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

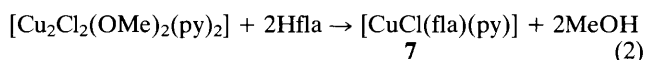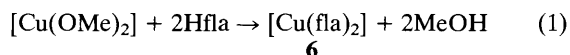## Éva Balogh-Hergovich,[a] Gábor Speier*[a] and Gyula Argay[b]

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Flavonol is oxygenated to the corresponding depside catalysed by Cu[I] and Cu[II] flavonolate complexes; X-ray structure determination of bis(flavonolato)copper(II)·2CHCl₃ shows that the two flavonolate ligands are coordinated to Cu[II] 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[II]-containing dioxygenase, in which the formation of a Cu[II] chelate of 1 has been postulated as the key intermediate (Scheme 1).[1–4] Quercetin coordinates to copper(II)[5] and flavonol forms stable copper(I) compounds.[6] Simple copper complexes have been used in model reactions.[7]

Here we report the preparation of copper(II) flavonolate complexes and some model catalytic oxygenations in various solvents using Cu[I] and Cu[II] flavonolate complexes. Flavonol reacts with equimolar amounts of [Cu(OMe)₂][8] or [Cu₂(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.

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

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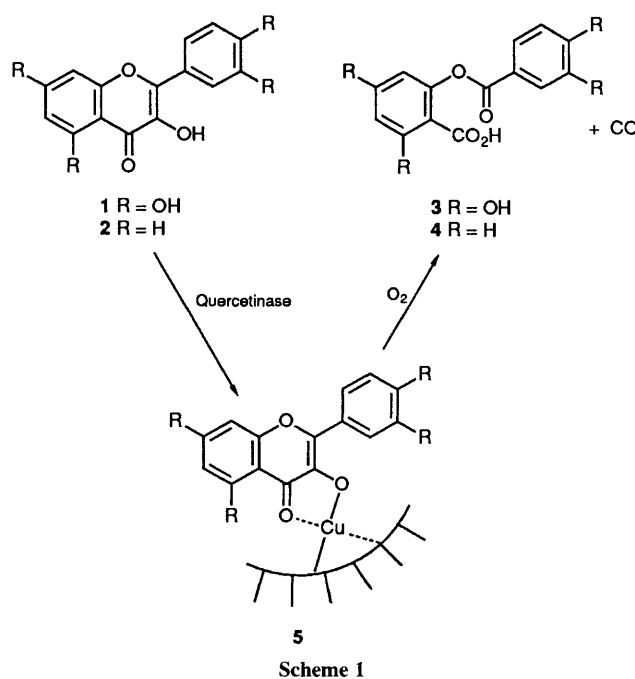$$\mathbf{7} \qquad \qquad \qquad (2)$$

Complex 6 shows bands in the UV–VIS region at 240sh (log ε 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⁻¹ assigned to ν(CO). It is paramagnetic with $\mu_{eff} = 2.10$ μ_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 ε 4.29), 256 (4.39), 326 (3.94), 407sh (4.19) and 425 (4.24) nm and IR absorption at 1537 cm⁻¹ [ν(CO)]. It is paramagnetic ($\mu_{eff} = 1.95$ μ_B) and has ESR parameters $g_1 = 2.2231$; $g_2 = 2.0717$; $g_3 = 2.0576$. On recrystallization from CHCl₃ the compounds [CuCl₂(py)₂] and [Cu(fla)₂] were formed.

The crystal structure of [Cu(fla)₂]·2CHCl₃† 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[II] show

high planarity to within 0.074 Å. The phenyl ring makes a dihedral angle of 6.4(1)° 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 [Cu₄(OBuᵗ)₄][10] [Cu–Oₐᵥ. 1.854(9) Å] and in [Cu₂Cl₂(OMe)₂(py)₂][11] [1.932(4) and 1.940(6) Å]. They are however shorter than in [Cu(fla)(PPh₃)₂] [Cu–O(2) 2.051(4) and Cu–O(3) 2.167(5) Å].[6] The O(2)–Cu–O(3) angle [85.7(2)°] is bigger than in [Cu(fla)(PPh₃)₂] [O(2)–Cu–O(3) 79.2(3)°].[6]

1 R = OH
2 R = H

3 R = OH
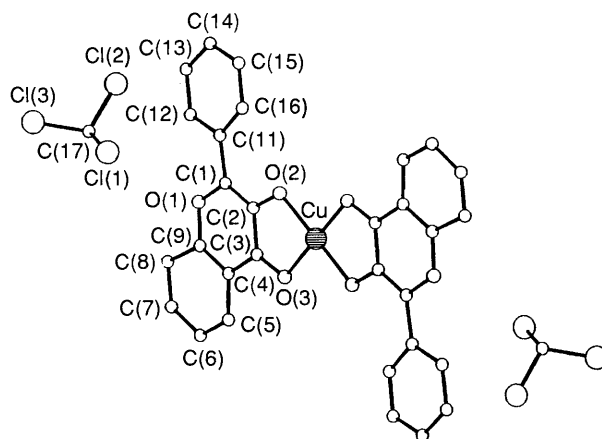**4** R = H

Quercetinase　　　O₂

+ CO

5

Scheme 1

Fig. 1 The structure of [Cu(fla)₂]·2CHCl₃. 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).
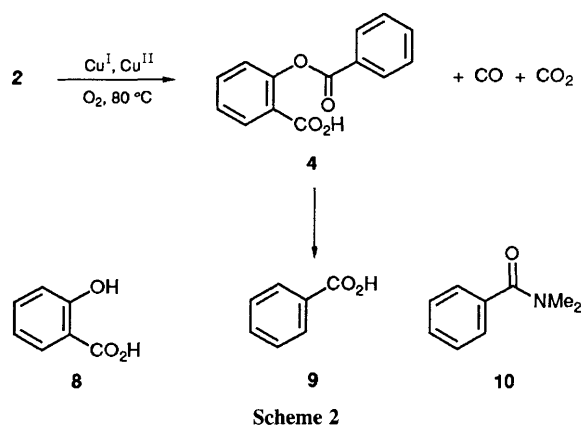
Scheme 2

Table 1 Dioxygenation of flavonol by Cu^I and Cu^{II} flavonolate complexes

| | | | Conv. | Products (%) | | | |
Catalyst[a]	Solvent	t/h	(%)	4	8	9	10
1	[Cu(fla)₂][b]	MeCN	10	22	42	33	25	—
		DMF	10	68	16	40	20	24
2	[CuCl(fla)(py)][c]	MeCN	10	92	36	33	31	—
		DMF	10	72	3	52	22	23
			20	94	0	48	26	26
3	[Cu(fla)(diphos)]	MeCN	20	23	52	24	23	—
		DMF	10	52	14	35	24	27
			20	98	11	42	24	23
4	[Cu(fla)(PPh₃)₂][d]	DMF	10	78	55	23	14	8
			20	96	27	41	16	16
		MeCN	20	98	30	29	41	—

[a] Substrate/Cu = 5. [b] After cooling [Cu(fla)₂] could be isolated.
[c] [CuCl₂(py)₂] is formed. [d] OPPh₃ is also formed.

Catalytic oxygenations of flavonol by the compounds [Cu(fla)(PPh₃)₂], [Cu(fla)(diphos)] [diphos = bis(diphenyl-phosphino)ethane], [CuCl(fla)(py)] and [Cu(fla)₂] 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.

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(I) or copper(II) flavonolate catalysts results in a very selective reaction, where only the depside and CO are formed as primary products along with some CO_2 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 copper-catalysed oxygenations of 3-hydroxyflavones where no carbon–carbon cleavage took place. In other oxidations[7] 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.

References

1 D. W. Westlake, G. Talbot, E. R. Blakely and F. J. Simpson, *Can. J. Microbiol.*, 1959, **5**, 62; F. J. Simpson, G. Talbot and D. W. S. Westlake, *Biochem. Biophys. Res. Commun.*, 1959, **2**, 621.
2 S. Hattori and I. Noguchi, *Nature*, 1959, **184**, 1145.
3 H. Sakamoto, *Seikagu (J. Jpn. Biochem. Soc.)*, 1963, **35**, 633.
4 T. Oka, F. J. Simpson and H. G. Krishnamurthy, *Can. J. Microbiol.*, 1977, **16**, 493.
5 E. Makasheva and N. T. Golovkina, *Zh. Obshch. 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 G. Speier, V. Fülöp and L. Párkányi, *J. Chem. Soc., Chem. Commun.*, 1990, 512.
7 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.
8 R. W. Adams, E. Bishop, R. L. Martin and G. Winter, *Aust. J. Chem.*, 1966, **19**, 207.
9 H. Finkbeiner, A. S. Hay, H. S. Blanchard and G. F. Endres, *J. Org. Chem.*, 1966, **31**, 549.
10 T. Greizer and E. Weiss, *Chem. Ber.*, 1976, **109**, 3142.
11 R. D. Willett and G. L. Breneman, *Inorg. Chem.*, 1983, **22**, 326.