

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

Miklós Czaun,^a Gábor Speier^{*ab} and László Párkányi^c

^a Department of Organic Chemistry, University of Veszprém, 8201 Veszprém, Hungary.

E-mail: speier@almos.vein.hu; Fax: +36 88 427 492; Tel: +36 88 422 022/4657

^b Research Group for Petrochemistry, Hungarian Academy of Sciences, 8201 Veszprém, Hungary

^c Hungarian Academy of Sciences, Chemical Research Center, Institute of Chemistry, H-1051 Budapest, Hungary

Received (in Cambridge, UK) 5th December 2003, Accepted 2nd March 2004

First published as an Advance Article on the web 18th March 2004

The reaction of 1*H*-2-phenyl-3-hydroxy-4-oxoquinoline (PhquinH₂; **1**) with metallic copper leads to Cu^{II}(PhquinH)₂ while in the presence of PPh₃ to Cu₂Cu^{II}(Phquin)₂(PPh₃)₄. In the presence of tmeda and O₂ 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-oxoquinoline 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 H₂ as found also in the similar reaction of Cu⁰ with **2** in the presence of 2,2'-bipyridine.⁵ The complex contains a Cu(II) centre with $\mu_B = 1.97$ 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) complex⁵ (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 $\mu_B = 1.64$ 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 O₂ are incorporated into **1**, based on ¹⁸O₂ 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 O₂ consumed and CO released). After acidic hydrolysis of **5** and methylation of the

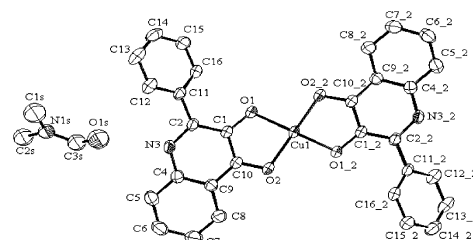


Fig. 1 The molecular structure of **3** with selected bond distances (Å) and angles (°): Cu(1)–O(1) 1.9067(13), Cu(1)–O(2) 1.9307(13), O(1)–C(1) 1.319(2), O(2)–C(10) 1.291(2), C(1)–C(10) 1.425(2), O(1)–Cu(1)–O(2) 85.74(6), O(1)–Cu(1)–O(2_2) 94.26(6).†

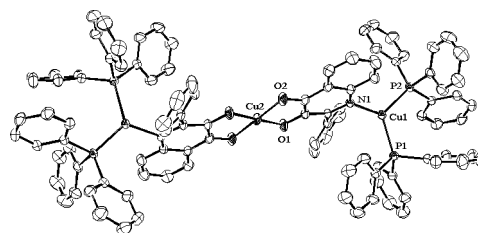


Fig. 2 The molecular structure of **4** with selected bond distances (Å) and angles (°): Cu(2)–O(1) 1.9177(13), Cu(2)–O(2) 1.9286(14), Cu(1)–N(1) 2.0175(14), Cu(1)–P(1) 2.2791(7), Cu(1)–P(2) 2.2558(6), O(1)–Cu(2)–O(2) 93.70(6), N(1)–Cu(1)–P(1) 117.76(5), N(1)–Cu(1)–P(2) 121.46(5), P(2)–Cu(1)–P(1) 119.09(2).†

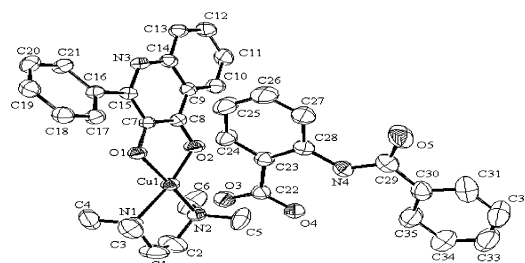
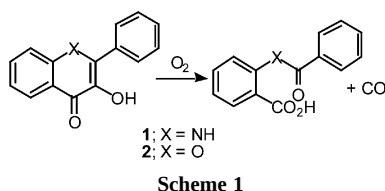
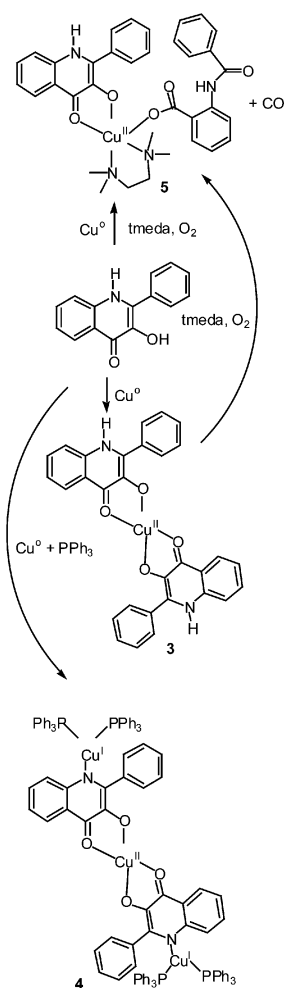


Fig. 3 The molecular structure of **5** with selected bond distances (Å) and angles (°): Cu(1)–O(1) 1.9250(19), Cu(1)–O(2) 1.955(2), Cu(1)–N(1) 2.049(3), Cu(1)–N(2) 2.033(3), C(7)–O(1) 1.323(3), C(8)–O(2) 1.290(4), C(8)–C(7) 1.418(4), O(1)–Cu(1)–O(2) 85.21(9), O(1)–Cu(1)–N(2) 170.78(10), O(2)–Cu(1)–N(2) 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 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 $\mu_B = 1.91$ 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) complex **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.

Financial support by the Hungarian National Research Fund (OTKA Nos. T030400 and T043414) is gratefully acknowledged. Thanks to Drs A. Rockenbauer and L. Korecz (Budapest) for EPR measurements.

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**: $\text{C}_{36}\text{H}_{34}\text{CuN}_4\text{O}_6$, $M_w = 682.21$, triclinic, space group $P\bar{1}$, $a = 9.340(2)$, $b = 9.626(3)$, $c = 10.522(1)$ Å, $\alpha = 101.86(1)^\circ$, $\beta = 125.64(1)^\circ$, $\gamma = 107.73(2)^\circ$, $V = 805.3(3)$ Å³, $Z = 1$, $D_c = 1.407$ g cm^{−3}, $\mu(\text{Cu–K}\alpha) = 1.396$ 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**: $\text{C}_{54}\text{H}_{46}\text{Cu}_{1.5}\text{N}_2\text{O}_3\text{P}_2$, $M_w = 928.18$, monoclinic, space group $C2/c$, $a = 40.058(4)$, $b = 10.251(2)$, $c = 27.769(4)$ Å, $\beta = 125.64(1)^\circ$, $V = 9267(2)$ Å³, $Z = 8$, $D_c = 1.331$ g cm^{−3}, $\mu(\text{Mo–K}\alpha) = 0.809$ 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**: $\text{C}_{41}\text{H}_{50}\text{CuN}_6\text{O}_7$, $M_w = 802.41$, monoclinic, space group Pc , $a = 10.033(3)$, $b = 12.778(11)$, $c = 17.681(15)$ Å, $\beta = 117.36(6)^\circ$, $V = 2013(3)$ Å³, $Z = 2$, $D_c = 1.21$ g cm^{−3}, $\mu(\text{Cu–K}\alpha) = 1.227$ 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.

- I. Bauer, N. Max, S. Fetzner and F. Lingens, *Eur. J. Biochem.*, 1996, **240**, 576.
- T. Oka, F. J. Simpson and H. G. Krishnamurthy, *Can. J. Microbiol.*, 1977, **16**, 493.
- S. Fetzner, B. Tshisuaka, F. Lingens, R. Kappl and J. Hüttermann, *Angew. Chem. Int. Ed.*, 1998, **37**, 576.
- É. Balogh-Hergovich, J. Kaizer, J. Pap, G. Speier, G. Huttner and L. Zsolnai, *Eur. J. Inorg. Chem.*, 2002, 2287 and references therein.
- I. Lippai, G. Speier, G. Huttner and L. Zsolnai, *Chem. Commun.*, 1997, 741.
- É. Balogh-Hergovich, G. Speier and G. Argay, *J. Chem. Soc., Chem. Commun.*, 1991, 551.
- G. A. Ardizzoia, S. Brenna, G. LaMonica, A. Maspero, N. Maciocchi and M. Moret, *Inorg. Chem.*, 2002, **41**, 610 and references therein.
- M. Czaun, I. Ganszky, G. Speier and L. Párkányi, *Z. Kristallogr. NCS*, 2002, **257**, 379 and unpublished results.
- M. Czaun and G. Speier, *Tetrahedron Lett.*, 2002, **43**, 5961.
- S. J. Beveridge and W. R. Walker, *Aust. J. Chem.*, 1981, **33**, 2331.