Copper(II)-catalysed Oxidation of Quercetin and 3-Hydroxyflavone

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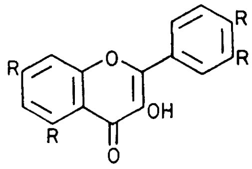
Quercetin and 3-hydroxyflavone are oxidized to the corresponding 2-alkoxyflavan-3,4-diones by $CuCl_2$ catalysis in MeOH or EtOH under oxygen or nitrogen, the mechanism of which is proposed.

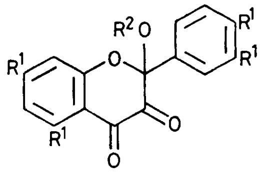
Quercetin (**1**), a yellow pigment widely distributed in plants, is known to form a stable Cu^{II} chelate at the 3-hydroxy and 4-carbonyl groups, (A).[1] Quercetin (**1**) is dioxygenated to a depside (phenolic carboxylic acid ester) and carbon monoxide by quercetinase, a Cu^{II}-containing dioxygenase, in which the formation of the Cu^{II} chelate of (**1**) is postulated as the key intermediate [equation (1)].[2] Therefore it is interesting to examine whether the Cu^{II} chelate (A) is dioxygenated in a similar way.[3]

Here we report that quercetin (**1**) and 3-hydroxyflavone (**2**) are oxidized to the corresponding 2-alkoxyflavan-3,4-diones (**3**) with $CuCl_2$ in methanol or ethanol, which are isolated as the hemiacetals (**4**) and (**5**) or the hydrate (**6**).

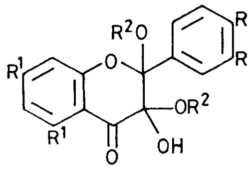
A typical reaction procedure is as follows. To a solution of



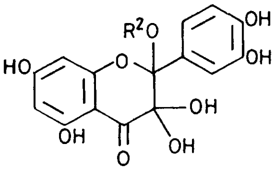
(1) R = OH
(2) R = H



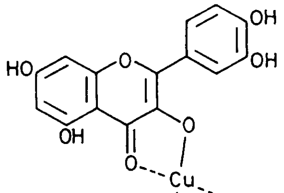
(3) R¹ = OH or H
R² = Et or Me



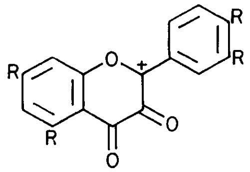
(4a) R¹ = OH, R² = Et
(4b) R¹ = OH, R² = Me
(5a) R¹ = H, R² = Et
(5b) R¹ = H, R² = Me



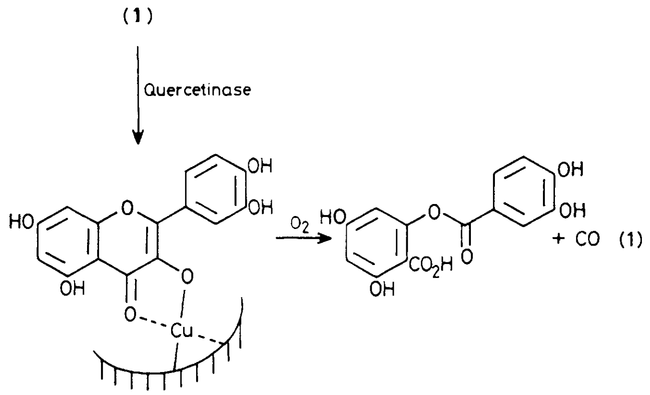
(6a) R² = Et
(6b) R² = Me



(A)



(B) R = OH or H



(1) (302 mg, 1.0 mmol) in anhydrous EtOH (20 ml) was added anhydrous $CuCl_2$ (67 mg, 0.5 mmol) under an oxygen atmosphere at 20 °C. The solution was stirred for 10 h. The absorption of oxygen was monitored by using a gas burette. After evaporation of the solvent, the residual oil was mixed with 10% HCl and extracted with diethyl ether. The extract, after drying (Na_2SO_4) and evaporation, gave a yellow solid of hydrate (**6a**) (319 mg, 88%).† The volume of oxygen absorbed was 12 ml [103% based on equation (4)].‡

It is obvious that (**6a**) was formed from (**1**) by a sequence of reactions, (**1**) → (**3**) → (**4a**) → (**6a**). When the reaction was carried out under a nitrogen atmosphere for 25—48 h, (**6a**) was obtained in 22—25% yields with 72—76% recovery of (**1**). This result and the observation that 1 equiv. of oxygen is absorbed lead to equations (2) and (3), which are summarized by equation (4).

$$(\mathbf{1})\text{ or }(\mathbf{2}) + 2\mathrm{Cu^{II}} + \mathrm{R^2OH} \rightarrow (\mathbf{3}) + 2\,\mathrm{Cu^{I}} + 2\mathrm{H^+} \quad (2)$$

$$2\mathrm{Cu^{I}} + \tfrac{1}{2}\mathrm{O_2} + 2\mathrm{H^+} \rightarrow 2\mathrm{Cu^{II}} + \mathrm{H_2O} \quad (3)$$

$$(\mathbf{1})\text{ or }(\mathbf{2}) + \tfrac{1}{2}\mathrm{O_2} + \mathrm{R^2OH} \xrightarrow{\mathrm{Cu^{II}}} (\mathbf{3}) + \mathrm{H_2O} \quad (4)$$

3-Hydroxyflavone (**2**), the parent compound of (**1**), was similarly oxidized by Cu^{II} and the product was isolated as (**5a**) or (**5b**). However, the reaction required a higher temperature and a longer reaction time, (**5a**) being obtained in 6% yield after 62 h at 20 °C and in 87% yield after 26 h at 50 °C and (**5b**) in 19% yield after 28 h at 50 °C. This sluggishness can be understood in terms of low electron density at the C-2 carbon atom owing to the absence of the electron-donating hydroxy groups. Compound (**2**) was oxidized more slowly in MeOH than in EtOH.

The hemiacetal (**5b**) has previously been obtained by oxidation of (**2**) with periodic acid in methanol.§[4] The mechanism was postulated to involve nucleophilic attack by solvent upon the positively charged C-2 carbon of the intermediate (B). Thus a similar ionic mechanism can be proposed for the present Cu^{II}-catalysed oxidation.¶ The role of Cu^{II} appears to be to abstract two electrons from the substrate to generate the cation (B). The oxygen does not oxidize the substrate directly but reoxidizes Cu^{I} to Cu^{II} as indicated in equations (2) and (3). This oxidation is in contrast to the direct oxygenation of the substrate that occurs in the enzyme reaction.‖

It is of interest that although quercetin (**1**) is thought to act as an antioxidant for ascorbic acid *in vitro* or *in vivo* by removing catalytic metal ions, such as Cu^{II}, through complex-

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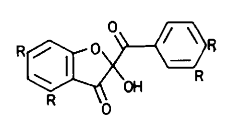
† The ¹H and ¹³C n.m.r. spectra were consistent with the structure (**6a**).

‡ No CO or CO_2 was detected by g.c.

§ The authentic sample of (**5b**) was obtained by oxidation of (**2**) with periodic acid. Its i.r. and n.m.r. spectra were identical with those for (**5b**) obtained by the Cu^{II}-catalysed oxidation.

¶ A radical process was proposed for the Cu^{II}-catalysed oxygenation of cyclohexa-1,2-diones which affords δ-keto acids with release of CO. See M. Utaka, M. Hojo, Y. Fujji, and A. Takeda, *Chem. Lett.*, 1984, 635.

‖ Nishinaga *et al.* (ref. 3c) reported that the $CuCl_2$-catalysed oxygenation of 3-hydroxyflavones in dimethylformamide (DMF) gave depsides. However we have found that the reaction of 3-hydroxyflavone (**2**) (1 mmol) in DMF (10 ml) with $CuCl_2$ (0.5 mmol) under oxygen at 20—50 °C for 6—12 h afforded (**7a**) as the major product, the depside, with liberation of CO, being a minor one. When quercetin (**1**) was used as the substrate at 20 °C for 11 h, (**7b**) (28% yield) was the sole product with 60% recovery of (**1**), no liberation of CO being detected.



(**7**) **a**; R = H
b; R = OH

ation,[1b,c,5] the oxidation of quercetin itself by Cu^{II} has not been investigated. The role of (**1**) will need to be re-examined in the light of present findings.

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