Crystal and molecular structure of a ketocarboxylatocopper(ii) intermediate in the oxygenation of a copper(i) flavonolate complex

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Flavonol reacts with metallic copper in the presence of 2,2′-bipyridine to give dihydrogen and a mixture of compounds with the stoichiometric composition [Cu^{I}(bpy)(fla)] from which on standing only [$Cu^{I}(bpy)_2]_2[Cu^{I}(fla)_3$] can be isolated; oxygenation of the solution of the mixture results in the ketocarboxylatocopper(II) complex [Cu^{II}(bpy)(fla)(2-$HOC_6H_4COCO_2$)], which hints at a copper-mediated oxidative cleavage of the pyranone ring in the flavonolate ligand *via* a 1,2-dioxethane intermediate by $^3O_2$.

Quercetin **1a** (3′,4′,5,7-tetrahydroxyflavonol) is metabolized in fungi to a depside (phenolic carboxylic acid ester) and carbon monoxide by quercetin 2,3-dioxygenase.[1] It is a Cu-containing dioxygenase and the coordination of **1a** to copper(ii) at its active site was assumed as the key intermediate.[2] Flavonol **1b** forms stable complexes with copper(i)[3] and copper(ii),[4] and simple copper complexes have been used in model reactions.[5] For the oxidative cleavage reaction of the heterocycle pathways *via* an endoperoxide (route a) and 1,2-dioxethane (route b) have been proposed (Scheme 1).[6]

Our aim was to prepare neutral mixed-ligand copper(i) flavonolate complexes and to investigate their oxygenation reaction in order to find possible chemical pathways of the enzymatic reaction. Equimolar amounts of flavonol **1b** (flaH) react with 2,2′-bipyridine (bpy) and metallic copper in acetonitrile at room temperature to yield a mixture of compounds with the stoichiometric composition of [Cu^{I}(fla)(bpy)] **6** according to Scheme 2. The compounds in the mixture are believed to be [Cu^{I}(fla)(bpy)] and anionic copper(i) species such as [$Cu^{I}(fla)_2]^-$, and [$Cu^{I}(fla)_3]_2^-$ with [$Cu^{I}(bpy)_2]^+$ counter cations from which on standing of the solution at room temperature only [$Cu^{I}(bpy)_2]_2[Cu^{I}(fla)_3$] **7** as red crystals are obtained. **7** consists of two cationic tetrahedral copper(i) ions each with two bpy ligands and a counter anion containing octahedral copper(i) with three flavonolate ligands. The structure of **7** was based on an X-ray structure determination, however the one N atom of bpy and one of the flavonolate ligands are heavily disordered, and thus full details are not provided. In this unique six-coordinated copper(i) species the average Cu–O distances are 2.069 Å (3 O–H) and 2.151 Å (4 C=O) and the average Cu–N bond length is 2.029 Å.

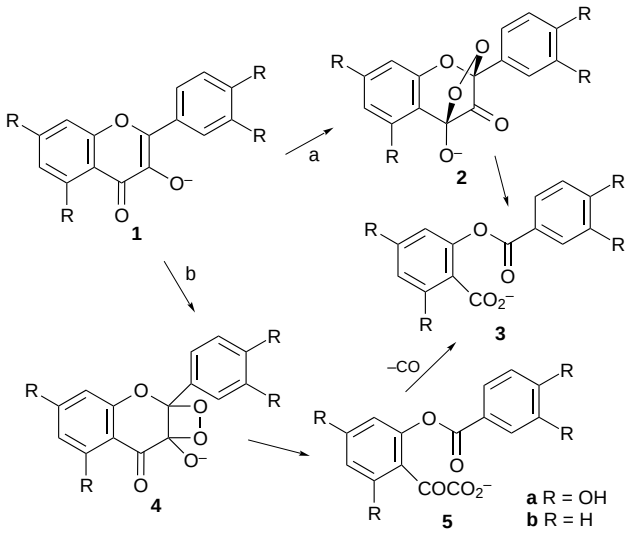
The oxygenation of the acetonitrile solution of the mixture **6** at room temperature and atmospheric dioxygen pressure proceeds very rapidly (few minutes) and green crystals of **8** are obtained in 11% yield (Scheme 2). Complex **8** shows bands in the UV–VIS region at 421 nm (log (ε/dm^3 mol^{-1} cm^{-1}) 4.15), 311 (4.26), 258 (4.39) and 615 (1.73) nm and IR absorptions at 1605 cm^{-1} [ν(CO)] and 3005 cm^{-1} [ν(OH)]. It is paramagnetic with μ_{eff} = 1.83 μ_B and EPR parameters in acetonitrile are g = 2.123 and A_{Cu} = 77.18 G.

The crystal structure of [Cu^{II}(bpy)(fla)(2-$HOC_6H_4COCO_2$)]† is shown in Fig. 1.

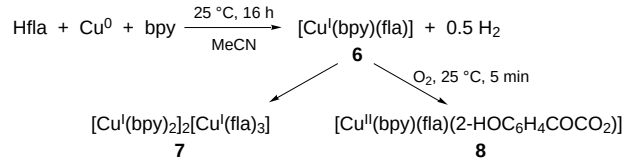
The complex has a square pyramidal geometry. Two oxygen atoms of the chelating flavonolate ligand and two nitrogen atoms of bpy occupy basal positions while the carboxylate oxygen atom of the ketocarboxylato ligand occupies the apical position. The copper–nitrogen bond distances [Cu–N(1) 1.982(7), Cu–N(2) 1.968(6) Å] do not differ much from those in [Cu^{II}(fla)(bpy)]ClO_4 [1.961(4), 1.978(4) Å] but are much shorter than those in [Cu^{II}(fla)(tmeda)(MeCN)]ClO_4 [2.023 (6), 2.024(7) Å].[7] The ketocarboxylate ligand is monodentate with a C–O bond distance of 2.231(5) Å. The plane of the keto group is perpendicular to the carboxylato group and lies in the plane of the 2-hydroxyphenyl moiety and forms through hydrogen-bonding with the OH group a stable six-membered ring. This may also contribute to the stability of its structure compared to that in bis(thienyl-2)-2-glyoxylatocopper(ii), and its dihydrated complex, where both the keto and carboxylato groups are bonded to the copper with average Cu–O distances of 2.077 Å.[8]

The copper–oxygen bond distances [Cu–O(5) 2.190(9), Cu–O(6) 1.760(11) Å] with the flavonolate ligand involving the 4-CO and 3-OH groups are very different from those found for [Cu(fla)$(PPh_3)_2$][3] [Cu–O(2) 2.051(4); Cu–O(3) 2.167(5) Å] and for [Cu$(fla)_2$][4] [Cu–O(2) 1.901(2); Cu–O(3) 1.944(3) Å].

Complex [Cu^{II}(bpy)(fla)(2-$HOC_6H_4COCO_2$)] is probably formed according to Scheme 3. The coordinated flavonolate ligand **1b** in **6** rapidly takes up triplet dioxygen to yield a 1,2-dioxethane species **9**, which breaks down to the *O*-benzoyl-2-hydroxyphenylglyoxylatocopper species **10**. This reacts then



Scheme 1



Scheme 2

probably with further flavonol, and hydrolysis of the ester group leads to 2-hydroxyphenylglyoxylato copper(ii) complex **8**. The ketocarboxylato copper(ii) complex **8** is surprisingly stable towards decarbonylation. At 80 °C in acetonitrile no decarbonylation occurs over 7 h. At 150 °C in dmf carbon monoxide and salicylic acid are formed due to decarbonylation as established by GCMS.

The formation of a ketocarboxylatocopper complex **8** in the oxygenation of a copper flavonolate may suggest that the oxidative cleavage reaction of the coordinated flavonolate ligand could proceed *via* a 1,2-dioxethane intermediate **9** which upon the usual decomposition and hydrolysis of the ester linkage leads to the ketocarboxylato complex **8**. The easiness of the oxygenation allows the reasoning that this route (route b) for the scission reaction may be favoured over the route a as shown in Scheme 1. Singlet oxygen in its [2 + 2] reaction with flavonol

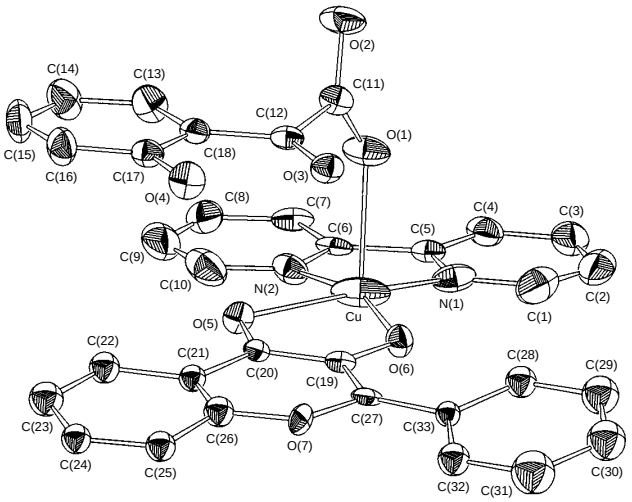
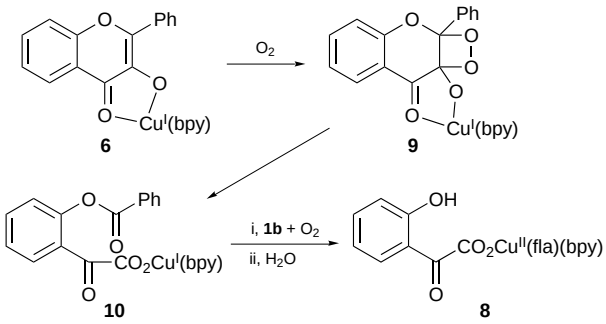


Fig. 1 The structure of [Cu^{II}(bpy)(fla)(2-$HOC_6H_4COCO_2$)]. Relevant bond distances (Å) and bond angles (°): Cu–N(1) 1.982(7), Cu–N(2) 1.969(6), Cu–O(1) 2.231(5), Cu–O(5) 2.190(9), Cu–O(6) 1.760(11), C(19)–O(6) 1.350(11), C(20)–O(5) 1.286(2), C(19)–C(20) 1.369(14), C(19)–C(27) 1.437(2); O(5)–Cu–O(6) 81.4(4), O(6)–Cu–N(1) 110.5(4), N(1)–Cu–N(2) 81.5(2), N(2)–Cu–O(5) 84.4(3), Cu–O(5)–C(20) 105.8(9), Cu–O(6)–C(19) 116.8(7), O(5)–C(20)–C(19) 117.1(12), O(6)–C(19)–C(20) 118.7(9), O(6)–C(19)–C(27) 120.5(9).



Scheme 3

was found to proceed according to this reaction pathway. $^3O_2$ in the presence of copper ions seems to afford similar reactions and is unique in this type of reactions. Kinetic, photochemical (testing of chemiluminescence), and decarbonylation reactions are being carried out to shed light on the mechanism of this reaction route of quercetinase mimicking C–C bond cleavage.

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Footnotes

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† *Crystal data*: Cu(fla)(2-$HOC_6H_4COCO_2$)(bpy), M = 621.06, monoclinic, space group $P2_1/c$, a = 10.285(5), b = 11.850(7), c = 21.892(9) Å, α = 90.00(0), β = 98.98(4), γ = 90.00(0)°, U = 2635(2) Å^3 (by least-squares refinement on diffractometer angles for 21 automatically centred reflections), λ = 0.71073 Å, Z = 4, D_c = 1.565 g cm^{-3}, $F(000)$ = 1272. Dark green prism. Crystal dimensions 0.20 × 0.20 × 0.30 mm.

Data were collected at 200 K using graphite-monochromated Mo-Kα radiation and ω scans on a Siemens R3m/V diffractometer in the 2θ range 5.1–47.1°, 3767 reflections measured with $I > 2\sigma(I)$.

The structure was solved by direct methods and refined by full-matrix least squares using SHELXS-86,[9] SHELXL-93.[9] All non-hydrogen atoms were refined using anisotropic thermal parameters; hydrogen atoms were included by use of a riding model and fixed isotropic thermal parameters. The final residual were R = 0.0765, R_w = 0.1812 and for 3524 reflections R_{tot} = 0.0707, $w^{-1} = [\sigma^2(F_o) + F_o^2]$, 402 parameters, maximum residual electron density = 0.636 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/369.

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