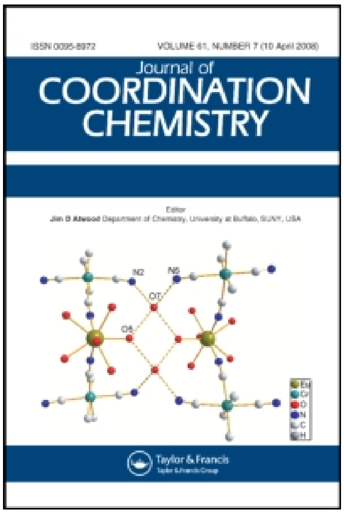

Journal of Coordination Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Crystal Structure and Superoxide Dismutase Activity of $[Cu(Imidazole)_2(Quinoline)Cl_2]\cdot 0.5[Cu(Imidazole)_4Cl_2]$

J. R. Anacona[a]; Carmen Gutierrez[a]; Osmar Nusetti[a]; Daniel LoroÑo[b]
[a] Departamento de Quimica, Universidad de Oriente, Cumana, Venezuela [b] Department of Chemistry, University of Edinburgh, Edinburgh, Scotland

To cite this Article Anacona, J. R. , Gutierrez, Carmen , Nusetti, Osmar and LoroÑo, Daniel(2002) 'Crystal Structure and Superoxide Dismutase Activity of $[Cu(Imidazole)_2(Quinoline)Cl_2]\cdot 0.5[Cu(Imidazole)_4Cl_2]$', Journal of Coordination Chemistry, 55: 12, 1433 — 1439

To link to this Article: DOI: 10.1080/0095897021000058826

URL: http://dx.doi.org/10.1080/0095897021000058826

J. Coord. Chem., 2002, Vol. 55, No. 12, pp. 1433–1439

CRYSTAL STRUCTURE AND SUPEROXIDE DISMUTASE ACTIVITY OF [Cu(IMIDAZOLE)$_2$(QUINOLINE)Cl$_2$] · 0.5[Cu(IMIDAZOLE)$_4$Cl$_2$]

J.R. ANACONA[a,]*, CARMEN GUTIERREZ[a], OSMAR NUSETTI[a] and DANIEL LOROÑO[b]

[a] *Departamento de Quimica, Universidad de Oriente, Apartado Postal 208, Cumana, Venezuela;*
[b] *Department of Chemistry, University of Edinburgh, Edinburgh, Scotland*

(Received 14 October 2001; Revised 6 January 2002; In final form 12 June 2002)

The preparation, spectroscopic properties and crystal structure of (bis-imidazole)quinoline-copper(II) dichloride [Cu(Im)$_2$(quin)Cl$_2$] (Im = imidazole, quin = quinoline) and tetraimidazole-copper(II)-dichloride [Cu(Im)$_4$Cl$_2$] are reported. Both cocrystallize on the triclinic system, space group P-1, with cell constants $a = 8.095(5)$ Å, $b = 12.141(5)$ Å, $c = 13.847(5)$ Å, $\alpha = 108.816(5)°$, $\beta = 104.173(5)°$, $\gamma = 94.965(5)°$ and $Z = 2$. In the [Cu(Im)$_2$(quin)Cl$_2$] complex the copper(II) ion is coordinated to two imidazole molecules, to one quinoline and two chlorine ions, with the copper(II) ion in a distorted trigonal bipyramidal coordination geometry. In the [Cu(Im)$_4$Cl$_2$] complex, the copper(II) ion has a distorted octahedral coordination geometry. The superoxide dismutase mimetic activity of the complexes was investigated using the indirect xanthine–xanthine oxidase–nitroblue tetrazolium method and compared to that of the native enzyme.

Keywords: [Cu(Im)$_2$(quin)Cl$_2$]; [Cu(Im)$_4$]Cl$_2$; Xanthine–Xanthine oxidase system

INTRODUCTION

The reactive superoxide radical anion is a product of the oxygen metabolic cycle. Superoxide dismutase (SOD) is an enzyme that catalyses the disproportionation of the toxic superoxide ions into molecular oxygen and H_2O_2 [1,2]. The *in vivo* ubiquity of the SODs makes them very efficient in normal conditions. However, in the case of an oxygen burst, the natural defenses of the organism are insufficient, leading to lipid peroxidation, membrane damage, and cell death. These effects are not directly due to the superoxide ion but rather to the more potent oxidant, the hydroxyl radical, which is generated *in situ*. The mechanism believed to be operating in the metalloproteins involves one-electron reduction of a metal ion by superoxide followed by reoxidation of the reduced metal ion by a second superoxide anion. Metal complexes

---

*Corresponding author. Fax: 58 293 4317787. E-mail: juananacona@hotmail.com

ISSN 0095-8972 print: ISSN 1029-0389 online
DOI: 10.1080/0095897021000058826

that can undergo such redox cycling are likely to function as superoxide scavengers. As copper has been proven to be the active center in the best studied SOD, many copper(II) complexes have been synthesized and tested for SOD-like activity [3–13], and most of them are efficient. We report here the preparation and superoxide dismutase activity of the title complex which was obtained as by product when attempting to form mixed copper(II) complexes containing imidazole and quinoline molecules.

EXPERIMENTAL

Materials

$CuCl_2 \cdot 2H_2O$ was purchased from Aldrich. Xanthine, xanthine oxidase, nitroblue tetrazolium chloride monohydrate (NBT) and superoxide dismutase (bovine erythrocytes) were from Sigma Chemical Co.

Synthesis

$CuCl_2 \cdot 2H_2O$ (0.17 g, 1 mmol) was added to a solution of imidazole (0.14 g, 2 mmol) in methanol (50 mL). Then to the resulting mixture, quinoline (1.30 g, 10 mmol) was added. The mixture was refluxed for two days and the boiling solution was filtered and concentrated to 10 mL. This solution was left standing at low temperature (5°C) and in a few days, blue prismatic crystals were obtained. Yield 82%. Anal. Calcd. for $[C_{21}H_{23}Cl_3N_9Cu_{1.50}]$%: C, 41.80; H, 3.82; N, 20.90; Cu, 15.80. Found: C, 41.65; H, 3.56; N, 21.10; Cu, 15.95.

Physical Techniques

IR spectra of the ligand and its metal complexes in KBr pellets were recorded in the 4000–400 cm^{-1} range with a Perkin-Elmer Series 2000 spectrophotometer. FTIR spectra as polyethylene pellets were recorded between 450–120 cm^{-1} using a Brucker IFS 66 V spectrophotometer. UV-vis spectra were recorded using a Perkin-Elmer recording spectrometer. C, H, N, and metal were analyzed by the microlabs in the Venezuelan Institute of Scientific Research (IVIC). Magnetic susceptibility was measured on a Johnson Matthey Susceptibility Balance to room temperature using $HgCo(NCS)_4$ as calibrant. Corrections for the diamagnetism of the complex were estimated from Pascal's constants. An EPR spectrum was recorded on a Brucker ECS 106 spectrometer by the X-band method.

Crystallographic Data Collection

Recrystallization of $[Cu(Im)_2(quin)Cl_2] \cdot 0.5[Cu(Im)_4Cl_2]$ from methanol gave blue prismatic crystals suitable for single crystal X-ray analysis. The crystal of approximately dimension of $0.16 \times 0.07 \times 0.10$ mm, was mounted on a SMART APEX diffractometer. X-ray data were collected using graphite-monochromated Mo-$K\alpha$ radiation ($\lambda = 0.71073$ Å) at 150 K. The data were resolved using SIR97 [14] while the refinement was carried out on F^2 using all reflections and SHELX97 [15]. Hydrogen atoms bonded to nitrogen were refined as rigid groups (initial positions were taken from Fourier synthesis and hydrogen atoms allowed to rotate) and the remaining hydrogen atoms were treated on riding mode with isotropic displacement parameters. An empirical absorption correction (φ-scan) was applied. The structure was solved using direct methods and refined by full-matrix least squares with anisotropic displacement parameters for the nonhydrogen atoms. Crystal parameters and details of data collection and refinement are summarized in Table I. The final conventional agreement factors were $R_1 = 0.0336$ and $wR_2 = 0.0766$ for the 5945 observed reflections and 329 variables. The function minimized was $\sum[w(F_o^2 - F_c^2)^2]$, $w = [\sigma^2(F_o^2) + (0.0405P)^2 + 0.00P]^{-1}$ where $P = (\max[F_o^2, 0] + 2F_c^2)/3$.

Superoxide Assays

Superoxide dismutase activity of the complex was determined by using its ability to inhibit the reduction of NBT by superoxide ions generated by the xanthine–xanthine oxidase system [16]. The extent of NBT reduction was followed spectrophotometrically by measuring the absorbance at 560 nm. The aqueous reaction mixture contained 2×10^{-4} M xanthine, 5×10^{-5} M NBT and 1.25×10^{-2} M sodium phosphate buffer at pH 7.5 and 25°C. For comparative purposes, we have also measured the activity of native superoxide dismutase, from bovine erythrocytes, under the same experimental conditions. Five assays were performed for each concentration of both SOD and the metal complex. We checked that the generating xanthine–xanthine oxidase system was not inhibited by our metal complex by following, at 295 nm, the uric acid produced

TABLE I Crystal data, data collection parameters and details of the structure refinement for $[Cu(Im)_2(quin)Cl_2] \cdot 0.5[Cu(Im)_4Cl_2]$

Empirical formula	$C_{21}H_{23}Cl_3Cu_{1.50}N_9$ $[C_{15}H_{15}Cl_2CuN_5]$, $0.50[C_{12}H_{16}Cl_2CuN_8]$
Color, Habit	Blue, prismatic
Crystal size	$0.16 \times 0.07 \times 0.10\,\mathrm{mm}^3$
Crystal system	Triclinic
Space group	P − 1
Unit cell dimensions	$a = 8.095(5)$, $b = 12.141(5)$, $c = 13.847(5)$ Å $\alpha = 108.816(5)^\circ$, $\beta = 104.173(5)^\circ$, $\gamma = 94.965(5)^\circ$
Volume	1228.5(10) Å^3
Z	2
Formula weight	603.14
Density (calc.)	$1.631\,\mathrm{g\,cm^{-3}}$
Absorption coefficient	$1.666\,\mathrm{mm}^{-1}$
$F(000)$	613
Radiation	Mo-$K\alpha$ ($\lambda = 0.71073$ Å)
Temperature	150(2) K
Reflections collected	11456
Independent reflections	5945 ($R_{int} = 2.40\%$)
Solution	Direct (Sir97)
Refinement method	Full-matrix least squares
Hydrogen atoms	Riding model, fixed isotropic U
Restraints, constraints	None
Weighting scheme	$w = [\sigma^2 (F_o^2) + (0.0405\ P)^2 + 0.00\ P]^{-1}$ where $P = (\max\ [F_o^2, 0] + 2F_c^2)/3$
Parameters refined	329
Final R indices ($I > 2\sigma(I)$)	$R_1 = 3.36\%$,. $wR_2 = 7.66\%$
Final R indices (all data)	$R_1 = 4.14\%$, $wR_2 = 7.77\%$

when xanthine is oxidized by xanthine oxidase in aerobic conditions concomitantly with production of superoxide ions.

RESULTS AND DISCUSSION

Elemental analysis agrees well with the stoichiometry of the complex. It is colored and appears to be air stable and soluble in methanol. The experimental conductivity value in MeOH falls in the range of 2 : 1 electrolytes.

The copper(II) complexes have a magnetic moment of 1.98 BM at room temperature and fall in the range associated with d^9 systems with one unpaired electron. The rather high value of the magnetic moment for the freshly prepared copper(II) complex could be explained, in part, by the fact that spin-orbital coupling in the ion can mix the ground state representing no orbital momentum with higher levels of identical multiplicity, resulting in a small orbital contribution [17]; however, the presence of impurities might be the entire cause.

The EPR spectrum of the copper(II) complex at room temperature showed a single broad signal with poor resolution of the hyperfine structure on both sides of the main signal. The calculated parallel and perpendicular tensors, $g_{\parallel} = 2.11$ and $g_{\perp} = 2.04$, indicate [18] that the unpaired electron most likely resides in the $d_{x^2-y^2}$ orbital having $^2B_{1g}$ as a ground state term. The axial symmetry parameter, $G = 2.75$, obtained by the relation $(g_{\parallel} - 2)/(g_{\perp} - 2)$, supports [17] the contention that there is a significant electron exchange interaction between the copper centers ($G < 4$).

The IR spectrum reveals two absorptions at 480 and 410 cm^{-1}, which may tentatively be assigned, respectively, to ν(Cu–Cl) and ν(Cu–N) stretching bands. The ν(N–H) stretching vibration is seen at 3300 cm^{-1} and the $\nu(C{=}C) + \nu(C{=}N)$ bands can also be observed in the 1590–1650 cm^{-1} region.

The UV-vis spectrum of the metal complexes in MeOH solution presents two absorption maxima at 240 and 290 nm, presumably due to intraligand excitation, and *d*-*d* transitions as very broad bands centered around 380, 770, and 850 nm. The bands at 380 and 850 nm can tentatively be assigned, in the [Cu(Im)$_4$Cl$_2$] complex, to $^2B_{1g} \rightarrow {}^2E_{2g}$ and $^2B_{1g} \rightarrow {}^2B_{2g}$ transitions for D_{4h} symmetry, characteristic of copper(II) in a tetragonally elongated octahedron [19]. The band at 770 nm falls in the range of those usually reported for five-coordinate copper complexes [20] and can be assigned to the [Cu(Im)$_2$(quin)Cl$_2$] complex.

An ORTEP representation including the atomic numbering scheme is given in Fig. 1 and the molecular interactions in the crystal extended along an axis can be seen in Fig. 2. Selected bond lengths and angles are listed in Table II. The data collected show the cocrystallization of two kind of complexes [Cu(Im)$_2$(quin)Cl$_2$] and [Cu(Im)$_4$Cl$_2$] (Fig. 1). For the [Cu(Im)$_2$(quin)Cl$_2$] complex, the average distance for the Cu–N(imidazole) is 2.010 Å, while the distance Cu–N(quin) was found to be 2.013 Å. In addition, the copper atom is also bound to two chlorides located at 2.3233 and 2.5757 Å, respectively. According to this, the structure presents a remarkable Jahn–Teller effect especially for the longer bond. Moreover, the structure can be described as substantially distorted trigonal bipyramidal in which the angles N–Cu–N, N–Cu–Cl and Cl–Cu–Cl are affected (Table II). Nonequivalent distances upon Jahn–Teller distortion have been reported [21–23]. For the [Cu(Im)$_4$Cl$_2$] complex the average distance for the Cu–N(imidazole) is 2.008 Å. Although the chloride atoms

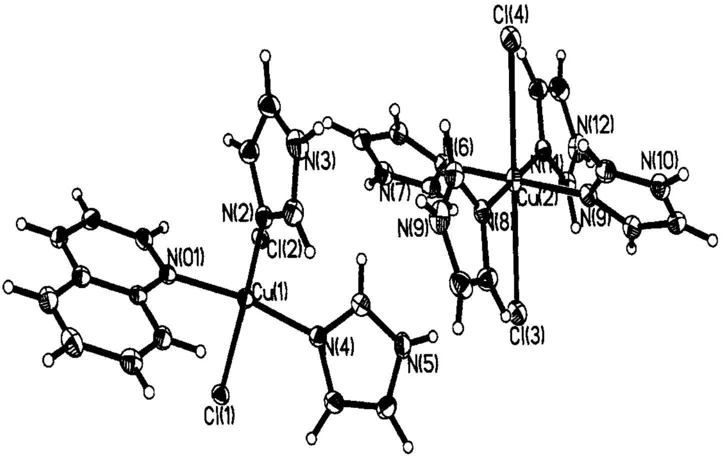

FIGURE 1 Molecular structure of the complexes showing the atomic numbering scheme.

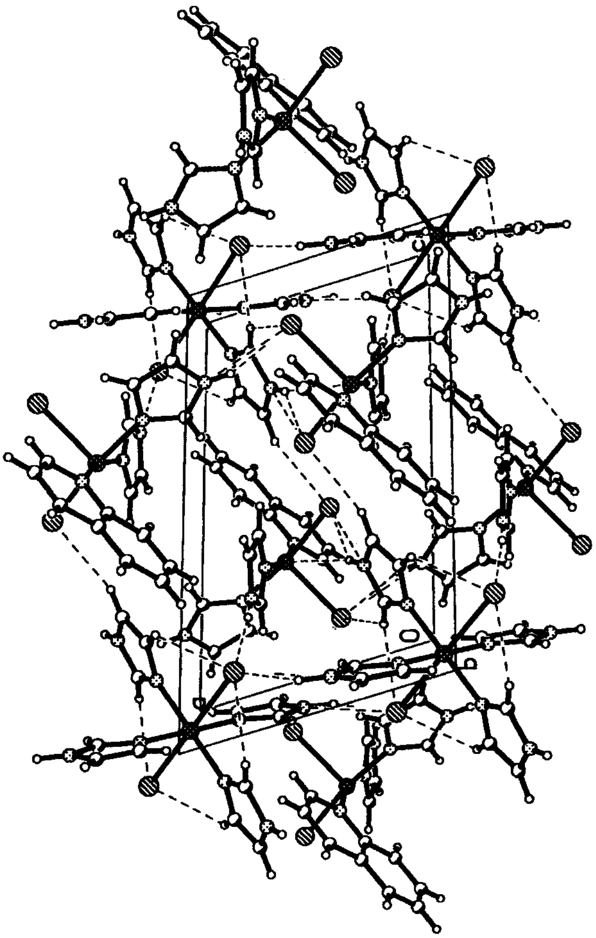

FIGURE 2 Perspective view of packing of the complexes along the *a* axis.

TABLE II Selected bond lengths (Å) and bond angles (°)

[Cu(Im)$_2$(quin)Cl$_2$]		*[Cu(Im)$_4$Cl$_2$]*	
Cu(1)–N(4)	2.005(2)	Cu(2)–N(8)[a]	1.9975(19)
Cu(1)–N(2)	2.014(2)	Cu(2)–N(8)	1.9975(19)
Cu(1)–N(01)	2.0314(19)	Cu(2)–N(6)	2.019(2)
Cu(1)–Cl(1)	2.3233(10)	Cu(2)–N(6)[a]	2.019(2)
Cu(1)–Cl(2)	2.5767(10)	Cu(2)–Cl(3)	2.9236(2)
N(4)–Cu(1)–N(2)	90.92(8)	Cu(2)–Cl(4)	2.9272(2)
N(4)–Cu(1)–N(01)	163.73(7)	N(8)–Cu(2)–N(8)[a]	180.00(10)
N(2)–Cu(1)–N(01)	88.99(7)	N(6)–Cu(2)–N(8)[a]	88.30(8)
N(4)–Cu(1)–Cl(1)	89.35(6)	N(8)–Cu(2)–N(6)	91.70(8)
N(2)–Cu(1)–Cl(1)	171.25(6)	N(6)–Cu(2)–N(6)[a]	180.00(10)

Symmetry transformations used to generate equivalent atoms.
[a] $1-x, -y+1, -z$.

TABLE III Hydrogen bonds with $H \cdots A < r(Å) + 2.000$ Å and $D–H \cdots A > 110°$. D represents the donor atom and A the acceptor atom

D	*H*	*A*	*Symmetry for A*	*D–H*	*H···A*	*D···A*	*D–H···A*
N(5)	H(5)	Cl(3)		0.8385	2.3449	3.1821	176.17
N(3)	H(3)	Cl(4)	$1+x, y, z$	0.8430	2.3578	3.1579	158.65
N(10)	H(10)	Cl(4)	$1-x, 1-y, -z$	0.9609	2.3218	3.1483	143.72
N(12)	H(12)	Cl(1)	$1+x, y, z$	0.8007	2.5441	3.2431	146.17
C(9)	H(9)	Cl(2)		0.9501	2.6733	3.4020	133.93
C(71)	H(71)	Cl(2)	$1+x, y, z$	0.9500	2.8253	3.4550	124.65
C(71)	H(71)	Cl(4)	$2-x, 1-y, -z$	0.9500	2.8160	3.4019	120.81
C(72)	H(72)	Cl(1)	$2-x, 1-y, 1-z$	0.9500	2.7672	3.6793	161.19

bonded to the copper(II) ion are situated at the same equivalent distances of 2.923 Å, the dynamic Jahn–Teller effect could explain the much longer distances for the chlorine atoms attached to the copper(II) ion. As a consequence of this a distortion of the octahedral structure can be appreciated (Table II).

On the other hand, studying with PLATON [24] the possible interactions between chlorine and hydrogen atoms gives us a possible reason of cocrystallization and the longer Cu–Cl distances in addition to the dynamic Jahn–Teller effects. Both structures present a close interaction which allow a nonbonding intramolecular and intermolecular stabilization (Fig. 2). The average distance for H···Cl in N–H···Cl is 2.3921 Å, which is comparable with the average distance for the interaction C–H···Cl, 2.7705 Å (Table III). All the effects named have produced two distorted structures with an extra stabilization which produces a stable structure.

Final position, thermal parameters and all distances and angles of the complex structure have been deposited with the Cambridge Crystallographic Data Centre, under the deposition number CCDC 170844.

The superoxide dismutase activity of the title complex was assayed by their ability to inhibit the reduction of nitroblue tetrazolium. In the SOD-like activity test, the metal complexes compete with NBT for the oxidation of the generated superoxide ions. The more efficient the complex, the lower the concentration that corresponds to 50% inhibition of NBT reduction; this concentration is termed IC_{50} for comparative purposes. However, in contrast with the SOD activity observed for some copper(II) complexes [3,8–10,25–27] the title complexes do not present an interesting inhibition activity and a proper IC_{50} could not be established.

Acknowledgment

Our sincere thanks to the Comision de Investigacion of the Universidad de Oriente for providing financial support.

References

[1] D. Salvemini and R. Botting (1993). *Drugs News Perspect.* **6**, 274.
[2] J.M. McCord and I. Fridovich (1969). *J. Biol. Chem.* **244**, 6049.
[3] A. Gartner and U. Weser (1986). In: F. Vogtle and E. Weber (Eds.), *Topics in Current Chemistry*, Vol. 132. Springer, Berlin.
[4] R. Brigelius, R. Spottl, W. Bors, E. Lengfelder, M. Saran and U. Weser (1974). *FEBS Lett.*, **47**, 72.
[5] S. Goldstein and G. Czapski (1983). *J. Am. Chem. Soc.*, **105**, 7276.
[6] A. Bury, A.E. Underhill, D.R. Kemp, N.J. O'Shea, J.P. Smith and P.S. Gomm (1987). *Inorg. Chim. Acta*, **138**, 85.
[7] C.J. Bijloo, H. Van der Goot, A. Bast and H. Timmerman (1990). *J. Inorg. Biochem.*, **40**, 237.
[8] R.G. Bhirud and R.S. Srivastava (1990). *J. Inorg. Biochem.*, **40**, 331.
[9] S. Goldstein, G. Czapski and D. Meyerstein (1990). *J. Am. Chem. Soc.*, **112**, 6489.
[10] R.G. Bhirud and T.S. Srivastava (1991). *Inorg. Chim. Acta*, **179**, 125.
[11] A.E. Underhill, S.A. Bougourd, M.L. Flugge, S.E. Gale and P.S. Gomm (1993). *J. Inorg. Biochem.*, **52**, 139.
[12] L.L. Costanzo, G. Deguidi, S. Giuffrida, E. Rizzarelli and G. Vecchio (1993). *J. Inorg. Biochem.*, **50**, 273.
[13] Q. Luo, Q. Lu, A. Dai and L. Huang (1993). *J. Inorg. Biochem.*, **51**, 655.
[14] J. Fait (1997). *XSCANS User's Manual*. Siemens Analytical X-Ray Instruments Inc. Madison, Wl, USA.
[15] G.M. Sheldrick (1997). *SHELXL97. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
[16] L.W. Oberley and D.R. Spitz (1986). In: R.A. Greenwald (Ed.), *Handbook of Methods for Oxygen Radicals Research*, 217. CRC Press, Boca Raton, FL.
[17] M.C. Jain, A.K. Srivastava and P.C. Jain (1977). *Inorg. Chim. Acta*, **23**, 199.
[18] M. Shakir, S.P. Varkey and P.S. Hameed (1994). *Polyhedron*, **13**, 1355.
[19] A.B.P. Lever (1984). *Inorganic Electronic Spectroscopy*. Elsevier, Amsterdam.
[20] J. Casanova, G. Alzuet, J. Borras, L. David and D. Gatteschi (1993). *Inorg. Chim. Acta*, **211**, 183.
[21] R. Allmann, W. Henke and D. Reinen (1978). *Inorg. Chem.*, **17**, 378.
[22] M. Arriortua, T. Rojo, J. Amigo, G. Germain and J.P. Declercq (1982). *Acta Crystallogr. Sect. B.*, **B38**, 1323.
[23] M. Mathew and G. Palenik (1971). *J. Coord. Chem.*, **1**, 243.
[24] A.L. Spek (1990). *Acta Crystallogr.*, **A46**, 34.
[25] M. Linss and U. Weser (1987). *Inorg. Chim. Acta*, **138**, 163.
[26] J.S. Richardson, D.C. Richardson, J.A. Trainer and E.D. Geltzoff (1983). *Nature* (London), **306**, 284.
[27] C. Amar, E. Wilkas and J. Foos (1982). *J. Inorg. Biochem.*, **17**, 313.