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Facile copper-mediated activation of the N–H bond and the oxidative cleavage of the C2–C3 bond in 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline

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The reaction of 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline (PhquinH$_2$; 1) with metallic copper leads to Cu^{II}(PhquinH)$_2$ while in the presence of PPh$_3$ to Cu$^{I}_2$Cu^{II}(Phquin)$_2$(PPh$_3$)$_4$. In the presence of tmeda and O$_2$ ring cleavage occurs to give Cu^{II}(tmeda)(PhquinH)(N-baa). Both reactions represent a mild N–H activation and an oxidative C–C bond scission.

1*H*-2-Phenyl-3-hydroxy-4-oxoquinoline (**1**) is isoelectronic with flavonol (**2**) and both compounds are degraded by microorganisms by the use of molecular oxygen. In both cases the C2–C3 bond in the heterocyclic ring is cleaved by the dioxygenases 1*H*-3-hydroxy-4-oxoquinaldine 2,4-dioxygenase (**1**)[1] and quercetin 2,3-dioxygenase (**2**)[2] with concomitant release of carbon monoxide (Scheme 1). The latter contains copper(II) ions at its active site, while that metabolizing **1** does not have any metallic cofactor.[3] In the course of model studies of quercetinase numerous copper complexes of flavonol have been prepared and characterized.[4] In all cases the flavonolate ligand coordinates to the copper ion as a bidentate ligand through its 3-hydroxy and 4-carbonyl groups. Since **1** has a nitrogen atom in position 1 of the heterocyclic ring it can also act as a binding site to metal ions. Here we wish to show that 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline coordinates to copper(II) in a similar fashion to flavonol. Furthermore metallic copper induces N–H activation in **1** and if dioxygen is present a facile oxidative cleavage of the C2–C3 bond can be observed which resembles the enzymatic reaction.

Metallic copper reacts with 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline (**1**) in DMF at 50 °C to give complex **3** in 33% yield and probably H_2 as found also in the similar reaction of Cu^0 with **2** in the presence of 2,2′-bipyridine.[5] The complex contains a Cu(II) centre with μ_B = 1.97 and EPR parameters of g = 2.128 and A = 71.8 G. It has a square planar geometry around the copper(II) ion and one Cu–O distance is somewhat longer and the other shorter than those in the corresponding bis(flavonolato)copper(II) complex[5] (Fig. 1). If the reaction is carried out in the presence of triphenylphosphine the trinuclear copper complex **4** is formed in good yield (30%). **4** contains a copper(II) ion in a square planar coordination. It is paramagnetic with μ_B = 1.64 and EPR parameters of g = 2.116 and A = 71.1 G. The other two copper(I) ions coordinate to the nitrogen atoms of the heterocycles. It represents a smooth activation of the N–H bond as found in a few cases with other metal complexes too.[7] The Cu(I) ions are tricoordinated and the geometry around the copper(I) ions is planar (Fig. 2). The bond lengths of the coordinated heterocycle indicate electron delocalization with longer C=N and C–O bond distances as in the uncoordinated compound.[8] When during the reaction of metallic copper and 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmeda) in DMF at 60 °C dioxygen is present even in a very small concentration, complex **5** is formed in 41% yield. During the reaction the C2–C3 bond in the 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline is cleaved, both oxygen atoms of O_2 are incorporated into **1**, based on $^{18}O_2$ experiments, and CO is released to give the mixed ligand copper(II) complex **5** (Fig. 3, Scheme 2). The CO content was determined by GC–MS (81–89%) and volumetric measurements (equimolar amount of O_2 consumed and CO released). After acidic hydrolysis of **5** and methylation of the

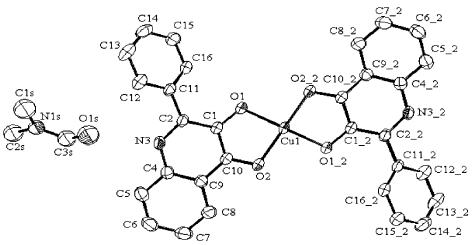


Fig. 1 The molecular structure of **3** with selected bond distances (Å) and angles (°): Cu(1)–O(1) 1.9067(13), Cu(1)–O(2) 1.9307(13), O(1)–C(1) 1.319(2), O(2)–C(10) 1.291(2), C(1)–C(10) 1.425(2), O(1)–Cu(1)–O(2) 85.74(6), O(1)–Cu(1)–O(2_2) 94. 26(6).†

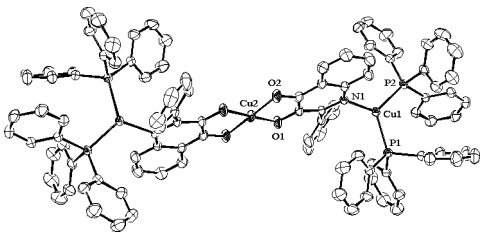


Fig. 2 The molecular structure of **4** with selected bond distances (Å) and angles (°): Cu(2)–O(1) 1.9177(13), Cu(2)–O(2) 1.9286(14), Cu(1)–N(1) 2.0175(14), Cu(1)–P(1) 2.2791(7), Cu(1)–P(2) 2.2558(6), O(1)–Cu(2)–O(2) 93.70(6), N(1)–Cu(1)–P(1) 117.76(5), N(1)–Cu(1)–P(2) 121.46(5), P(2)–Cu(1)–P(1) 119.09(2).†

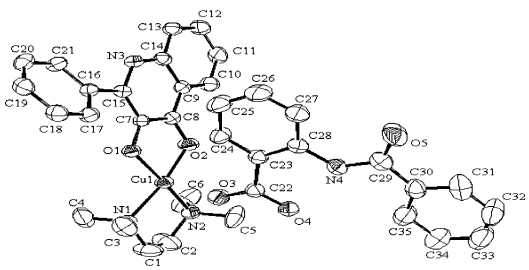
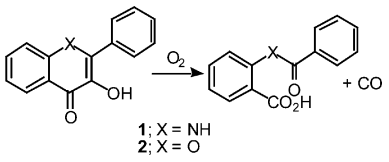


Fig. 3 The molecular structure of **5** with selected bond distances (Å) and angles (°): Cu(1)–O(1) 1.9250(19), Cu(1)–O(2) 1.955(2), Cu(1)–N(1) 2.049(3), Cu(1)–N(2) 2.033(3), C(7)–O(1) 1.323(3), C(8)–O(2) 1.290(4), C(8)–C(7) 1.418(4), O(1)–Cu(1)–O(2) 85.21(9), O(1)–Cu(1)–N(2) 170.78(10), O(2)–Cu(1)–N(2) 92.81(12), O(1)–Cu(1)–N(1) 92.82(10), O(2)–Cu(1)–N(1) 167.02(10), N(2)–Cu(1)–N(1) 87.09(11).†



Scheme 1

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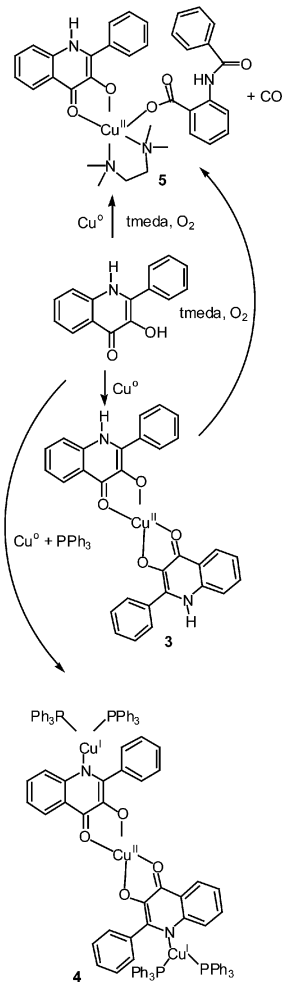

Scheme 2

products MS data evidenced both labelled O-atoms in the products,[9] however some scrambling during the workup occurred. Preliminary kinetic data show first order dependence of the reaction rate on both **3** and O_2. It is paramagnetic with μ_B = 1.91 and EPR parameters of g = 2.129 and A = 55.9 G, and the geometry around the Cu(II) centre is square pyramidal. The two N-atoms of tmeda and the two O-atoms of the deprotonated **1** occupy basal positions.

The results outlined show that copper metal probably deliberates H_2 from **1** to give **3** which in the presence of triphenylphosphine reacts further with scission of the N–H bond to give the trinuclear copper(I)(II) compex **4**. The driving force for these reactions are the formation of the very stable chelate complexes **3** and **4**. The formation of the highly delocalized tridentate ligand in **4** may ease the scission reaction of the N–H bond. **4** can not be considered as a clear Cu(I) amido complex since the C=N bond length is longer than that in the parent compound and the heterocycle is delocalized.[8] In the presence of tmeda and dioxygen **3** may be formed first, which is oxygenated subsequently to **5** with cleavage of the C2–C3 bond in **1** and incorporation of two O-atoms into **3** and concomitant CO release. Similar reactions of metallic copper with acidic compounds leading to copper complexes in the presence of O_2 are well documented (*e.g.* copper bracelet).[10] The oxygenation of **3** resembles the enzyme reaction of **1** to give the cleavage product as shown in Scheme 1.

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Notes and references

† Intensity data were measured on an Enraf-Nonius CAD4 diffractometer at 293 K. The structures were solved by direct methods. The structures were refined by full-matrix anisotropic least-squares on F^2. The N–H hydrogen atoms were located in difference maps (**3,5**), other hydrogen atoms were added at idealized positions. All hydrogen atoms were included in structure factor calculations but were not refined.

Crystal data. Compound **3**: $C_{36}H_{34}CuN_4O_6$, M_w = 682.21, triclinic, space group $P\bar{1}$, a = 9.340(2), b = 9.626(3), c = 10.522(1) Å, α = 101.86(1), β = 125.64(1), γ = 107.73(2)°, V = 805.3(3) Å^3, Z = 1, D_c = 1.407 g cm^{-3}, μ(Cu–Kα) = 1.396 cm^{-1}, 2904 reflections measured, 212 parameters refined on F^2 using 2697 unique reflections to final indices $R[F^2 > 3\sigma F^2)]$ = 0.043, wR = 0.115, $w = 1/[\sigma^2(F_o^2) + (0.0787P)^2 + 0.0874P]$, $P = (F_o^2+2F_c^2)/3$. The final residual Fourier positive and negative peaks were 0.505 and −0.767 e Å^{-3}.

Compound **4**: $C_{54}H_{46}Cu_{1.5}N_2O_3P_2$, M_w = 928.18, monoclinic, space group $C2/c$, a = 40.058(4), b = 10.251(2), c = 27.769(4) Å, β = 125.64(1)°, V = 9267(2) Å^3, Z = 8, D_c = 1.331 g cm^{-3}, μ(Mo–Kα) = 0.809 cm^{-1}, 13945 reflections measured, 586 parameters refined on F^2 using 13366 unique reflections to final indices $R[F > 3\sigma F)]$ = 0.038, wR = 0.083, $w = 1/[\sigma^2(F_o^2) + (0.0526P)^2]$, $P = (F_o^2+2F_c^2)/3$. The final residual Fourier positive and negative peaks were 0.349 and −0.345 e Å^{-3}.

Compound **5**: $C_{41}H_{50}CuN_6O_7$, M_w = 802.41, monoclinic, space group Pc, a = 10.033(3), b = 12.778(11), c = 17.681(15) Å, β = 117.36(6)°, V = 2013(3) Å^3, Z = 2, D_c = 1.21 g cm^{-3}, μ(Cu–Kα) = 1.227 cm^{-1}, 5677 reflections measured, 504 parameters refined using 5190 unique reflections to final indices $R[F > 3\sigma F)]$ = 0.030, wR = 0.077, $w = 1/[\sigma^2(F_o^2) + (0.0536P) + 0.2737P]$, $P = (F_o^2+2F_c^2)/3$. The final residual Fourier positive and negative peaks were 0.256 and −0.206 e Å^{-3}. CCDC 222925–222927. See http://www.rsc.org/suppdata/cc/b3/b315919a/ for crystallographic data in .cif or other electronic format.

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