## The Oxygenation of Flavonol by Copper(1) and Copper(1) Flavonolate Complexes. The Crystal and Molecular Structure of Bis(flavonolato)copper(1)

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Flavonol is oxygenated to the corresponding depside catalysed by Cu<sup>1</sup> and Cu<sup>11</sup> flavonolate complexes; X-ray structure determination of bis(flavonolato)copper(II)·2CHCl<sub>3</sub> shows that the two flavonolate ligands are coordinated to Cu<sup>11</sup> through their 3-hydroxy and 4-carbonyl groups to result in a square planar geometry around copper(II).

Quercetin (1, 3', 4', 5, 7-tetrahydroxyflavonol) is metabolized in fungi to a depside (phenolic carboxylic acid ester) and carbon monoxide by quercetinase, a Cu<sup>II</sup>-containing dioxygenase, in which the formation of a Cu<sup>II</sup> chelate of 1 has been postulated as the key intermediate (Scheme 1).<sup>1-4</sup> Quercetin coordinates to copper(II)<sup>5</sup> and flavonol forms stable copper(I) compounds.<sup>6</sup> Simple copper complexes have been used in model reactions.<sup>7</sup>

Here we report the preparation of copper(II) flavonolate complexes and some model catalytic oxygenations in various solvents using Cu<sup>I</sup> and Cu<sup>II</sup> flavonolate complexes. Flavonol reacts with equimolar amounts of  $[Cu(OMe)_2]^8$  or  $[Cu_2(OMe)_2(py)_2]^9$  (py = pyridine) in dichloromethane at room temperature according to equations (1) and (2) to give the compounds  $[Cu(fla)_2]$  6 and [CuCl(fla)(py)] 7 (fla = flavonolate) in good yields.

$$[Cu(OMe)_2] + 2Hfla \rightarrow [Cu(fla)_2] + 2MeOH$$
(1)  
6

$$[Cu_2Cl_2(OMe)_2(py)_2] + 2Hfla \rightarrow [CuCl(fla)(py)] + 2MeOH$$
7
(2)

Complex **6** shows bands in the UV–VIS region at 240sh (log  $\varepsilon$  4.52), 258 (4.63), 273sh (4.53), 329 (4.18), 410 (4.53) and 426 (4.58) nm and IR absorption at 1537 cm<sup>-1</sup> assigned to v(CO). It is paramagnetic with  $\mu_{eff} = 2.10 \ \mu_B$  and solid state ESR parameters  $g_{\parallel} = 2.2519$  and  $g_{\perp} = 2.0849$ .

Complex 7 exhibits absorptions in the UV–VIS region at 238sh (log  $\varepsilon$  4.29), 256 (4.39), 326 (3.94), 407sh (4.19) and 425 (4.24) nm and IR absorption at 1537 cm<sup>-1</sup> [ $\nu$ (CO)]. It is paramagnetic ( $\mu_{eff} = 1.95 \ \mu_B$ ) and has ESR parameters  $g_1 = 2.2231$ ;  $g_2 = 2.0717$ ;  $g_3 = 2.0576$ . On recrystallization from CHCl<sub>3</sub> the compounds [CuCl<sub>2</sub>(py)<sub>2</sub>] and [Cu(fla)<sub>2</sub>] were formed.

The crystal structure of  $[Cu(fla)_2]$ ·2CHCl<sub>3</sub>† is shown in Fig. 1. The complex has high symmetry with *trans* coordination of the flavonolate ligands. It has a square planar geometry. The two 3-hydroxychromanone moieties and the central Cu<sup>II</sup> show high planarity to within 0.074 Å. The phenyl ring makes a dihedral angle of  $6.4(1)^{\circ}$  with the least-squares plane of the 3-hydroxychromanone moiety. Copper-oxygen bond distances are close [Cu-O(2) 1.901(2); Cu-O(3) 1.944(3) Å] to those found in [Cu<sub>4</sub>(OBu<sup>+</sup>)<sub>4</sub>]<sup>10</sup> [Cu-O<sub>av</sub>. 1.854(9) Å] and in [Cu<sub>2</sub>Cl<sub>2</sub>(OMe)<sub>2</sub>(py)<sub>2</sub>]<sup>11</sup> [1.932(4) and 1.940(6) Å]. They are however shorter than in [Cu(fla)(PPh<sub>3</sub>)<sub>2</sub>] [Cu-O(2) 2.051(4) and Cu-O(3) 2.167(5) Å].<sup>6</sup> The O(2)-Cu-O(3) angle [85.7(2)°] is bigger than in [Cu(fla)(PPh<sub>3</sub>)<sub>2</sub>] [O(2)-Cu-O(3) 79.2(3)°].<sup>6</sup>



Fig. 1 The structure of  $[Cu(fla)_2]$ -2CHCl<sub>3</sub>. Relevant bond distances (Å) and angles (°): Cu–O(2) 1.901(2), Cu–O(3) 1.944(3), O(2)–C(2) 1.318(5), O(3)–C(3) 1.266(5), C(2)–C(3) 1.445(4); O(2)–Cu–O(3) 85.7(2).

<sup>†</sup> Crystal data: Cu(C<sub>15</sub>H<sub>9</sub>O<sub>3</sub>)<sub>2</sub>·2CHCl<sub>3</sub>, triclinic, space group P1(no. 2), a = 7.273(1), b = 10.691(1), c = 11.229(1) Å,  $\alpha = 103.77(1)$ ,  $\beta = 105.76(1)$ ,  $\gamma = 99.61(1)^{\circ}$ , U = 790.8(4) Å<sup>3</sup>, Z = 1,  $D_c = 1.631$  g cm<sup>-3</sup>,  $\mu = 61.30$  cm<sup>-1</sup>. Data were collected using an Enraf-Nonius CAD-4 diffractometer (Cu-K $\alpha$  radiation,  $\lambda = 1.54184$  Å) in the range  $1.5^{\circ} < \theta$ < 75°. 2717 Reflections with  $I > 3\sigma(I)$  were used after Lorentzpolarization and empirical absorption corrections. The structure was solved by direct methods and refined by full matrix least squares. All non-hydrogen atoms were refined anisotropically, the hydrogen atoms were introduced in idealized positions with isotropic temperature factors  $B_{iH} = B_{iC} + 1$  Å<sup>2</sup>, where  $B_{iC}$  is the  $B_{eq}$  of the adjacent carbon atom. The final *R* values were R = 0.060,  $R_w = 0.060$  (w = 1) and for 3020 reflections  $R_{tot} = 0.075$ . The largest parameter shift/e.s.d. was 0.29. Atomic scattering factors were taken from standard tables [International Tables for X-ray Crystallography Vol. III. Kynoch Press, Birmingham, 1962 (present distributor, Reidel D., Dordrecht)]. Calculations were performed by Enraf-Nonius program system (B. A. Frenz, The Enraf-Nonius CAD-4 Structure Determination Package, Enraf-Nonius, Delft, 1983) run on a PDP 11/34 minicomputer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Table 1 Dioxygenation of flavonol by Cu<sup>I</sup> and Cu<sup>II</sup> flavonolate complexes

	Catalyst <sup>a</sup>	Solvent	t/h	Conv. (%)	Products (%)			
					4	8	9	10
1	$[Cu(fla)_2]^b$	MeCN DMF	10 10	22 68	42 16	33 40	25 20	<u></u> 24
2	[CuCl(fla)(py)] <sup>c</sup>	MeCN DMF	10 10 20	92 72 94	36 3 0	33 52 48	31 22 26	$\frac{-}{23}$
3	[Cu(fla)(diphos)]	MeCN DMF	20 10 20	23 52 98	52 14 11	24 35 42	23 24 24	 27 23
4	$[Cu(fla)(PPh_3)_2]^d$	DMF MeCN	10 20 20	78 96 98	55 27 30	23 41 29	14 16 41	8 16 —

<sup>*a*</sup> Substrate/Cu = 5. <sup>*b*</sup> After cooling  $[Cu(fla)_2]$  could be isolated. <sup>c</sup> [CuCl<sub>2</sub>(py)<sub>2</sub>] is formed. <sup>d</sup> OPPh<sub>3</sub> is also formed.

Catalytic oxygenations of flavonol by the compounds  $[Cu(fla)(PPh_3)_2], [Cu(fla)(diphos)] [diphos = bis(diphenyl$ phosphino)ethane], [CuCl(fla)(py)] and [Cu(fla)<sub>2</sub>] were carried out by using 0.1 mmol of the catalyst, 0.5 mmol of 2 and 20 ml of solvent [dimethylformamide (DMF) or MeCN] at 80 °C.

## J. CHEM. SOC., CHEM. COMMUN., 1991

Conversions and composition of the products are shown in Scheme 2 and Table 1.

The results show clearly that the oxygenation of flavonol by the use of either copper(1) or copper(11) flavonolate catalysts results in a very selective reaction, where only the depside and CO are formed as primary products along with some CO<sub>2</sub> as a result of concomitant oxidation of CO. Secondary products derived from 4 such as salicylic acid 8, benzoic acid 9 and N, N-dimethylbenzamide 10 due to hydrolysis and amidation of 4 by DMF were also formed during the relatively long reaction time. The catalytic data presented here show that these oxygenations differ significantly from other coppercatalysed oxygenations of 3-hydroxyflavones where no carbon-carbon cleavage took place. In other oxidations7 the six membered heterocyclic ring is opened, then closed to a five membered ring. The role of copper flavonolate complexes in these reactions seems to be decisive in cleaving the heterocyclic ring and they are assumedly similar to the enzyme reaction. However, further research has to be done to elucidate the detailed mechanism of quercetinase-like action in these model systems.

Received, 3rd December 1990; Com. 0/05439I

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