ values are between 178 and 209; it is assumed that they have geometry distorted from

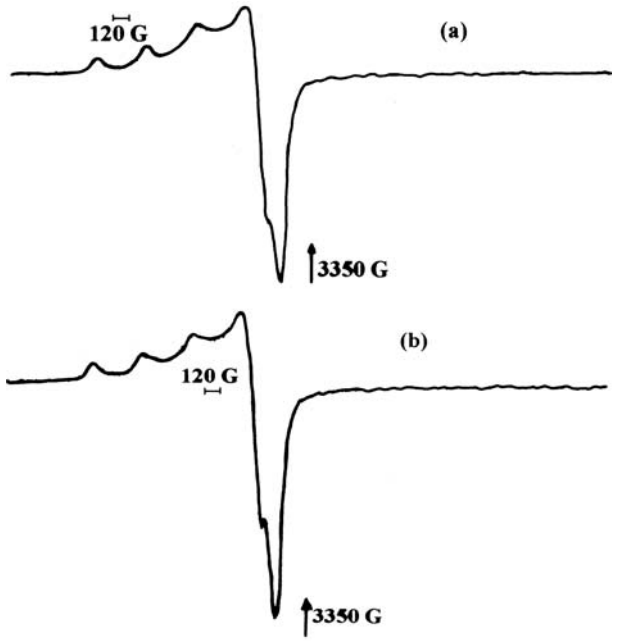


Fig. 3. E.p.r. spectra of complexes (a) *(3)* and (b) *(6)* in DMSO at LNT.

planarity towards tetrahedral. It is also reflected in the unusual gain in intensity in the visible spectra.

Electrochemical behaviour

The cyclic voltammograms of all the copper complexes were recorded in MeCN with BAS CV-50 at room temperature. The electrochemical data are given in Table 3. All these complexes show one well-defined redox couple corresponding to copper(II/I), as expected [18]. The cathodic peak appearing in the positive potential of 502–138 mV range corresponds to the one electron reduction of copper(II) and the corresponding anodic peak also appears in the 430–640 mV positive potential region. The measured ΔE_p values (87–335 mV) clearly indicate that these redox couples are quasi-reversible. The i_{pa}/i_{pc} falls at *ca.* 0.9–1.1, clearly confirming one electron transfer in this redox process. This copper(II/I) redox couple is found to be stable on multicycles as well as at different scan rates. The anodic (E_{pa}) peak potentials of these complexes in the positive region are comparable [19] with the naturally occurring blue copper proteins and synthetic models containing S-donor ligands. The ligand system with extended π orbitals and the distortions in the copper geometry might have forced the central copper to reduce at a positive reduction potential. Addition of any base (*N*-methylimidazole) to the experimental solution moves the redox potentials towards a less positive direction (negative direction, as for normal copper) and the peak-to-peak separation is greatly reduced due to the axial addition of base molecules to form six coordinated copper(II) complexes (Figure 4).

This quasi-reversible copper(II/I) redox couple was not altered on scanning at different sweep rates, showing

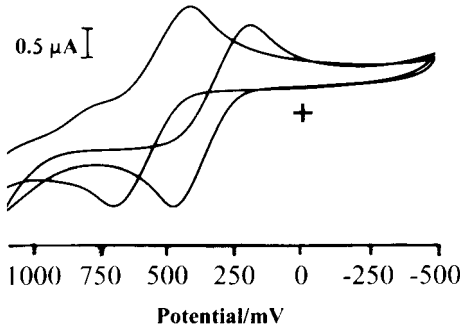


Fig. 4. Cyclic voltammogram of 0.5×10^{-3} M of *(5)* (a) *(5)* with *N*-methyl-imidazole (b) in MeCN *versus* Ag/AgCl with TBAP as supporting electrolyte at 100 mV s^{-1}

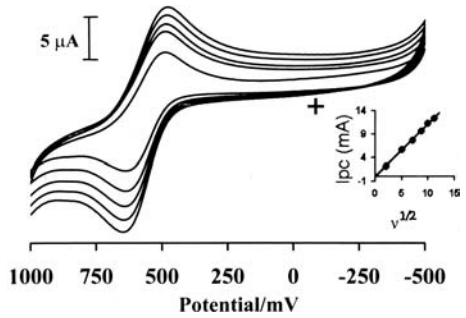


Fig. 5. Cyclic voltammograms of *(2)* in MeCN *versus* Ag/AgCl with TBAP as supporting electrolyte at 25,50,75,100 and 125 mV s^{-1}. Inset; plot of square root of scan rate *versus* current in μA

that the redox peak current intensity increases on higher scan rates (Figure 5). The cathodic peak current was found to be proportional to the square root of the scan rates indicates that the charge transfer process are diffusion controlled, which is confirmed by the observed linear plot of [Figure 5 (inset)] square root of the scan rate *versus* cathodic peak current.

The higher ε-values of the d–d band, low $A_{||}$ values and the positive reduction potential of these copper complexes suggest that they can serve as synthetic models without sulphur for the blue copper proteins.

Acknowledgements

We thank the DST, New Delhi for financial assistance in the form a project, and Prof. J. Subramanian, Department of Chemistry, Pondicherry University for providing e.s.r. facilities.

References

1. E.L. Solomon, M.J. Baldwin and M.D. Lowery, *Chem. Rev.*, **92**, 521 (1995).
2. L. Lu, C.Y. Duan, Y.P. Tian and X. You, *Polyhedron*, **15**, 1769 (1998).
3. P. Rajesh and P. Mathur, *Polyhedron*, **17** (1998) 2607.

4. J.A. Larrabee and T.G. Spiro, *J. Am. Chem. Soc.*, **102**, 4217 (1980).
5. B. Xie, L.J. Wilson and D.M. Stanbury, *Inorg. Chem.*, **40**, 3606 (2001).
6. K.D. Karlin and A.D. Zuberbuhler, in: J. Reedijk and E. Bouwman, (Eds), *Bioinorganic Catalysis*, 2nd edit, Marcel Dekker, New York, pp. 469–534, 1999.
7. K.D. Karlin and Z. Tyeklar (Eds) *Bioinorganic Chemistry of Copper*, Chapman & Hall, New York, 1993.
8. P.V. Takalkar and V. Ramachandra Rao, *Ind. J. Chem.*, **7**, 943 (1969).
9. S. Srinivasan, G. Rajagopal and PR. Athappan, *Transition Met. Chem.*, **26**, 588 (2001).
10. S.K. Chapman in: R.W. Hay, K.B. Nolan and J.R. Dilworth (Eds) *Perspectives on Bioinorganic Chemistry*, vol. 1, 1991, p. 95.
11. M. Yamamata, Y. Watanabe, T. Mitsudo and Y. Nakagami, *Bull. Chem. Soc. Jpn*, **51**, 835 (1978).
12. H. Beinert, *J. Inorg. Biochem.*, **44**, 17 (1991).
13. E.T. Adman in: C.B. Anfinsen, F.M. Richards, J.T. Edsall and D.S. Eisenberg (Eds) *Advances in Protein Chemistry*, Academic Press, New York, (1991) vol. 42, p.145.
14. A.M. Tait and D.H. Busch, *Inorg. Chem.*, **15**, 197 (1976).
15. D.M. Dooley, J. Rawlings, J.H. Dawson, P.J. Stephens, L.-E. Andreasson, B.G. Malmstrom and H.B. Gray, *J. Am. Chem. Soc.*, **101**, 5038 (1979).
16. E.I. Solomon, J.W. Hare and H.B. Gray, *Proc. Natl. Acad. Sci., USA*, **73**, 1389 (1976).
17. N. Kitajima, in: A.G. Sykes (Ed.) *Advances in Inorganic. Chemistry.*, Academic Press, New York, (1992) vol. 39, p. 1.
18. K. Jeyasubramanian, S. Thambidurai, S.K. Ramalingam and R. Murugesan, *J. Inorg. Biochem.*, **72**, 101 (1998).
19. A.W. Addison, T. Nageswara Rao and E. Sinn. *Inorg. Chem.*, **23**, 1957 (1984).

TMCH 5877