DALTON
FULL PAPER

Kinetic studies on the copper(II)-mediated oxygenolysis of the flavonolate ligand. Crystal structures of $[Cu(fla)_2]$ (fla = flavonolate) and $[Cu(O\text{-}bs)_2(py)_3]$ (O-bs = *O*-benzoylsalicylate)†

Éva Balogh-Hergovich,[a] József Kaizer,[b] Gábor Speier,*[b] Gyula Argay[c] and László Párkányi[c]

[a] *Research Group for Petrochemistry of the Hungarian Academy of Sciences, 8201 Veszprém, Hungary*
[b] *Department of Organic Chemistry, University of Veszprém, 8201 Veszprém, Hungary*
[c] *Central Research Institute for Chemistry, Hungarian Academy of Sciences, 1525 Budapest, Hungary*

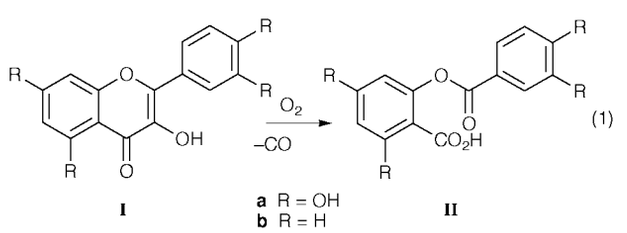
Received 14th July 1999, Accepted 3rd September 1999

The complex $[Cu(fla)_2]$ has been prepared by treating copper(II) chloride with sodium flavonolate in tetrahydrofuran solution. Crystallographic characterisation of the complex $[Cu(fla)_2]\cdot 2CHCl_3$ has shown that the co-ordination geometry around the copper(II) ion is square planar. Oxygenation of $[Cu(fla)_2]$ in dimethylformamide solution at ambient conditions gives $[Cu(O\text{-}bs)_2]$ (O-bs = *O*-benzoylsalicylate) and carbon monoxide. Crystallographic characterisation of $[Cu(O\text{-}bs)_2]$ on crystals obtained from pyridine as $[Cu(O\text{-}bs)_2(py)_3]\cdot 0.91py$ revealed that the co-ordination geometry of the copper(II) ion is square pyramidal with *trans* O atoms of O-bs and N atoms of py ligands in basal and an N atom of py in apical position. The oxygenolysis of $[Cu(fla)_2]$ in DMF was followed by electron spectroscopy and the rate constants were determined according to the rate law $-d[Cu(fla)_2]/dt = k[Cu(fla)_2][O_2]$. The rate constant, activation enthalpy, entropy and free energy at 373 K are as follows: $k/mol\,dm^{-3}\,s^{-1} = (1.57 \pm 0.08) \times 10^{-2}$, $\Delta H^{\ddagger}/kJ\,mol^{-1} = 53 \pm 6$, $\Delta S^{\ddagger}/J\,K^{-1}\,mol^{-1} = -138 \pm 11$, $\Delta G^{\ddagger}/kJ\,mol^{-1} = 105 \pm 2$. The reaction fits a Hammett linear free energy relationship and a higher electron density on copper results in a faster oxygenation reaction.

Introduction

The oxidative degradation of organic molecules by the use of dioxygen is accomplished widely in nature aided by a variety of enzyme systems. Some of these metalloenzymes contain copper and/or iron ions at their active sites. Oxygenases catalyse the incorporation of oxygen atom(s) (mono- and di-oxygenases) of molecular oxygen into the substrate under ambient conditions.[1] There is great interest for the elucidation of the structures and mechanistic features of such enzymes. The question is put forward as to how the reactions are accelerated and what is the role of the redox metal ions in terms of activation of either dioxygen or the substrate.[2] Besides direct enzymatic methods, studies on structural and functional models are thought to be helpful means for obtaining information on the mode of activation of reactants and understanding the mechanism of oxygenations and the chemistry of metal-based oxidation reactions.[3]

Fungi such as *Aspergillus* or *Pullularia* species metabolise quercetin (**Ia**, 3′,4′,5,7-tetrahydroxyflavonol) into a depside (**IIa**, phenolic carboxylic acid ester) and carbon monoxide [eqn. (1)].[4] The copper-containing metalloenzyme quercetin 2,3-dioxygenase is responsible for this reaction. In the resting state of the enzyme copper is in the copper(II) form, its ligand environment is still obscure and the flavonol moiety seems to be co-ordinated through its 3-hydroxy and 4-carbonyl group to the metal.[5]



a R = OH
b R = H

I **II**

Few model reactions on the oxygenation of flavonol (**Ib**) and quercetin (**Ia**) have been carried out with the aim to shed light on this curious reaction leading to oxidative ring cleavage of the pyranone ring with concomitant extrusion of carbon monoxide. Base catalysed oxygenation of quercetin and 3-hydroxyflavones under aqueous[6] and non-aqueous conditions,[7] photosensitised oxygenations,[8] and reactions with superoxide anions[9] have been studied. Cobalt[10] and copper[11] complexes were applied as suitable catalysts for the oxygenation reaction. Copper(I)[12] and copper(II)[13] flavonolate complexes were also found to catalyse the reaction.

Following our studies on the preparation, characterisation and oxygenation of copper(I) flavonolate complexes[12,14] we tried to isolate and characterise copper(II) flavonolate complexes and to study their oxygenation. This paper deals with the preparation and structural characterisation of a copper(II) flavonolate complex[13] and its oxygenated product copper(II) *O*-benzoylsalicylate and with the kinetics of this reaction.

Experimental

Materials and methods

All manipulations were performed under a pure dinitrogen or argon atmosphere unless otherwise stated using standard Schlenk-type inert gas techniques.[15] The compounds $Cu(OMe)_2$,[16] 3-hydroxyflavone,[6] 3-hydroxy-4′-methoxyflavone,[6] 3-hydroxy-4′-methylflavone,[17] 4′-chloro-3-hydroxyflavone,[17] and *O*-benzoylsalicylic acid[18] were prepared according to literature methods; $CuCl_2$ was prepared from $CuCl_2\cdot 5H_2O$

† *Supplementary data available*: rotatable 3-D crystal structure diagram in CHIME format. See http://www.rsc.org/suppdata/dt/1999/3847/

This journal is © The Royal Society of Chemistry 1999

by heating at 180 °C in vacuum for 8 h. Dichloromethane, chloroform, toluene, acetonitrile, pyridine, and DMF were purified in the usual manner and stored under argon.[19] All other chemicals were commercial products used as received without further purification. Infrared spectra were recorded on a Specord 75 IR (Carl Zeiss) spectrophotometer using samples mulled in Nujol between KBr plates or in KBr pellets. GC Analyses were performed on a HP 583OA gas chromatograph equipped with a flame ionisation detector and a 25 m (0.2 mm i.d., 0.25 μm film thickness) CP-SIL-8CB fused silica capillary column, and a thermal conductivity detector and a 27.5 m (0.53 mm i.d., 0.2 μm film thickness) Poraplot Q fused silica capillary column. GC-MS Analyses were performed on a HP 5890II/5971 GC/MSD apparatus equipped with a column identical to that used for GC analyses. ESR Spectra were recorded on a JEOL.JES-FE3X spectrometer at temperatures given either on solid samples or solutions sealed under argon and referenced to Mn^{II} as external standard. Magnetic susceptibilities were determined on a Bruker-B-E 10B8 magnetometer.[20] Reactions under controlled pressure of O_2 were performed with a double-wall reaction vessel equipped with a mercury manometer, inlet for sampling, and a Carl Zeiss (Jena) temperature controller. UV-vis Spectra were recorded on a Shimadzu UV-160 spectrophotometer using quartz cells. CV Measurements were carried out on a BAS CV-1B cyclic voltammeter in DMF solution at room temperature with *ca.* 10^{-3} M solutions and NBu_4PF_6 as supporting electrolyte, and scan speeds 100 mV cm^{-1} unless otherwise stated, the potential values are relative to the saturated calomel electrode (SCE) using an Ag–AgCl reference electrode, the potential of which was −0.02 V *vs.* SCE.[21]

Preparations

[Cu(fla)$_2$] 1a. To a stirred solution of flavonol (2.38 g, 10 mmol) in anhydrous dichloromethane (100 cm^3) $Cu(OMe)_2$ (0.63 g, 5 mmol) was added under argon. The mixture was stirred for 8 h, the solvent evaporated off in vacuum, and the residue treated with diethyl ether, filtered off and dried to give a greenish yellow powder of complex **1a** (2.4 g, 88%), mp 295–297 °C (Found: C, 66.03; H, 3.38. $C_{30}H_{18}CuO_6$ requires C, 66.97; H, 3.37%); λ_{max}/nm (CH_2Cl_2) 240(sh) (log ε/mol^{-1} dm^3 cm^{-1} 4.52), 258 (4.63), 273(sh) (4.53), 329 (4.18), 410 (4.53) and 426 (4.58); $\tilde{\nu}_{max}$/cm^{-1} (KBr) 1609w, 1590m, 1567w, 1537s, 1508s, 1491s, 1456w, 1432m, 1416s, 1353m, 1319m, 1309w, 1296w, 1249w, 1229w, 1215s, 1183w, 1153m, 1115w, 1096w, 1070w, 907m, 760(sh), 750s, 705w, 674m, 659w, 569m and 476m; $\mu_B = 1.76$; ESR parameters $g_\parallel = 2.2519$ and $g_\perp = 2.0849$. On recrystallisation from $CHCl_3$ yellow plates of [Cu(fla)$_2$]·2$CHCl_3$ were formed suitable for X-ray diffraction experiments.

[Cu(4′R-fla)$_2$] 1b–1d. Complexes **1b–1d** were prepared by the same method as described above. Properties, analyses, IR, UV-vis, μ_B and ESR data of the complexes are summarized in Tables 1, 2 and 3.

[Cu(O-bs)$_2$] 2a. *Method A.* The complex [Cu(fla)$_2$] (0.538 g, 1 mmol) in DMF (50 cm^3) was treated with dioxygen (1 atm) at 80 °C for 5 h yielding a greenish yellow solution. On addition of ether a blue solid precipitated, from which after filtration and recrystallisation from ethanol [{Cu(O-bs)$_2$·C_2H_5OH}$_2$] [**2a**·EtOH]$_2$ was obtained (280 mg, 46%).

Method B. To a solution of $Cu(OAc)_2·2H_2O$ (2.00 g, 10 mmol) in ethanol (80 cm^3) benzoylsalicylic acid (4.84 g, 20 mmol) in ethanol (20 cm^3) was added with stirring at 40 °C. The solution was stirred for 3 h and allowed to cool to room temperature. The blue crystalline product was collected by filtration, washed with ethanol and dried under vacuum to give [{Cu(O-bs)$_2$·C_2H_5OH}$_2$] [**2a**·EtOH]$_2$ (5.12 g, 85%); mp 136–138 °C (Found: C, 59.55; H, 3.97; Cu, 10.38. $C_{30}H_{24}CuO_9$ requires C, 59.84; H, 4.01; Cu, 10.55%); λ_{max}/nm (DMF) 263 (log ε/mol^{-1} dm^3 cm^{-1} 3.95) and 730 (2.31); $\tilde{\nu}_{max}$/cm^{-1} (Nujol) 3614, 1740, 1627, 1447, 1406, 1256, 1207, 1094, 1056, 1014, 774 and 700; $\mu_B = 1.30$. Crystals of [Cu(O-bs)$_2$(py)$_3$]·0.91py **2a**·3.91py suitable for crystallographic studies were obtained from pyridine on layering diethyl ether onto the solution, mp 76 °C (decomp.); $\tilde{\nu}_{max}$/cm^{-1} (KBr) 3614, 1734, 1625, 1454, 1375, 1274, 1194, 1067, 1030, 760 and 714; $\mu_B = 2.12$.

Table 1 Analytical[a] and physical data for green complexes [Cu(4′R-fla)$_2$] **1a–1d**

Compound	R	Yield[b] (%)	mp/°C	Analysis (%) C	H
1a	H	88	295–297	66.03 (66.97)	3.38 (3.37)
1b	CH_3	80	294–296	67.45 (67.89)	4.03 (3.91)
1c	Cl	90	297–299	60.84 (59.37)	2.77 (2.65)
1d	OCH_3	90	323–325	64.90 (64.26)	3.77 (3.71)

[a] Required values are given in parentheses. [b] Isolated yields.

Table 2 Characteristic absorption bands of complexes [Cu(4′R-fla)$_2$] **1a–1d**

Complex	$\tilde{\nu}$(CO)[a]/cm^{-1}	$\Delta\tilde{\nu}$(CO)/cm^{-1}	UV-vis (DMF) λ/nm (log ε/M^{-1} cm^{-1})		
1a	1537	71	268 (3.54)	433 (4.45)	719 (1.72)
1b	1534	81	263 (4.61)	435 (4.58)	702 (1.56)
1c	1548	67	263 (4.46)	434 (4.29)	703 (2.14)
1d	1538	70	268 (4.37)	440 (4.24)	769 (1.56)

[a] In Nujol.

Table 3 Magnetic properties of complexes [Cu(4′R-fla)$_2$] **1a–1d**

Complex	μ_{eff}/μ_B	$g_\perp$	$g_\parallel$	g_a[a]	G[b]
1a	1.76	2.0849	2.2519	2.1420	2.97
1b	1.98	2.0722	2.2476	2.1323	3.43
1c	1.64	2.0969	2.2908	2.1635	3.00
1d	1.49	2.0687	2.2438	2.1287	1.87

[a] $g_a = [(2g_\perp^2 + g_\parallel^2)/3]^{1/2}$. [b] $G = (g_\parallel - 2)/(g_\perp - 2)$.

Crystal structure determination

[Cu(fla)$_2$]·2$CHCl_3$ 1a·2$CHCl_3$. Single crystals were obtained by recrystallization of **3a** from dichloromethane. Crystal data and experimental conditions are listed in Table 4. The structure was solved by direct methods (SHELXS 86[22]) and then subjected to full-matrix least squares refinement based on F^2 (SHELXL 93[23]).

[Cu(O-bs)$_2$(py)$_3$]·0.91py 2a·3.91py. Crystals obtained by recrystallisation of complex **2a** from pyridine were mounted in a sealed capillary. Crystallographic data are recorded in Table 4. The structure was solved by direct methods (SHELXS 97[24]) and then subjected to full-matrix least squares refinement based on F^2 (SHELXL 97[25]).

The C13–C18 phenyl ring is disordered. The C13–C18, C13a–C18a moieties were refined as rigid groups (regular hexagons, C–C 1.390 Å). A three atom moiety was detected in a difference map around the inversion centre at (1/4,−1/4,1/2) that is expanded to a hexagon by symmetry. This solvent molecule was considered as pyridine that must be disordered by site symmetry as the nitrogen atom is reflected through the inversion center. The occupancy factor for the solvent atoms was refined by isotropic refinement that resulted in full occupancy. The disordered positions, are, therefore, filled by

1/2 nitrogen and 1/2 carbon atoms that were introduced in the same position. There must also be a hydrogen atom with half occupancy linked to the disordered carbon. The atoms of the solvent behaved well in the final anisotropic refinement cycles.

CCDC reference number 186/1640.

See http://www.rsc.org/suppdata/dt/1999/3847/ for crystallographic files in .cif format.

Kinetic measurements

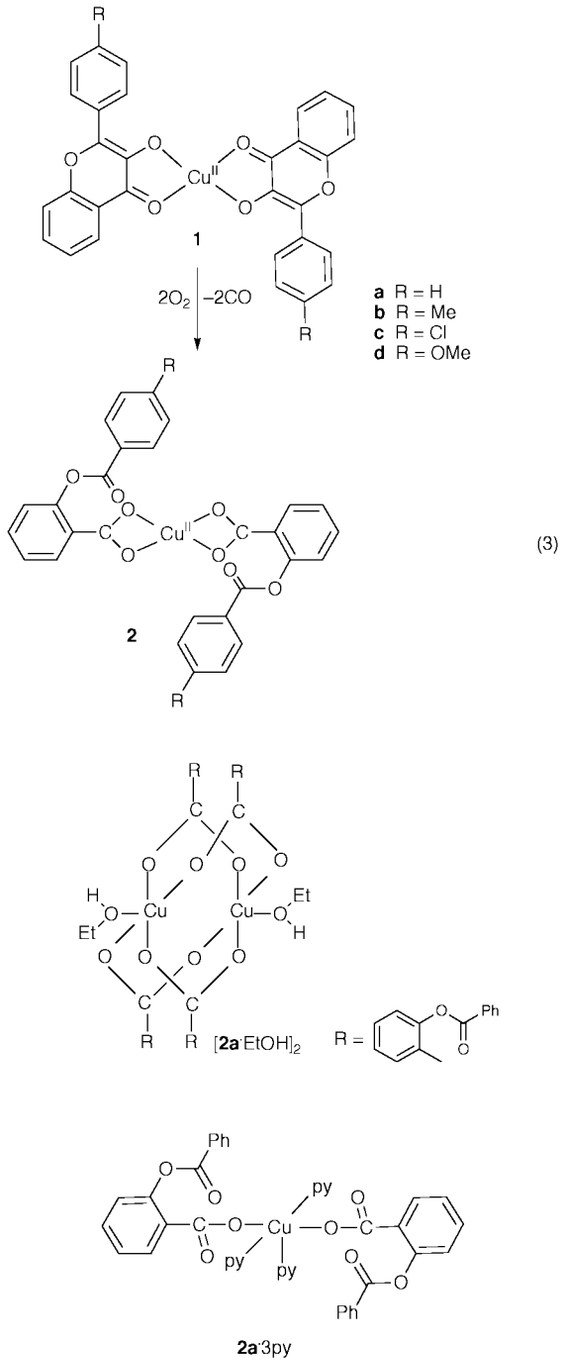
Reactions between $[Cu(fla)_2]$ and O_2 were performed in DMF solutions. In a typical experiment $[Cu(fla)_2]$ was dissolved under an argon atmosphere in a thermostatted reaction vessel with inlets for taking samples by a syringe, and connected to a mercury manometer to regulate constant pressure. The solution was then heated to the appropriate temperature. A sample was taken by syringe and the initial concentration of $[Cu(fla)_2]$ determined by UV-vis spectroscopy measuring the absorbance at 430.5 nm (λ_{max} of a typical band of $[Cu(fla)_2]$). Then the argon was replaced with dioxygen and the consumption of $[Cu(fla)_2]$ analysed periodically (*ca.* every 5 min). Experimental temperatures were determined with an accuracy of ±0.5 °C; the concentrations of $[Cu(fla)_2]$ were measured with a relative mean error of *ca.* ±2%; the pressure of dioxygen was determined with an accuracy of ±0.5%. The O_2 concentration was calculated from literature data[26] taking into account the partial pressure of DMF,[27] and assuming the validity of Dalton's law.

Results

Potassium or sodium salts of flavonol react with copper(I) and copper(II) chloride to give the corresponding flavonolato copper complexes.[12] In the presence of phosphine coligand tetrahedral $[Cu(PR_3)_2(fla)]$ products are obtained; with nitrogen-donor ligands the formation of similar compounds failed.[28] The complex $[Cu(fla)_2]$ **1a** was obtained in small quantities, which could be prepared in excellent yield starting from $Cu(OMe)_2$ and flavonol, eqn. (2).

$$Cu(OMe)_2 + 2Hfla \longrightarrow [Cu(fla)_2] + 2\ MeOH \quad (2)$$
1a

Oxygenation of $[Cu(fla)_2]$ in several solvents under ambient conditions (and even faster at temperatures around 100 °C) resulted in the bis(*O*-benzoylsalicylato)copper(II) complex **2a** and carbon monoxide contaminated with a small amount of CO_2 (GC analyses), eqn. (3). Both complexes have been fully characterised and the results of this investigation are described below. Complex **2a** has been recrystallised from ethanol to give blue $[\{Cu(O\text{-}bs)_2 \cdot EtOH\}_2]$. It shows an IR absorption at 1740 cm^{-1} [ν(CO)] indicating that the carbonyl group of the benzoyl group is not co-ordinated; ν(OH) absorption due to the co-ordinated ethanol could be found at 3614 cm^{-1}. The absorptions at 1627 and 1406 cm^{-1} are due to the co-ordinated carboxylato group. The difference between the asymmetric and symmetric stretching frequencies of the carboxylato group, $\Delta\nu = \nu_{asym}(CO_2) - \nu_{sym}(CO_2)$, is 221 cm^{-1} rendering these to a bridging carboxylate bonding mode. In the UV-vis spectrum the d–d transition may be assigned to the 730 nm absorption and the ligand to metal charge transfer at 263 nm. The room temperature magnetic susceptibility of $\mu_B = 1.30$ is less than expected for two d^9 atoms due to antiferromagnetic interactions as found in many other dicopper carboxylato complexes.[29] For the complex $[Cu(O\text{-}bs)_2(py)_3]$ **2a**·3py absorptions due to ethanol are missing and the difference in the asymmetric and symmetric stretching frequencies of the carboxylato group (250 cm^{-1}) is characteristic for monodentate carboxylate co-ordination.[29] The magnetic moment of $\mu_B = 2.12$ indicates a mononuclear complex as usually found for d^9 ions.



$[Cu(fla)_2]\cdot 2CHCl_3$ 1a·2CHCl₃. Crystallographic characterisation of $[Cu(fla)_2]\cdot 2CHCl_3$ isolated from a chloroform solution shows that the molecule is monomeric with two solvate molecules. The view of the molecule in Fig. 1 shows the square planar co-ordination geometry around the metal ion; the flavonolate ligands are arranged in *trans* position. The molecule is centrosymmetric at copper. Selected bond distances and angles are given in Table 5 and show that the Cu–O lengths [Cu(1)–O(2) 1.900(2) and Cu(1)–O(3) 1.942(2) Å] are significantly shorter than those in $[Cu(PPh_3)_2(fla)]$ [2.051(4) and 2.167(5) Å].[12] These are even a bit longer than the Cu–O bond lengths in the terminal alkoxide $[Cu_4(OBu^t)_4]$ [$Cu–O_{av}$ 1.854(9) Å][30] but shorter than those in bridging alkoxides, *e.g.* $[Cu_2Cl_2(OMe)_2(py)_2]_2$ [1.932(4) and 1.940(6) Å].[31] That means that the flavonolate ligand is more strongly bonded to copper(II) than to copper(I).[12] The C(2)–O(2) bond distance is shorter and the C(3)–O(3) bond length longer than those in free flavonol [1.357(3) and 1.232(3) Å].[32]

Table 4 Crystallographic data for complexes **1a**·2$CHCl_3$ and **2a**·3.91py

	1a·2$CHCl_3$	**2a**·3.91py
Molecular formula	$C_{32}H_{20}Cl_6CuO_6$	$C_{43}H_{33}CuN_3O_8$·0.91C_5H_5N
M	776.72	855.84
T/K	293(2)	293(2)
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	*C*2/*c*
a/Å	7.273(1)	30.948(3)
b/Å	10.691(1)	9.641(1)
c/Å	11.229(1)	16.159(1)
α/°	103.77(2)	
β/°	105.76(2)	115.53(1)
γ/°	99.61(2)	
U/Å^3	790.7(2)	4350.6(7)
Z	1	4
μ/mm^{-1}	6.023	1.184
Reflections collected	3250	4650
Independent reflections	3250 [*R*(int) = 0.000]	4478 [*R*(int) = 0.0117]
Final *R*1, *wR*2 [$I > 2\sigma(I)$]	0.0529, 0.1472	0.0463, 0.1376
(all data)	0.0714, 0.1717	0.0486, 0.1404

Table 5 Selected bond lengths (Å) and angles (°) of complex **1a**·2$CHCl_3$

Cu(1)–O(2)	1.900(2)	O(2)–C(2)	1.321(4)
Cu(1)–O(2′)	1.900(2)	O(3)–C(3)	1.268(4)
Cu(1)–O(3′)	1.942(2)	C(1)–C(2)	1.383(4)
Cu(1)–O(3)	1.942(2)	C(1)–C(11)	1.456(4)
O(1)–C(1)	1.366(4)	C(2)–C(3)	1.445(4)
O(1)–C(9)	1.357(4)	C(3)–C(4)	1.431(4)
O(2)–Cu(1)–O(2′)	179.999(1)	O(1)–C(1)–C(2)	120.1(3)
O(2)–Cu(1)–O(3′)	94.31(9)	O(1)–C(1)–C(11)	111.8(3)
O(2′)–Cu(1)–O(3′)	85.69(9)	C(2)–C(1)–C(11)	128.1(3)
O(2)–Cu(1)–O(3)	85.69(9)	O(2)–C(2)–C(1)	125.1(3)
O(2′)–Cu(1)–O(3)	94.31(9)	O(2)–C(2)–C(3)	115.7(3)
O(3′)–Cu(1)–O(3)	180.0	C(1)–C(2)–C(3)	119.2(3)
C(1)–O(1)–C(9)	112.2(3)	O(3)–C(3)–C(4)	123.2(3)
C(2)–O(2)–Cu(1)	110.6(2)	O(3)–C(3)–C(2)	118.0(3)
C(3)–O(3)–Cu(1)	110.0(2)	C(4)–C(3)–C(2)	118.8(3)

Symmetry operation 1 − *x* + 2; −*y*; −*z* + 2.

Table 6 Selected bond lengths (Å) and angles (°) for complex **2a**·3.91py

Cu–O(1)	1.973(1)	C(2)–O(3)	1.222(2)
Cu–O(1a)	1.973(1)	C(2)–C(4)	1.508(3)
Cu–N(19)	2.030(1)	C(9)–O(10)	1.398(3)
Cu–N(19a)	2.030(1)	O(10)–C(11)	1.364(4)
Cu–N(25)	2.280(2)	C(11)–O(12)	1.181(4)
O(1)–C(2)	1.272(2)	C(11)–C(13)	1.494(3)
O(1)–Cu–O(1a)	178.90(7)	O(3)–C(2)–C(4)	119.3(2)
O(1)–Cu–N(19a)	90.24(6)	O(1)–C(2)–C(4)	115.8(2)
O(1a)–Cu–N(19a)	89.89(6)	C(11)–O(10)–C(9)	116.6(2)
O(1)–Cu–N(19)	89.89(6)	O(12)–C(11)–O(10)	123.1(2)
N(19a)–Cu–N(19)	165.9(1)	O(12)–C(11)–C(13)	117.6(8)
O(1)–Cu–N(25)	89.45(4)	O(10)–C(11)–C(13)	119.2(8)
N(19)–Cu–N(25)	97.02(5)	C(24)–N(19)–Cu	121.4(2)
C(2)–O(1)–Cu	119.0(1)	C(20)–N(19)–Cu	120.5(1)
O(3)–C(2)–O(1)	124.9(2)	C(26)–N(25)–Cu	121.4(1)

Symmetry operation 1 − *x*; *y*; $-z + \frac{1}{2}$.

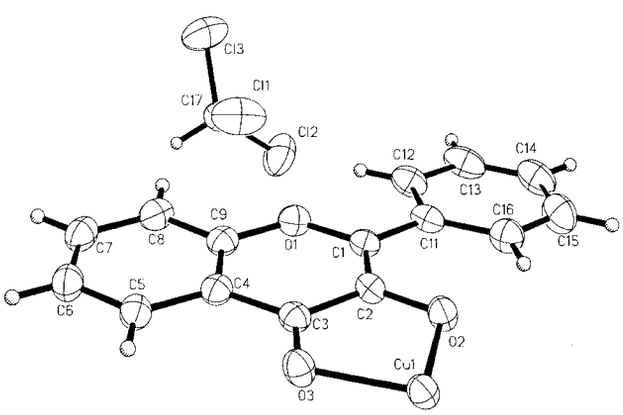


Fig. 1 View of [Cu(fla)$_2$]·2$CHCl_3$ **1a**·2$CHCl_3$.

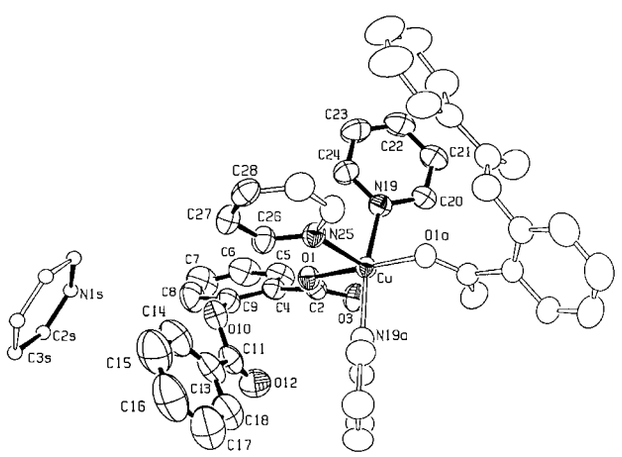


Fig. 2 View of [Cu(O-bs)$_2$(py)$_3$]·0.91py **2a**·3.91py.

[Cu(O-bs)$_2$(py)$_3$]·0.91py 2a·3.91py. Crystallographic characterisation of [Cu(O-bs)$_2$(py)$_3$]·0.91py crystallised from a pyridine solution shows that the co-ordination geometry around the copper ion is square pyramidal. A view of the molecule is shown in Fig. 2 and selected bond distances and angles are listed in Table 6. Monodentate carboxylato ligands (O-bs) and two pyridine nitrogens occupy *trans* positions in the basal plane. The Cu–O bond lengths are identical [1.9727(13) Å] and the same is true for the Cu–N bond distances [2.0301(16) Å] as well. The Cu–N distance of the apical pyridine ligand is however longer [2.280(2) Å]. The same geometry and similar values were obtained for the complex [Cu(PhCO$_2$)$_2$(py)$_3$][33] [Cu–O 1.9471(1) and 1.96(3); Cu–N 2.045(4), 2.049(4) and 2.367(4) Å] and for the square planar [Cu(PhCO$_2$)$_2$(tmeda)][34] [Cu–O 1.985(2) and Cu–N 2.038(3) Å]. Comparing these bond distances with those of the dinuclear copper benzoate complex [{Cu(PhCO$_2$)$_2$(py)}$_2$][35] [Cu–O from 1.960 to 1.979 and Cu–N 2.170 Å] not much difference can be seen. The C13–C18 phenyl ring is disordered.

Electrochemistry

A solution of complex [Cu(fla)$_2$] in DMF containing NBu_4PF_6 (0.1 M) under argon showed very weak redox currents in a

Table 7 Kinetic data for the oxygenation of $[Cu(fla)_2]$ in DMF solution

Expt. no.	T/°C	$10^3[O_2]$/ mol dm^{-3}	10^4[Cu][a]/ mol dm^{-3}	$10^4k'$/s^{-1}	R[b](%)	10^2k_{obs}/mol^{-1} dm^3 s^{-1}	10^8d[Cu]/dt mol dm^{-3} s^{-1}
1	100	7.70	0.62	0.26 ± 0.02	97.31	0.34 ± 0.03	0.60
2	100	7.70	1.27	1.71 ± 0.07	99.60	2.22 ± 0.09	1.90
3	100	7.70	1.62	2.23 ± 0.15	99.66	2.89 ± 0.20	2.70
4	100	7.70	1.71	1.49 ± 0.12	98.34	1.93 ± 0.16	3.15
5	100	7.70	2.02	1.21 ± 0.06	99.34	1.57 ± 0.08	3.46
6	100	7.70	2.99	0.91 ± 0.06	97.07	1.19 ± 0.08	5.58
7	100	1.93	2.64	0.14 ± 0.01	99.48	0.75 ± 0.02	0.57
8	100	4.90	2.63	0.83 ± 0.03	99.31	1.70 ± 0.07	2.02
9	100	7.70	2.65	0.89 ± 0.06	98.56	1.16 ± 0.08	2.73
10	100	9.95	2.64	1.24 ± 0.04	99.37	1.25 ± 0.04	3.83
11	100	11.65	2.62	1.93 ± 0.15	98.87	1.66 ± 0.20 0.87 ± 0.15[c]	4.40
12	90	7.84	2.38	0.78 ± 0.06	98.61	0.99 ± 0.08	
13	116	6.73	1.94	2.36 ± 0.08	99.67	3.50 ± 0.08	
14[d]	100	7.70	2.03	3.13 ± 0.09	99.24	4.07 ± 0.12	

[a] In 50 cm^3 DMF. [b] Correlation coefficients of least-squares regressions. [c] Mean value of the kinetic constant k and its standard deviation $\sigma(k)$ were calculated as $k = (\Sigma_i w_i/\Sigma_i w_i)$ and $\sigma(k) = (\Sigma_i w_i(k_i - k)^2/(n-1)\Sigma_i w_i)^{1/2}$, where $w_i = 1/\sigma_i^2$. [d] In DMF–py (48 cm^3–2 cm^3).

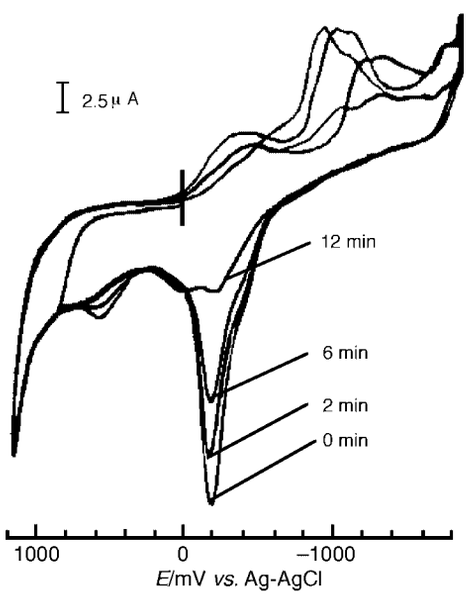


Fig. 3 Cyclic voltammograms upon oxygenation of $[Cu(fla)_2]$·**1a** in DMF–py.

platinum electrode system. The oxygenated product [Cu(O-bs)$_2$]·EtOH showed an irreversible redox current at 1090 mV. After addition of pyridine to the solution of $[Cu(fla)_2]$ in DMF a strong anodic peak current at −280 mV emerges rapidly under argon. This can be rationalised by assuming that complex **1a** dissociates in DMF to generate a free flavonolate anion and $[Cu(fla)(py)_3]^+$. When oxygen was bubbled through the solution (5 min) with disconnection of the electrode and then measurements were made under argon a decrease in i_{pa} of fla$^-$ was observed (Fig. 3). These results provide evidence that the oxygenation of $[Cu(fla)_2]$ occurs also after dissociation has taken place. However the rate of oxygenation of $[Cu(fla)_2]$ in DMF is much smaller (k^{DMF}/mol^{-1} dm^3 s^{-1} = (1.57 ± 0.08) × 10^{-2}) than in a DMF + pyridine mixture (k^{py}/mol^{-1} dm^3 s^{-1} = (4.07 ± 0.12) × 10^{-2}) (experiments 5, 14; in Table 7). This difference in reaction rate indicates that there are two pathways for the oxygenation of **1a**, namely a slower process in DMF where the flavonolate ligand is bonded to copper, and a faster one in the presence of an excess of py ligand where dissociation is enforced by the strongly ligating py and the dissociated flavonolate is being oxygenated.

Kinetic measurements

The kinetics of the oxygenation reaction was followed by determining the concentration of $[Cu(fla)_2]$ in the reaction solution as a function of time by UV-vis spectroscopic measurements under constant dioxygen pressure, determining the variations of the absorbance maxima of the flavonolate band at 430.5 nm. A simple rate law for the reaction between $[Cu(fla)_2]$ and O_2 is given in eqn. (4). In order to determine the

$$-\mathrm{d}[Cu(fla)_2)]/\mathrm{d}t = \mathrm{d}[Cu(O\text{-}bs)_2]/\mathrm{d}t = k[Cu(fla)_2]^m\,[O_2]^n \quad (4)$$

rate dependence on the various reactants, oxygenation runs were performed at various initial substrate concentrations (Table 7; experiments 1–6) and at different dioxygen pressures (Table 7, experiments 7–11 under pseudo first order conditions with a constant dioxygen pressure). Eqn. (4) can then have a more simple feature as written in eqn. (5), k' being the pseudo first order rate constant.

$$-\mathrm{d}[Cu(fla)_2]/\mathrm{d}t = k'[Cu(fla)_2]^m \quad (5)$$

The time dependence of the change of concentration of $[Cu(fla)_2]$ during the oxygenation and plots of log$[Cu(fla)_2]$ *versus* time were linear in experiments 1–6, indicating that the reaction is first order with respect to substrate concentration. Columns k' and R in Table 7 report slopes and the correlation coefficients obtained by the least-squares method for these linear regressions. A typical first order plot is shown in Fig. 4 for experiment 5; the reaction remains first order for the whole time in which the experiment was followed (63% conversion, 2 h). From variations of the reaction rates, plots of $-\mathrm{d}[Cu(fla)_2]/\mathrm{d}t$ *versus* $[Cu(fla)_2]$ were also linear in experiments 1–6, reinforcing that the reaction is indeed first order with respect to substrate concentration.

Experiments made at different dioxygen concentrations (calculated from literature data assuming the validity of Dalton's law, the dissolved concentration of O_2 being 7.7 × 10^{-3} mol dm^{-3} at 100 °C and 760 mmHg O_2 pressure) show that the dioxygen concentration affects the rate of the reaction (experiments 7–11; columns k' and R in Table 7) and that the reaction is first order with respect to dioxygen concentration. According to the kinetic data obtained the oxygenation of $[Cu(fla)_2]$ obeys a second order rate equation with $m = n = 1$ [eqn. (4)], from which a mean value of the kinetic constant k of (0.87 ± 0.15) × 10^{-2} mol^{-1} dm^3 s^{-1} at 373 K was obtained (Table 7).

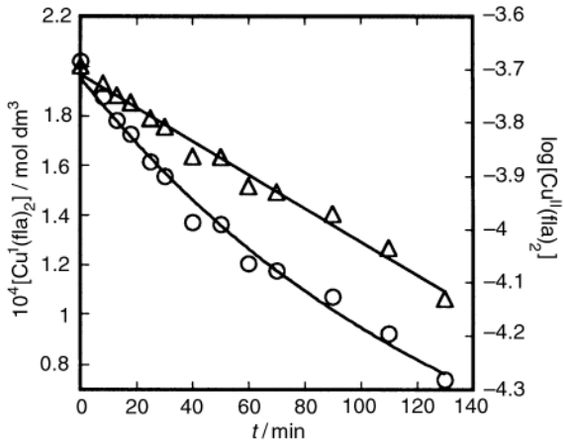


Fig. 4 Time course for the oxygenation of $[Cu(fla)_2]$ in DMF (○) and plot of log$[Cu(fla)_2]$ (Δ) *versus* reaction time for the oxygenation of $[Cu(fla)_2]$ (experiment 5, Table 7).

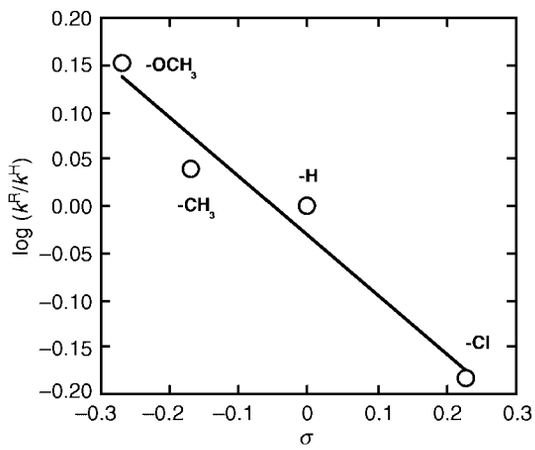


Fig. 5 Hammett plot for the oxygenation of $[Cu(4'R\text{-}fla)_2]$ complexes (Table 8).

The activation parameters for the oxygenation reaction were determined from the temperature dependence of the kinetic constant k. The Eyring plot of log (k/T) *versus* $1/T$ (k is expressed in mol^{-1} dm^3 s^{-1} and $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are assumed temperature-independent in the range examined) by using the k values at 373, 363 and 389 K (experiments 5, 12, 13 in Table 7) was linear with a correlation coefficient of 99.88%. The slope and the ordinate intercept of this line gave $\Delta H^{\ddagger} = 53 \pm 6$ kJ mol^{-1}, $\Delta S^{\ddagger} = -138 \pm 11$ J K^{-1} mol^{-1}, and $\Delta G^{\ddagger}(373\ \text{K}) = 105 \pm 2$ kJ mol^{-1}.

Reaction rates for the oxygenation of 4′-substituted flavonolato copper complexes $[Cu(4'R\text{-}fla)_2]$ **1a–1e** [eqn. (3)] under identical conditions were determined (with various electron-withdrawing and releasing substituents R) in order to determine electronic effects on the reaction rate. The Hammett plot obtained is shown in Fig. 5. Electron-releasing substituents enhanced the reaction rate and the reaction constant ρ was found to be −0.63.

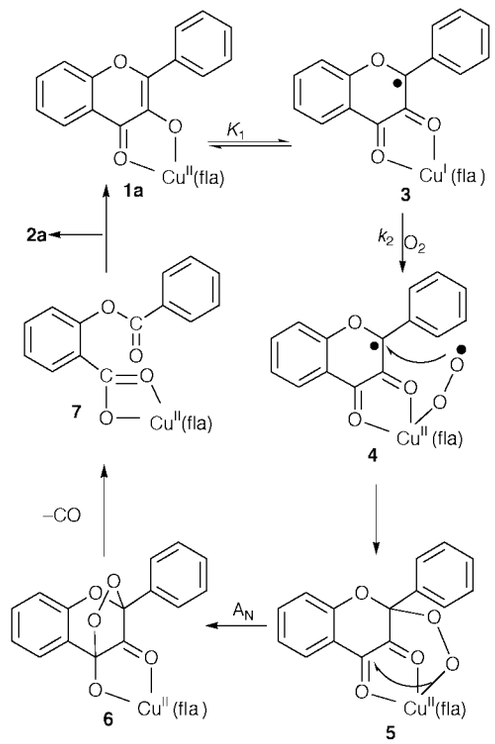
Discussion

From the experimental data a mechanism for the reaction of the flavonolatocopper complex **1** with dioxygen can be proposed (Scheme 1). Catechols[36] and quercetin (and 3-hydroxyflavone as well)[5] are assumed to be reactive substrates in enzyme reactions. However it is known that these substrates are inert towards dioxygen in their protonated forms. Deprotonation of catechols[37] and also of 3-hydroxyflavone[10b] enhances the activity of the corresponding anions toward dioxygen, yielding cleavage products such as those found in the enzyme reactions. Copper(II) has been found in the resting state of quercetinase.[5] Copper(II) ions differ from copper(I) ions in their reactivity toward dioxygen. The latter has a rich dioxygen chemistry[38] while the former is very stable and non-reactive.[39] Now in the case of flavonolatocopper complexes the question arises as to whether simple deprotonation (formation of the copper complex) is the activation step producing free flavonolate ions through dissociation of the complex as found in the case of cobalt complexes,[10b] leading to a direct reaction of it with dioxygen, or a certain role of copper may also be rendered to the activation process. The overall second order reaction expression and the CV measurements, which exclude dissociation of the flavonolate ligand of $[Cu(fla)_2]$ in DMF, support the proposal that in a fast preequilibrium the copper(II) flavonolate complex **1** undergoes intramolecular electron transfer from the ligand fla$^-$ to Cu^{II} resulting in the copper(I) flavonoxy radical complex **3** (Scheme 1). The equilibrium is largely shifted to the left (K_1 is rather small). In **3** there are two redox-active centers, the radical ligand and the copper(I) species. The biradical dioxygen may react at both sites, in an oxidative addition to the copper leading to a superoxocopper complex **4**, or in a radical–radical reaction with the flavonoxy ligand. We believe the former is the rate determining step, supported by the kinetic data and the negative entropy of activation. This is followed then in a fast consecutive formation of the trioxametallocycle **5** which reacts by a nucleophilic addition on the C4 carbon to give the endoperoxide **6**. The endoperoxide decomposes then in a fast step to the *O*-benzoylsalicylato copper complex **7** and carbon monoxide.

Table 8 Hammett data for the oxygenation of $[Cu(4'R\text{-}fla)_2]$

Complex	σ	$10^2 k_{obs}$ [a]/mol^{-1} dm^3 s^{-1}
1a	0.000	3.23 ± 0.30
1b	−0.170	3.53 ± 0.35
1c	+0.227	2.11 ± 0.16
1d	−0.268	4.59 ± 0.15

[a] In DMF at 120 °C.



Scheme 1

Owing to a ligand scrambling reaction, thereafter the starting copper flavonolate complex **1** and the bis(*O*-benzoylsalicylato)copper(II) complex **2** is formed.

Assuming steady state conditions for species **3**, the rate eqn. (6) can be deduced which after some simplification

$$-\frac{d[Cu]}{dt} = \frac{k_1k_2[Cu][O_2]}{k_1 + k_{-1} + k_2[O_2]} = \frac{k_1k_2[Cu][O_2]}{k_1 + k_{-1}} = k_{obs}[Cu][O_2] \quad (6)$$

($k_2[O_2] \ll k_1 + k_{-1}$ and [Cu] means the total complex) is in good agreement with an overall second order dependence according the experimental data obtained in the kinetic measurements.

The Hammett relationship shows that higher electron density at the copper ion enhances the rate of the reaction, which is consistent with an electrophilic attack of dioxygen at the copper(I) center, however the reaction constant of the oxygenation reaction is somewhat less ($\rho = -0.63$, $R = 0.977$) than that found for oxygenation of copper(I) chloride in pyridine ($\rho = -1.24$).[40] This may be due to the buffering effect of the other flavonolato ligand still co-ordinated to the copper ion which reduces the redox potential on the copper, reducing also the sensitivity of the reaction rate to electronic effects.

The reaction rate in acetonitrile was found to be rather slow. In order to isolate or at least detect any intermediates during the oxygenation reaction of complex **1** we conducted oxygenations at room temperature for a few days. In that case the presence of peroxidic products could be demonstrated either by titration by iodide or oxidising triphenylphosphine to triphenylphosphine oxide by the oxygenated product. In the IR spectrum bands at 1820 and at 860 cm^{-1} were found which were assigned to the ν(CO) absorption of the 3C=O in **6** and the ν(OO) of the endoperoxide. Unfortunately the endoperoxide was not stable enough to make the determinations quantitative and to make a firm characterisation of it. However the data presented here unequivocally show its presence during the oxygenation. It seems likely that endoperoxides of the type **6** can extrude CO easily and the stable carbonyl compounds formed are good driving forces for their decomposition.

As a conclusion it can be said that in the enzyme-like oxygenation of the co-ordinated flavonolato ligand of copper(II) the formation of an endoperoxide in the bimolecular reaction can be assumed and the unique decomposition of this endoperoxide accompanied by loss of carbon monoxide results in the copper(II) *O*-benzoylsalicylate complex as a good mimic of the enzyme action. Work is still in progress on model studies to disclose more details of this cleavage reaction.

Acknowledgements

Financial support of the Hungarian National Research Fund (OTKA T-7443, T-016285 and T-30400) is gratefully acknowledged.

References

1 B. G. Fox and J. D. Lipscomb, in *Biological Oxidation Systems*, ed. C. Reddy and G. A. Hamilton, Academic Press, New York, 1990, vol. 1, pp. 367–388; K. D. Karlin and Z. Tyeklár, *Bioinorganic Chemistry of Copper*, Chapman & Hall, New York, 1992; E. I. Solomon, M. J. Baldwin and M. D. Lowery, *Chem. Rev.*, 1992, **92**, 521; K. D. Karlin, *Science*, 1993, **261**, 701; W. G. Levine, in *The Biochemistry of Copper*, eds. J. Peisach, P. Aisen and W. E. Blumberg, Academic Press, New York, 1966, pp. 371–387; J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, L. Que, Jr., A. D. Zuberbühler and W. B. Tolman, *Science*, 1996, **271**, 1397.

2 K. D. Karlin, S. Kaderli and A. D. Zuberbühler, *Acc. Chem. Res.*, 1997, **30**, 139; K. D. Karlin, Z. Tyeklár and A. D. Zuberbühler, in *Bioinorganic Catalysis*, ed. J. Reedijk, Marcel Dekker, New York, 1993, pp. 261–315; V. Mahadevan, Z. Hou, A. P. Cole, D. E. Root, T. K. Lal, E. I. Solomon and T. D. P. Stack, *J. Am. Chem. Soc.*, 1997, **119**, 11996; S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, J. V. G. Young, C. J. Cramer, L. Que, Jr. and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **119**, 11555.

3 T. Funabiki, *Catalysis by Metal Complexes*, *Oxygenases and Model Systems*, Kluwer Academic Press, Dordrecht, 1997, vol. 19; M. Sono, M. P. Roach, E. D. Coulter and J. H. Dawson, *Chem. Rev.*, 1996, **96**, 2841; G. Speier, *New J. Chem.*, 1994, **18**, 143; G. Speier, Z. Tyeklár, L. Szabó II, P. Tóth, C. G. Pierpont and D. N. Hendrickson, in *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*, eds. D. H. R. Barton, A. E. Martell and D. T. Sawyer, Plenum Press, New York, 1993, pp. 423–436; L. Que, Jr. and R. Y. N. Ho, *Chem. Rev.*, 1996, **96**, 2607; C. G. Pierpont and C. W. Lange, *Prog. Inorg. Chem.*, 1994, **41**, 331.

4 D. W. Westlake, G. Talbot, E. R. Blakely and F. J. Simpson, *Can J. Microbiol.*, 1959, **5**, 62; S. Hattori and I. Noguchi, *Nature* (*London*), 1959, **184**, 1145; H. Sakamoto, *Seikagu* (*J. Jpn. Biochem. Soc.*), 1963, **35**, 633; T. Oka, F. J. Simpson and H. G. Krishnamurty, *Can. J. Microbiol.*, 1977, **16**, 493.

5 E. Makasheva and N. T. Golovkina, *Zh. Obsch. Khim.*, 1973, **43**, 1640; M. Thomson and C. R. Williams, *Anal. Chim. Acta*, 1976, **85**, 375; K. Takamura and M. Ito, *Chem. Pharm. Bull.*, 1977, **25**, 3218.

6 A. Nishinaga, T. Tojo, H. Tomita and T. Matsuura, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2511.

7 V. Rajananda and S. B. Brown, *Tetrahedron Lett.*, 1981, **22**, 4331.

8 T. Matsuura, H. Matsushima and R. Nakashima, *Tetrahedron*, 1970, **26**, 435.

9 M. M. A. El-Sukkary and G. Speier, *J. Chem. Soc., Chem. Commun.*, 1981, 745.

10 (*a*) A. Nishinaga, T. Tojo and T. Matsuura, *J. Chem. Soc., Chem. Commun.*, 1974, 896; (*b*) A. Nishinaga, T. Kuwashige, T. Tsutsui, T. Mashino and K. Maruyama, *J. Chem. Soc., Dalton Trans.*, 1994, 805.

11 M. Utaka, M. Hojo, Y. Fujii and A. Takeda, *Chem. Lett.*, 1984, 635; M. Utaka and A. Takeda, *J. Chem. Soc., Chem. Commun.*, 1985, 1824; É. Balogh-Hergovich and G. Speier, *J. Mol. Catal.*, 1992, **71**, 1.

12 G. Speier, V. Fülöp and L. Párkányi, *J. Chem. Soc., Chem. Commun.*, 1990, 512.

13 É. Balogh-Hergovich, G. Speier and G. Argay, *J. Chem. Soc., Chem. Commun.*, 1991, 551.

14 I. Lippai, G. Speier, G. Huttner and L. Zsolnai, *Chem. Commun.*, 1997, 741; I. Lippai and G. Speier, *J. Mol. Catal.*, 1998, **130**, 139; I. Lippai, G. Speier, G. Huttner and L. Zsolnai, *Acta Crystallogr., Sect. C*, 1997, **53**, 1547; É. Balogh-Hergovich, J. Kaizer and G. Speier, *Inorg. Chim. Acta*, 1997, **256**, 9.

15 D. F. Shriver and M. A. Drezdzon, *The Manipulation of Air-sensitive Compounds*, Wiley, New York, 1986.

16 R. W. Adams, E. Bishop, R. L. Martin and G. Winter, *Aust. J. Chem.*, 1966, **19**, 207.

17 M. A. Smith, R. M. Newman and R. A. Webb, *J. Heterocycl. Chem.*, 1968, **5**, 425.

18 A. Einhorn, L. Rothlauf and R. Seuffert, *Chem. Ber.*, 1911, **44**, 3309.

19 D. D. Perrin, W. L. Armarego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon, New York, 2nd edn., 1990.

20 R. L. Carlin, *Magnetochemistry*, Springer, Berlin, 1986, p. 311.

21 A. B. P. Lever, E. R. Milaeva and G. Speier, in *Phthalocyanines Properties and Applications*, eds. C. C. Leznoff and A. B. P. Lever, VCH, New York, 1993, vol. 3, p. 8.

22 G. M. Sheldrick, SHELXS 86, Program for Crystal Structure Determinations, University of Göttingen, 1990.

23 G. M. Sheldrick, SHELXL 93, Program for Crystal Structure Determinations, University of Göttingen, 1993.

24 G. M. Sheldrick, SHELXS 97, Program for Crystal Structure Determinations, University of Göttingen, 1997.

25 G. M. Sheldrick, SHELXL 97, Program for Crystal Structure Determinations, University of Göttingen, 1997.

26 A. Kruis, in *Landolt-Börnstein*, Springer, Berlin, 1976, bd. 4, teil 4, p. 269.

27 G. Ram and A. R. Sharaf, *J. Indian Chem. Soc.*, 1968, **45**, 13.

28 G. Speier, in *Bioinorganic Chemistry of Copper*, eds. K. D. Karlin and Z. Tyeklár, Chapman & Hall, New York, 1993, pp. 382–394.

29 R. C. Mehrotra and R. Bohra, *Metal Carboxylates*, Academic Press, London, 1983.

30 T. Grezier and E. Weiss, *Chem. Ber.*, 1976, **109**, 3142.

31 R. D. Willett and G. L. Breneman, *Inorg. Chem.*, 1983, **22**, 326.

32 M. C. Etter, Z. Urbanczyk-Lipkowska, S. Baer and P. F. Barbara, *J. Mol. Struct.*, 1986, **144**, 155.

33 G. Speier, K. Selmeczi, Z. Pintér, G. Huttner and L. Zsolnai, *Z. Kristallogr.*, 1998, **213**, 263.

34 L. Párkányi and G. Speier, *Z. Kristallogr.*, 1995, **210**, 307.

35 G. Speier and V. Fülöp, *J. Chem. Soc., Dalton Trans.*, 1989, 2331.

36 L. Que, Jr. and R. Y. N. Ho, *Chem. Rev.*, 1996, **96**, 2607.
37 C. A. Tyson and A. E. Martell, *J. Phys. Chem.*, 1970, **74**, 2601.
38 W. B. Tolman, *Acc. Chem. Res.*, 1997, **30**, 227; H. V. Obias, Y. Lin, N. N. Murthy, E. Pidcock, E. I. Solomon, M. Ralle, N. J. Blackburn, Y. M. Neuhold, A. D. Zuberbühler and K. D. Karlin, *J. Am. Chem. Soc.*, 1998, **120**, 12960.
39 F. A. Cotton and G. Wilkinson, *Basic Inorganic Chemistry*, Wiley, New York, 1976, pp. 412–416.
40 É. Balogh-Hergovich and G. Speier, *Transition Met. Chem.*, 1982, **7**, 177.

Paper 9/05684J