Copper-Mediated Oxygenolysis of Flavonols via Endoperoxide and Dioxetan Intermediates; Synthesis and Oxygenation of $[Cu^{II}(Phen)_2(Fla)]ClO_4$ and $[Cu^{II}(L)(Fla)_2]$ [FlaH = Flavonol; L = 1,10-Phenanthroline (Phen), 2,2′-Bipyridine (Bpy), *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA)] Complexes

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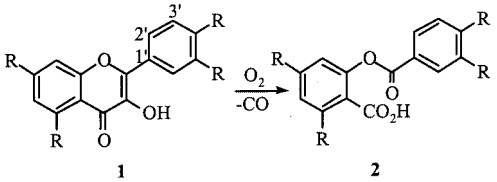
$[Cu(phen)_2(fla)]ClO_4$ was prepared by treating $[Cu(CH_3CN)_4]$-ClO_4 with flavonol (flaH) in the presence of 1,10-phenanthroline (phen) as a co-ligand. Its oxygenation in DMF (or CH_3CN) solution at elevated temperature gave the (*O*-benzoylsalicylato)copper(II) complex $[Cu(phen)_2(O\text{-bs})]ClO_4$ (bs = benzoylsalicylato) and carbon monoxide via an endoperoxide intermediate. Crystallographic characterisation of $[Cu(phen)_2(O\text{-bs})]ClO_4$ as the CH_2Cl_2 solvate [triclinic, space group $P\bar{1}$, a = 10.499(3) Å, b = 12.556(4) Å, c = 17.094(5) Å, α = 72.69(2), β = 89.35(2), γ = 69.19(2)°, V = 1999.7(10) Å^3, Z = 2, $R1$ = 0.0962] shows that the molecule has a distorted trigonal-bipyramidal structure (τ = 0.96). The oxygenolysis was monitored by spectrophotometry, and the pseudo-first-order rate constant k'_{phen} was found to be $(2.47 \pm 0.11) \times 10^{-4}$ s^{-1} at 120 °C. Complexes of $[Cu(L)(4'R\text{-fla})_2]$ (L = phen, bpy, TMEDA; R = H, OCH_3, CH_3, Cl) were also prepared by treating the complexes $Cu(4'R\text{-fla})_2$ with nitrogen-containing co-ligands. Their oxygenation resulted in the corresponding complexes $Cu(L)(2HOpg)_2$ (2HOpg =2-hydroxyphenylglyoxylate) derived by spontaneous hydrolysis of $Cu(L)(bpg)_2$ (bpg = 2-benzoatophenylglyoxylate). The (phenylglyoxylato)-copper complexes were probably formed via 1,2-dioxetan intermediates, since the oxygenation of $Cu(phen)(fla)_2$ showed chemiluminescence with bands at 506, 546, and 578 nm in the emission spectrum due to the decomposition of a 1,2-dioxetan species. Labelling experiments with an $^{18}O_2/^{16}O_2$ mixture (1:3) showed the incorporation of both ^{18}O atoms of $^{18}O_2$ into the flavonolate ligand. The kinetics of the oxygenolysis of $Cu(L)(fla)_2$ gave rate constants according to the rate law $-d[Cu(L)(4'R\text{-fla})_2]/dt = k[Cu(L)(4'R\text{-fla})_2][O_2]$: k/m^{-1} s^{-1} = $(9.50 \pm 0.60) \times 10^{-2}$ (L = phen), $(2.40 \pm 0.10) \times 10^{-2}$ (L = bpy), $(2.00 \pm 0.10) \times 10^{-2}$ (L = TMEDA) m^{-1} s^{-1} at 353.16 K. The oxygenolysis of the complexes $Cu(phen)(4'R\text{-fla})_2$ fits a Hammett linear free energy relationship and an increase of the electron density on the copper ion makes the oxygenation reaction faster.

Introduction

Flavonols are widely distributed in vascular plants,[1,2] and flavonoids form active constituents of a number of herbal and traditional medicines.[3] Flavonols are readily degraded by microorganisms, especially by fungi such as *Aspergillus* or *Pullularia* species.[4] Flavonol 2,4-dioxygenase (quercetinase), which catalyses the oxidative degradation of flavonols (**1**) to a depside (phenolic carboxylic acid esters, **2**) with concomitant evolution of carbon monoxide [Equation (1)], was purified from culture filtrate of *Aspergillus niger*.[4b]



1 **2** (1)

This reaction is rather exceptional as it involves the oxygenolytic cleavage of two carbon−carbon bonds. Carbon monoxide forming enzymes are rare. To date, three prokaryotic dioxygenases are known that catalyse a dioxygenolytic release of CO in a manner analogous to that of fungal quer-

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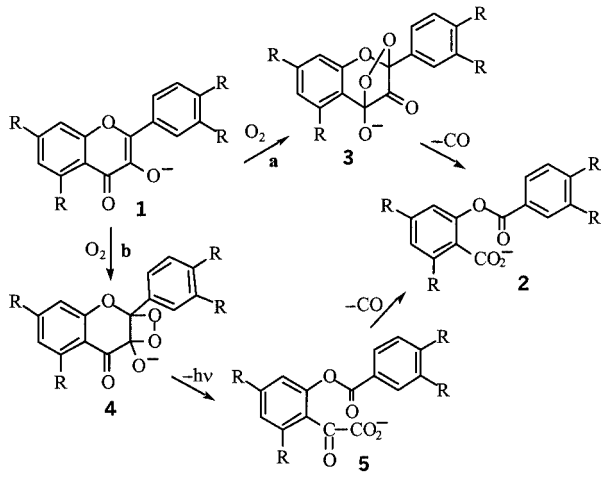
cetinase, these being 3-hydroxyquinaldin-4(1*H*)-one 2,4-dioxygenase, 3-hydroxyquinolin-4(1*H*)-one 2,4-dioxygenase,[5] and 1,2-dihydroxy-5-(methylthio)pent-1-en-3-one anion 1,3-dioxygenase.[6] These prokaryotic enzymes were claimed not to contain any metal ion or organic cofactor[5b] and thus differ fundamentally from the copper-containing flavonol 2,4-dioxygenase. However, it was reported recently, that the 1,2-dihydroxy-5-(methylthio)pent-1-en-3-one anion 1,3-dioxygenase is a Ni-containing enzyme.[6c]

For the oxidative cleavage reaction of the heterocycle in flavonols, two pathways have been proposed (Scheme 1),[7] the first via an endoperoxide **3** (route a) and the other via a 1,2-dioxetan **4** (route b).



Scheme 1

Since flavonol 2,4-dioxygenase is a copper-containing metalloenzyme, metal complexes of copper[8,9] and cobalt[10] have been used in model reactions. Autoxidation reactions of potassium[11] and zinc flavonolates[12] have also resulted in enzyme-like products, and some efforts have been made to elucidate the mechanism of the reaction. From our earlier results obtained both with redox and non-redox metal-containing systems, the conclusion could be drawn that the oxygenolysis of the flavonolate ion in aprotic solvents takes place via an endoperoxide intermediate.[9e−9h,11,12]

Flavonol 2,4-dioxygenase has been claimed to contain nonblue type 2 Cu^{II} ions at its active site.[4b] Recent crystal structure determination of quercetin 2,3-dioxygenase from *Aspergillus japonicus* reveal that it forms homodimers. The mononuclear type 2 copper centre displays two distinct geometries: a distorted tetrahedral coordination, formed by three histidine residues and one water molecule, and a distorted trigonal-bipyramidal environment, which additionally comprises a glutamate.[4i] In this paper we report details for the synthesis and characterisation of $[Cu(phen)_2(fla)]ClO_4$ (**6**) and $[Cu(L)(4'R\text{-}fla)_2]$ [L = phen (**7**), bpy (**8**), TMEDA (**9**); R = H (a), OCH_3 (**7b**), CH_3 (**7c**), Cl (**7d**)] complexes, which are models for the enzyme−substrate (ES) complex. Spectrophotometric and kinetic studies aimed at elucidating the mechanism of the stoichiometric oxygenation of the two systems are also reported on.

Results and Discussion

Synthesis and Characterisation of the Complex $[Cu(phen)_2(fla)]ClO_4$

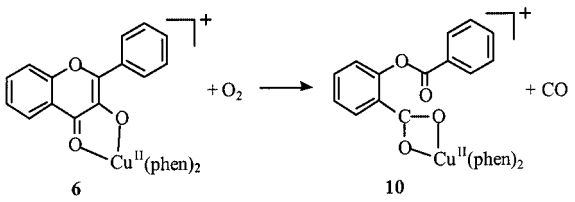
Complex $[Cu(phen)_2(fla)]ClO_4$ was isolated as a green solid by the reaction of $[Cu(CH_3CN)_4]ClO_4$, flavonol (**1**) and 1,10-phenanthroline monohydrate at room temperature in acetonitrile under dioxygen. Its IR spectrum shows the principal band corresponding to the coordinated flavonolate at 1581 cm^{-1}. The decrease of approximately 20 cm^{-1} of the ν(CO) band compared to that of free flavonol [ν(CO): 1602 cm^{-1}] is due to chelation and formation of a stable five-membered ring.[13] The absorption bands at 1082 and 626 cm^{-1} can be assigned to the perchlorate anion. A very strong band at 1608 cm^{-1} [ν(C=N)] is due to the coordinated 1,10-phenanthroline. The electronic spectrum of the complex in the charge transfer region exhibits a band of the coordinated flavonolate ligand at 419 nm. The band at 702 nm is associated with the d−d transition of Cu^{II}. Room-temperature magnetic measurements yielded a value of μ_B = 1.92, consistent with a copper(II) ion.

Synthesis and Characterisation of $Cu(L)(4'R\text{-}fla)_2$

$Cu(4'R\text{-}fla)_2$ (R = H, CH_3, OCH_3, Cl) complexes reacted with 1,10-phenanthroline at room temperature in acetonitrile under argon to give the corresponding complexes $Cu(phen)(4'R\text{-}fla)_2$ in fairly good yields. Similarly, in the presence of TMEDA or bpy co-ligands $Cu(TMEDA)(fla)_2$ or $Cu(bpy)(fla)_2$ was obtained. Satisfactory elemental analyses were obtained for all of the new complexes. Compounds $Cu(L)(fla)_2$ have very similar IR and electronic spectra. The IR spectrum shows the principal bands corresponding to the coordinated flavonolate in the 1560−1580 cm^{-1} region. Decreases of approximately 40 cm^{-1} of the ν(CO) bands compared to that of the 4′-substituted flavonols [ν(CO): ca. 1605 cm^{-1}] are due to chelation and formation of a stable five-membered ring.[13] In the case of complexes with 2,2′-bipyridine and 1,10-phenanthroline, a strong band in the 1590−1600 cm^{-1} region is seen due to the coordinated nitrogen donor ligands ν(C=N). The π−π* transitions in the 420−435 nm region arise from the coordinated flavonolate ligands.

Oxygenation of $[Cu(phen)_2(fla)]ClO_4$

Treatment of $[Cu(phen)_2(fla)]ClO_4$ with dioxygen in DMF or CH_3CN solution at elevated temperature led to the corresponding (*O*-benzoylsalicylato)copper complex $[Cu(phen)_2(O\text{-}bs)]ClO_4$ (**10**) and carbon monoxide contaminated with a small amount of CO_2 [Equation (2)]. The formation of **10** from **6** required dioxygen, which was measured by volumetry (no apparent dioxygen uptake was observed, because the absorption of dioxygen and the liberation of CO compensate each other).



6 10 (2)

The oxygenation of **6** was monitored by UV/Vis spectroscopy. The time course of the variation of $[Cu(phen)_2(fla)]ClO_4$ (**6**) in DMF solution at 120 °C is shown in Figure 1. Plots of $\log[Cu(phen)_2(fla)]ClO_4$ vs. time show a linear dependence under pseudo-first-order conditions[14] (constant dioxygen pressure), in agreement with a rate equation of first-order dependence with respect to the complex **6**. The pseudo-first-order rate constant k' was found to be $(2.47 \pm 0.11) \times 10^{-4}$ s^{-1} at 120 °C. This value is very close to that found for the oxygenation of $[Cu(idpaH)(fla)]ClO_4$ [idpaH = 3,3′-iminobis(*N*,*N*-dimethylpropylamine)] in DMF [$k'_{120\ °C} = (1.45 \pm 0.06) \times 10^{-4}$ s^{-1})].[9g]

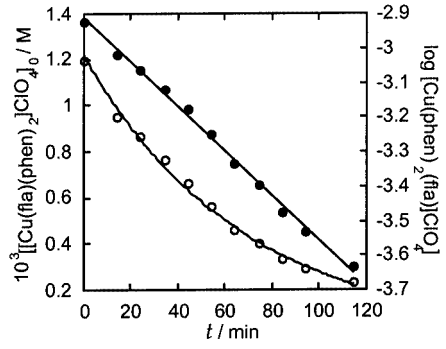


Figure 1. Time course for the oxygenation of $[Cu(phen)_2(fla)]ClO_4$ in DMF (o) and plot of $\log[\{Cu(phen)_2(fla)]ClO_4\}]$ (•) vs. reaction time for the oxygenation of $[Cu(phen)_2(fla)]ClO_4$ ($[\{Cu(phen)_2(fla)]ClO_4\}]_0 = 1.35 \times 10^{-3}$ M, $[O_2] = 6.1 \times 10^{-3}$ M, 120 °C)

Characterisation of $[Cu(phen)_2(O\text{-bs})]ClO_4$

The complex $[Cu(phen)_2(O\text{-bs})]ClO_4$ can also be prepared by the reaction of $[Cu(CH_3CN)_4]ClO_4$, *O*-benzoylsalicylic acid and 1,10-phenanthroline monohydrate at room temperature in acetonitrile under dioxygen. Its IR spectrum shows bands corresponding to the coordinated *O*-benzoylsalicylate at 1741 [ν(CO), indicating that the carbonyl group of the benzoyl group is not coordinated], 1572 and 1388 [$\nu(CO_2)$] cm^{-1}. The difference between the asymmetric and symmetric stretching frequencies of the carboxylato group [$\Delta\tilde{\nu} = \nu_{as}(CO_2) - \nu_s(CO_2)$] is 184 cm^{-1}, rendering these to a monodentate carboxylate bonding mode. Absorption bands at 1068 and 635 cm^{-1} are associated with the perchlorate anion. In the UV/Vis spectrum the d−d transition may be assigned to the 694 nm absorption and the ligand-to-metal charge transfer at 271 and 294 nm. The magnetic moment of $\mu_B = 2.06$ is in agreement with a d^9 Cu^{II} ion without magnetic interactions.

X-ray Crystal Structure of $[Cu(phen)_2(O\text{-bs})]ClO_4$

The molecular structure and atom numbering scheme for $[Cu(phen)_2(O\text{-bs})]ClO_4$ is shown in Figure 2, and selected bond lengths and angles are listed in Table 1. The copper ion has a slightly distorted trigonal-bipyramidal geometry with $\tau = 0.96$.[9g] Two nitrogen atoms of the 1,10-phenanthroline ligands [Cu(1)−N(1) 2.176(5), Cu(1)−N(3) 2.074(5) Å] and one oxygen atom of the *O*-benzoylsalicylate ligand [Cu(1)−O(1) 1.993 Å] occupy basal positions. The two other nitrogen atoms of the phenanthroline ligands [Cu(1)−N(2) 1.992(5) and Cu(1)−N(4) 1.987(5)] are in apical positions. The Cu−N distances in the basal plane are longer than those in apical positions.

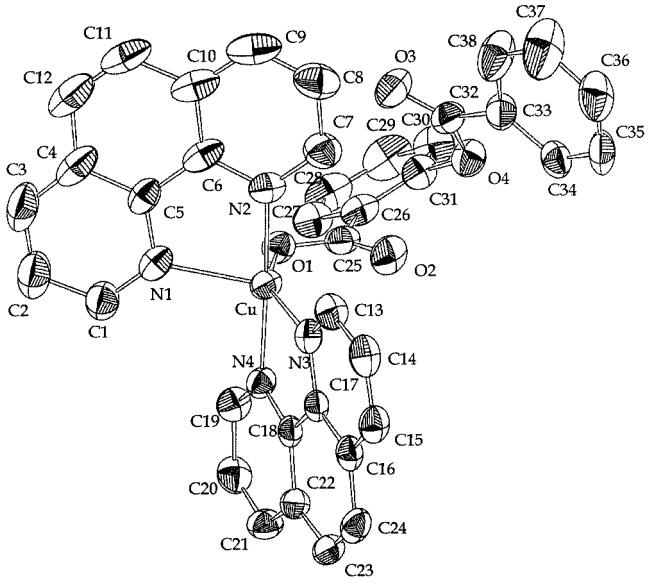


Figure 2. Molecular structure of $[Cu(phen)_2(O\text{-bs})]ClO_4\ 1.5CH_2Cl_2$

Table 1. Selected bond lengths [Å] and angles [°] for $[Cu(phen)_2(O\text{-bs})]ClO_4 \cdot 1.5CH_2Cl_2$

Cu(1)−N(4)	1.987(5)	Cu(1)−N(3)	2.074(5)
Cu(1)−N(2)	1.992(5	Cu(1)−N(1)	2.176(5)
Cu(1)−O(1)	1.993(4)		
N(4)−Cu(1)−N(2)	176.4(2)	N(4)−Cu(1)−O(1)	90.7(2)
N(2)−Cu(1)−O(1)	92.5(2)	N(4)−Cu(1)−N(3)	81.4(2)
N(2)−Cu(1)−N(3)	96.8(2)	O(1)−Cu(1)−N(3)	148.0(2)
N(4)−Cu(1)−N(1)	97.5(2)	N(2)−Cu(1)−N(1)	80.6(2)
O(1)−Cu(1)−N(1)	92.9(2)	N(3)−Cu(1)−N(1)	118.8(2)

Oxygenation of the Complexes $Cu(L)(4'R\text{-fla})_2$

Treatment of the complexes $Cu(L)(4'R\text{-fla})_2$ (L = bpy, phen, TMEDA; R = H, CH_3, OCH_3, Cl) with dioxygen in DMF or CH_3CN solution at elevated temperature led to the corresponding (2-hydroxyphenylglyoxylato)copper complexes $Cu(L)(2HOpg)_2$ and 4-substituted benzoic acids [Equation (3)]. According to gas-volumetric and GC measurements, the stoichiometry of the oxygenation reactions

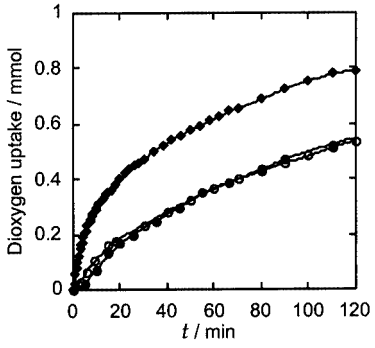
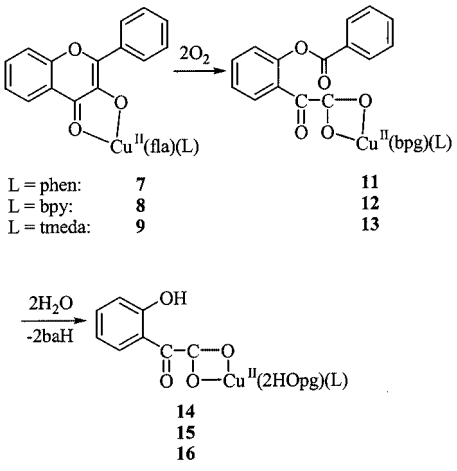


Figure 3. Time course for the oxygenation of the complexes Cu(L)-(fla)$_2$ (**7**−**9**) (L = phen (◆), bpy (●), TMEDA (○); [Cu(L)(fla)$_2$]$_0$ = 0.4 mmol in 50 mL of DMF, [O_2] = 6.91 × 10^{-3} M, 80 °C)

corresponds to Equation (3). Figure 3 shows typical dioxygen uptakes vs. time curves for the complexes [Cu(L)(fla)$_2$] (L = bpy, phen, TMEDA). No other oxidation products could be detected.



(3)

The GC and GC-MS analyses of the reaction mixture obtained by the oxygenation of Cu(phen)(fla)$_2$, after treatment with dilute HCl solution (10%) and ethereal diazomethane, show the presence of methyl benzoate {136 (23) [M^+], 105 (100), 77 (87)}, coumaronedione {148 (3) [M^+], 120 (100), 92 (59), 64 (22), 63 (14)}, and methyl 2-hydroxyphenylglyoxylate {180 (7) [M^+], 121 (100), 93 (11), 65 (11)}. In the case of complex Cu(phen)(fla)$_2$, during the oxygenation reaction chemiluminescence was observed, which is crucial evidence for the decomposition of a 1,2-dioxetan[15] intermediate to carbonyl compounds. Figure 4 shows the electron spectrum of the emitted light (λ = 506, 546, 578 nm). Compound Cu(phen)(2HOpg)$_2$ does not seem to be involved in the chemiluminescence process since its fluorescence spectrum in DMF excited by 430 nm shows bands at 480 and 535 nm with a shoulder at 557 nm (Figure 5), which does not match the spectrum of the emitted light of the chemiluminescence process. It seems likely that the real emitter is Cu(phen)(bpg)$_2$ (**11**), which could not be isolated due to its extreme sensitivity toward hydrolysis.

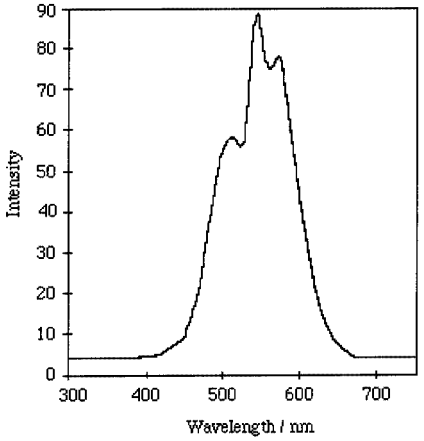


Figure 4. Electron spectrum of the emitted light during the oxygenation of Cu(phen)(fla)$_2$ in DMF

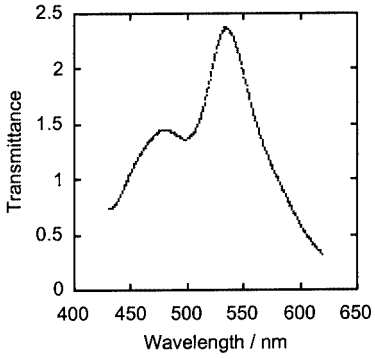


Figure 5. Fluorescence spectrum of Cu(phen)(2HOpg)$_2$ in DMF

Characterisation of the Complexes Cu(L)(2HOpg)$_2$ (L = phen, bpy, TMEDA)

Satisfactory elemental analyses were obtained for the three new (2-hydroxyphenylglyoxylato)copper complexes, namely Cu(phen)(2HOpg)$_2$ (**14**), Cu(bpy)(2HOpg)$_2$ (**15**), and Cu(TMEDA)(2HOpg)$_2$ (**16**). The IR spectrum shows the presence of the coordinated α-oxocarboxylato ligand {ca. 1616 [ν(CO)], ca. 1575, ca. 1375 [ν(CO_2)] cm^{-1}, respectively}.

Kinetic Measurements

The kinetics of the oxygenation of Cu(phen)(fla)$_2$ were monitored by electron spectroscopy at 432 nm. Experimental conditions are summarised in Table S1 (Supporting Information). To determine the rate dependence on the two reactants, oxygenation runs were performed at various initial Cu(phen)(fla)$_2$ concentrations and different dioxygen pressures. A simple rate law for the reaction between Cu-(phen)(fla)$_2$ and O_2 is as shown in Equation (4).

$$-d[Cu(phen)(fla)_2]/dt = d[Cu(phen)(2HOpg)_2]/dt = k_{phen}[Cu(phen)(fla)_2]^m[O_2]^n \quad (4)$$

Under pseudo-first-order conditions (constant dioxygen concentration) for the oxygenation of **7** a typical time course and first-order plot are shown in Figure 6; the reaction remained first-order in **7** during the whole time in which the experiment was monitored (81% conversion, 0.6 h). The first-order dependence on the reaction rate on **7** could also be confirmed by plotting the initial reaction rate $-d[Cu(phen)(fla)_2]/dt$ vs. initial substrate concentration. The straight line obtained [as shown in Figure S1 (Supporting Information)] validates the first-order dependence in $Cu(phen)(fla)_2$ with the pseudo-first-order rate constant $k'_{phen} = 6.86 \times 10^{-4}\ s^{-1}$ and a correlation coefficient of 99.5%.

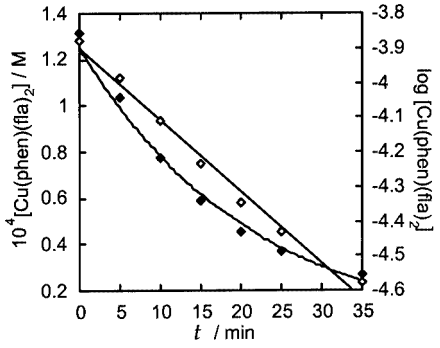


Figure 6. Time course for the oxygenation of $Cu(phen)(fla)_2$ in DMF (◆) and plot of $\log[Cu(phen)(fla)_2]$ (□) vs. reaction time for the oxygenation of $Cu(phen)(fla)_2$

Experiments made at different dioxygen pressures show that p_{O2} appreciably influences the rate of the reaction. Kinetic measurements of the reaction rate indicate a first-order dependence with respect to the dioxygen concentration. Plots of k'_{phen} vs. $[O_2]$ for the above experiments give a straight line with $k_{phen} = 0.10\ M^{-1}\ s^{-1}$ and a correlation coefficient of 99.1% (Figure 7). On the basis of the results above, it can be concluded that the reaction follows the rate law of Equation (4) with $m = n = 1$, from which a mean value of the kinetic constant k_{phen} of $(9.50 \pm 0.60) \times 10^{-2}\ M^{-1}\ s^{-1}$ at 353.16 K can be obtained. In the case of the oxygenation of $Cu(bpy)(fla)_2$ and $Cu(TMEDA)(fla)_2$ the mean values of the kinetic constants at 353.16 K were found to be $k_{bpy} = (2.40 \pm 0.10) \times 10^{-2}\ M^{-1}\ s^{-1}$ and $k_{TMEDA} = (2.00 \pm 0.10) \times 10^{-2}\ M^{-1}\ s^{-1}$.

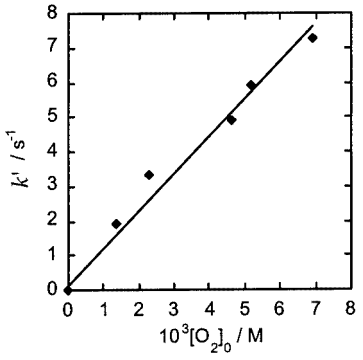


Figure 7. Plot of pseudo-first-order rate constant k' vs. O_2 pressure

The activation parameters for the oxygenation reactions were determined from the temperature dependence of the kinetic constant k_{phen} in the temperature range of 348.16−363.16 K. From the straight line in the Eyring plot [Figure S2 (Supporting Information)], with a correlation coefficient of 99.7% the activation parameters $\Delta H^{\ddagger} = 79 \pm 16\ kJ\ mol^{-1}$ and $\Delta S^{\ddagger} = -40 \pm 44\ J\ mol^{-1}\ K^{-1}$ were calculated at 353.16 K.

Reaction rates on the oxygenation of the 4′-substituted complexes $Cu(phen)(4'R\text{-}fla)_2$ under identical conditions were also determined (with various electron-withdrawing or releasing substituents R) in order to find out electronic effects on the reaction rate. The Hammett plot obtained is shown in Figure 8. Electron-releasing substituents enhanced the reaction rate, and the reaction constant ρ_{phen} was found to be −1.03 (R = 98.3%).

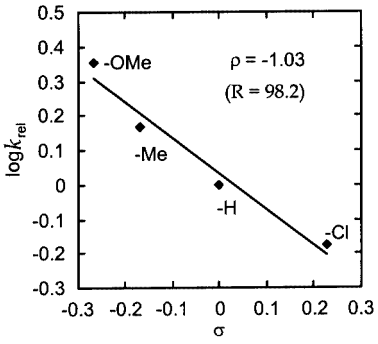
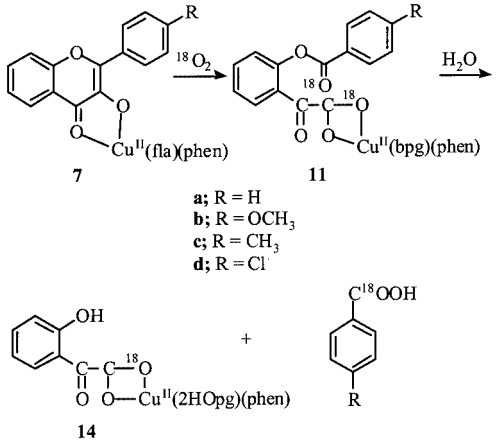


Figure 8. Hammett plot for the oxygenation of $Cu(phen)(4'R\text{-}fla)_2$ complexes

$^{18}O_2$ Labelling Experiments

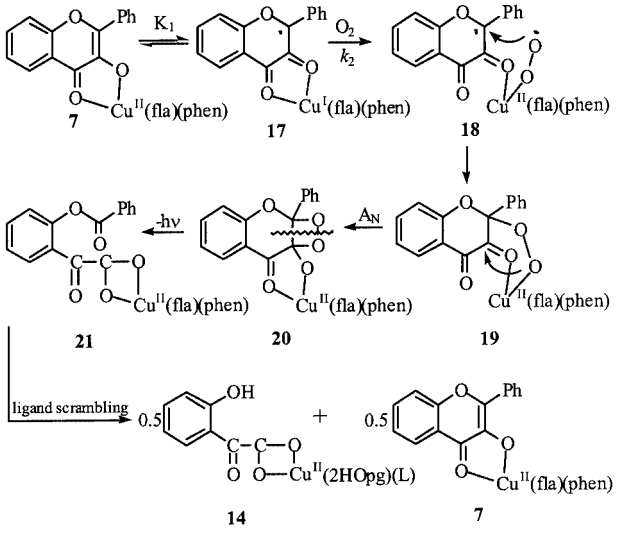
Oxygenation of $Cu(phen)_2(fla)$ was also carried out with a mixture of $^{16}O_2$ and $^{18}O_2$ (3:1) in acetonitrile. After stirring the reactants at 25 °C for 48 h, the unchanged starting material was filtered off (ca. 50%), and the green solution was concentrated to dryness, giving a mixture of $Cu(phen)(^{16}O\text{-}bpg)_2$ and $Cu(phen)(^{18}O\text{-}bpg)_2$ {IR (Nujol): 1685 [$\nu(C^{18}O)$], 1716 [$\nu(C^{16}O)$] cm^{-1}}, $Cu(phen)(^{18}O\text{-}2HOpg)_2$ and $Cu(phen)(^{16}O\text{-}2HOpg)_2$, respectively. The GLC-MS analysis of the residue, after treatment with ethereal diazomethane, showed the presence of ^{16}O- and ^{18}O-containing methyl benzoate: *m/z* (%) = 136 (23) [M^+], 105 (100), 77 (87); 138 (8) [$M^+ + 2$], 181 (9), 107 (26), 105 (100), 77 (87); methyl 2-methoxyphenylglyoxylate: *m/z* (%) = 194 (32) [M^+], 179 (22), 135 (100), 120 (29), 105 (15), 92 (15); 196 (12) [$M^+ + 2$], 181 (9), 135 (100), 120 (29), 105 (15), 92 (28); methyl 2-hydroxyphenylglyoxylate: *m/z* (%) = 180 (7) [M^+], 121 (100), 93 (17), 65 (23); 182 (2.2) [$M^+ + 2$], 121 (100), 93 (17), 65 (23); and coumaronedione: *m/z* (%) = 148 (4.3) [M^+], 120 (100), 92 (69), 64 (27), 63 (30); 138 (8) [$M^+ + 2$], 107 (26), 105 (100), 77 (87); in the appropriate ratio. On the bases of the above results it can be said that both ^{18}O atoms of $^{18}O_2$ are incorporated into the primary oxygenated product 2-benzoatophenylglyoxylic acid from molecular oxygen (Scheme 2).



Scheme 2

All experimental data reported in the previous sections can be used for the interpretation of the mechanism of copper-assisted oxygenolysis of coordinated flavonolate to *O*-benzoylsalicylate or 2-benzoatophenylglyoxylate. Flavonolate as a chelating ligand forms stable complexes with copper ions. In most cases they are stable toward dioxygen in the solid form or even in solution at ambient conditions. At elevated temperatures the oxygenolysis proceeds reasonably rapidly. Recently, we have found that copper(II) flavonolate complexes with simple N-containing tridentate ligands reacted with dioxygen to the corresponding enzyme-like (*O*-benzoylsalicylato)copper complexes and CO. On the basis of kinetic measurements of the reaction of the complexes above with dioxygen, a mechanism was proposed to proceed via an endoperoxide intermediate according to route a in Scheme 1.[9g,9h] Treatment of the (flavonolato)copper complex $[Cu(phen)_2(fla)]ClO_4$ with dioxygen in DMF or CH_3CN solution at elevated temperature leads also to an (*O*-benzoylsalicylato)copper complex $[Cu(phen)_2(O\text{-}bs)]ClO_4$ and carbon monoxide, indicating that the mechanism of this reaction is the same as that proposed for copper-containing model systems investigated earlier by us.

Recently, we have published that the oxygenolysis of $Cu(fla)_2$ in DMF resulted in the $Cu(O\text{-}bs)_2$ complex and CO.[9e] We found that this reaction proceeded in a bimolecular step via an endoperoxide intermediate (Scheme 1, route a), and the kinetic constant k_{obs} was found to be $9.90 \pm 0.80 \times 10^{-3}$ mol^{-1} dm^3 s^{-1} at 90 °C.[9e] This value is much smaller than that obtained for the oxygenolysis for $Cu(phen)(fla)_2$ ($21.3 \pm 1.8 \times 10^{-2}$ mol^{-1} dm^3 s^{-1} at 90 °C). This difference in the reaction rates indicates that there are two different pathways for the above reactions. The formation of (oxocarboxylato)copper(II) complexes **14**−**16** in the oxygenation of the complexes $Cu(L)(fla)_2$ (L = phen, bpy, TMEDA) also suggest that the oxidative cleavage reaction of the coordinated flavonolate ligand can only proceed via a 1,2-dioxetan intermediate, which, upon the usual decomposition and hydrolysis of the ester linkage, leads to the corresponding (oxocarboxylato)copper complexes **14**−**16**. The $^{18}O_2$ labelling experiments on the oxygenation of $Cu(phen)(fla)_2$ revealed that both ^{18}O atoms of the $^{18}O_2$ molecule are incorporated into the substrate. A reaction mechanism that nicely fits the chemical, photochemical, spectroscopic, labelling, kinetic, and thermodynamic data is shown in Scheme 3.



Scheme 3

The second-order overall rate expression for the oxygenation of the flavonolato complexes **7** supports the proposal that in a fast pre-equilibrium the copper(II) flavonolate complex **7** undergoes intramolecular electron transfer from the ligand fla^- to Cu^{II}, resulting in the copper(I) flavonoxy radical complex **17**. The equilibrium is largely shifted to the left (K_1 is rather small). In **17** there are two redox-active centres, the radical ligand and the copper(I) ion. The biradical dioxygen may react at both sites; in an oxidative addition to the copper ion [leading to a (superoxo)copper(II) complex **18**], or in a radical-radical reaction with the flavonoxy ligand. We believe that the former is the rate-determining step. The Hammett relationship shows that higher electron density at the copper ion enhances the rate of the reaction. This is consistent with an electrophilic attack of dioxygen at the copper(I) centre.

The reaction constant of the oxygenation reaction is almost the same ($\rho_{phen} = -1.03$, $R = 98.2\%$) as that found for the oxygenation of copper(I) chloride in pyridine ($\rho = -1.24$).[16] The crucial evidence for a bimolecular reaction step is the negative $\Delta S^{\ddagger}$ value (−40.3 J mol^{-1} K^{-1}). The (superoxo)copper(II) complex **18** is possibly then transformed in a fast consecutive coupling reaction to **19**, which reacts by an intramolecular nucleophilic addition on C3 to give the 1,2-dioxetan **20**. The main difference between the two types of mechanistic routes can be explained by this step. The nucleophilic attack of the bound peroxide could also take place on the 4-C=O group as well giving rise to an endoperoxide intermediate, but in that case the higher electron density on the 4-C=O carbon atom compared to that on the 3-C=O carbon atom renders this pathway unlikely. The 1,2-dioxetan **20** is then believed to decompose in a fast step to the (oxocarboxylato)copper complex **21**. Ow-

ing to a ligand scrambling reaction, the starting copper flavonolate complex **7** and the product (2-hydroxyphenylglyoxylato)copper complex **14** are formed by hydrolysis of the ester linkage in complex **11**. In order to prove the formation of 1,2-dioxetan during the oxygenolysis the chemiluminescence of the reaction was tested. In the emission spectrum bands at 506, 546, and 578 nm were found, which were assigned to the decomposition of the 1,2-dioxetan species.[15] Light emission is a result of the transition of the exited complex **21** to its ground state. Assuming steady-state conditions for species **17** the rate according to Equation (5) can be deduced, which after some simplification ($k_2[O_2] << k_1 + k_{-1}$ and [Cu] means the total copper concentration) is in good agreement with an overall second-order dependence according the experimental data obtained in the kinetic measurements.

$$-\frac{d[Cu]}{dt} = \frac{k_1 k_2 [Cu][O_2]}{k_1 + k_{-1} + k_2[O_2]} = \frac{k_1 k_2 [Cu][O_2]}{k_1 + k_{-1}} = k_{obs}[Cu][O_2] \quad (5)$$

Conclusion

From the results obtained the conclusion may be drawn that the oxidative ring-cleavage reaction of the flavonolate ligand coordinated to the copper ion may take place by two different reaction routes, namely through an endoperoxide or a 1,2-dioxetan intermediate. We believe that the coordination mode and the ligand environment around the metal centre, and the Lewis acidity of the copper ion influence the mechanism of this unusual reaction. Both complexes $Cu(phen)(fla)_2$ and $[Cu(phen)_2(fla)]ClO_4$ are sterically very crowded so that the discrimination of the intramolecular nucleophilic peroxide group between the 4-C=O and 3-C=O carbon atoms seems to be governed by the different electron densities on the carbon atoms, which is influenced by changing the ligand environment. Further work is in progress to better understand the reasons and factors affecting the selectivity between this two types of C−C cleavage reactions.

Experimental Section

General Remarks: Solvents used for the reactions were purified using literature methods[17] and stored under argon. Flavonol,[18] 4′-methoxyflavonol,[18] 4′-methylflavonol,[19] 4′-chloroflavonol,[19] O-benzoylsalicylic acid,[20] $Cu(OCH_3)_2$,[21] $[Cu(CH_3CN)_4]ClO_4$,[22] and $Cu(fla)_2$ [9b] were prepared using literature methods. The ligands 1,10-phenanthroline, 2,2′-bipyridine, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Aldrich) were used as provided.

CAUTION: Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with great care.

Preparation of $[Cu(phen)_2(fla)]ClO_4$ (6): $[Cu(CH_3CN)_4]ClO_4$ (0.328 g, 1 mmol) was dissolved in acetonitrile (60 mL), and flavonol (0.238 g, 1 mmol) and 1,10-phen·H_2O (0.396 g, 2 mmol) were added and stirred under argon for 1 h, and then under dioxygen (0.1 MPa) for 2 h. A green solid formed, which was filtered, washed with acetonitrile, and dried under vacuum (0.66 g, 87%). The product was recrystallised from acetonitrile. M.p. 195 °C. IR (KBr): $\tilde{\nu}$ = 1608 (vs, C−N), 1581 (vs, C−O), 1511, 1493, 1416, 1207, 1141, 1082 (vs, ClO_4), 845, 756, 719, 626 cm^{-1} (vs, ClO_4). UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 229 (67608), 269 (69183), 419 (8318), 702 nm (51). μ_B = 1.92. $C_{39}H_{25}ClCuN_4O_7$ (760.7): calcd. C 61.58, H 3.31, N 7.36; found C 61.04, H 3.16, N 7.18.

Preparation of $Cu(phen)(fla)_2$ (7a): To a solution of $Cu(fla)_2$ (0.538 g, 1 mmol) in acetonitrile (35 mL) was added 1,10-phen·H_2O (0.198 g, 1 mmol) and the reaction mixture stirred under argon for 4 h. A green precipitate formed, which was filtered off, washed with ether, and dried under vacuum (0.65 g, 90%). M.p. 236 °C. IR (KBr): $\tilde{\nu}$ = 3059 vw, 3044 vw, 1595 vs, 1564 vs, 1508 s, 1485 m, 1465 m, 1408 vs, 1350 m, 1310 s, 1221 vs, 1187 m, 1144 m, 1109 m, 1077 m, 1033 m, 995 w, 913 m, 859 s, 774 s, 747 s, 735 m, 721 w, 698 s, 571 m, 533 m, 499 m cm^{-1}. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 265 (64125), 432 nm (63658). μ_B = 1.98. $C_{42}H_{26}CuN_2O_6$ (718.2): calcd. C 70.24, H 3.64, N 3.90; found C 69.88, H 3.48, N 3.98.

$Cu(phen)(4'OCH_3\text{-}fla)_2$ (7b): Yield 0.66 g (85%). M.p. 200 °C. IR (KBr): $\tilde{\nu}$ = 3052 vw, 2924 vw, 2823 w, 1591 vs, 1568 vs, 1542 s, 1491 s, 1416 vs, 1355 m, 1305 s, 1249 vs, 1216 vs, 1181 s, 1116 s, 1046 s, 1003 m, 923 m, 852 s, 761 s, 742 s, 691 m, 642 m, 578 m, 529 m cm^{-1}. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 271 (70018), 434 (67844) nm. μ_B = 2.01. $C_{44}H_{30}CuN_2O_8$ (778.3): calcd. C 67.90, H 3.38, N 3.82; found C 67.29, H 3.48, N 3.98.

$Cu(phen)(4'CH_3\text{-}fla)_2$ (7c): Yield 0.62 g (83%). M.p. 197 °C. IR (KBr): $\tilde{\nu}$ = 3030 vw, 2895 vw, 2841 wv, 1590 vs, 1576 vs, 1495 vs, 1476 s, 1412 vs, 1353 m, 1312 s, 1217 vs, 1189 s, 1147 m, 1112 s, 1050 w, 1029 w, 1001 m, 916 s, 861 s, 834 s, 766 s, 738 s, 689 m, 663 w, 638 m, 514 s cm^{-1}. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 271 (80041), 429 (63062) nm. μ_B = 1.86. $C_{44}H_{30}CuN_2O_6$ (746.3): calcd. C 70.81, H 4.05, N 3.75; found C 69.84, H 3.89, N 3.88.

$Cu(phen)(4'Cl\text{-}fla)_2$ (7d): Yield 0.59 g (75%). M.p. 238 °C. IR (KBr): $\tilde{\nu}$ = 3048 vw, 1595 vs, 1568 vs, 1510 m, 1483 vs, 1410 vs, 1355 m, 1316 s, 1219 vs, 1149 m, 1109 s, 1093 m, 1022 m, 1003 m, 916 s, 849 s, 758 s, 736 s, 691 w, 661 w, 616 m, 551 w, 505 m. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 271 (73578), 424 (60173) nm. μ_B = 1.81. $C_{42}H_{28}Cl_2CuN_2O_6$ (788.1): calcd. C 64.01, H 3.67, N 3.56; found C 63.68, H 3.89, N 3.66.

$Cu(bpy)(fla)_2$ (8): Yield 0.22 g (40%). M.p 280 °C. IR (KBr): $\tilde{\nu}$ = 3023 vw, 1588 vs, 1578 vs, 1513 m, 1484 m, 1465 s, 1438 m, 1405 vs, 1348 m, 1305 vs, 1239 vs, 1142 w, 1117 w, 1078 m, 1057 vw, 1032 m, 997 w, 913 m, 857 vw, 765 vs, 742 w, 719 w, 703 s, 671 m, 591 vw, 532 m, 507 s cm^{-1}. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 273 (67640), 431 (58829) nm. μ_B = 1.89. $C_{40}H_{26}CuN_2O_6$ (694.2): calcd. C 69.21, H 3.77, N 4.04; found C 68.79, H 3.92, N 4.11.

$Cu(TMEDA)(fla)_2$ (9): Yield 0.43 g (65%). M.p. 160 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3055 vw, 2999 vw, 2873 vw, 2827 vw, 1573 vs, 1524 m, 1473 s, 1440 m, 1427 vs, 1352 m, 1318 vs, 1298 w, 1256 w, 1226 vs, 1188 w, 1150 w, 1124 w, 1086 m, 1061 vw, 1037 w, 973 w, 937 vw, 918 m, 863 vw, 822 m, 783 s, 751 vs, 749 vw, 724 w, 705 s, 692 vw, 674 m, 612 vw, 537 m, 501 s cm^{-1}. UV/Vis (DMF): λ_{max}(ε/L mol^{-1} cm^{-1}) = 272 (51368), 430 (59979), 674 (380) nm. μ_B = 1.91. $C_{36}H_{34}CuN_2O_6$ (654.2): calcd. C 66.09, H 5.24, N 4.28; found C 65.79, H 4.95, N 4.21.

Preparation of [Cu(phen)$_2$(*O*-bs)]ClO$_4$ (10): [Cu(CH$_3$CN)$_4$]ClO$_4$ (0.328 g, 1 mmol) was dissolved in acetonitrile (30 mL), then *O*-benzoylsalicylic acid (0.242 g, 1 mmol) and 1,10-phen·H$_2$O (0.360 g, 2 mmol) were added and the reaction mixture was stirred under argon for 1 h and then under dioxygen (0.1 MPa) for 4 h. A blue crystalline solid formed, which was filtered, washed with acetonitrile, and dried under vacuum (0.69 g, 90%). Recrystallisation of the product from dichloromethane gave blue crystals. The dichloromethane solution produced crystals suitable for X-ray analysis upon standing at room temperature for a few days. M.p. 262 °C. IR (KBr): $\tilde{\nu}$ = 741 (vs, C−O), 1600 (vs, C−N), 1572 (vs, CO$_2$), 1420, 1388 (vs, CO$_2$), 1253, 1200, 1143, 1094, 1068 (vs, ClO$_4$), 841, 800, 731, 719, 635 (vs, ClO$_4$) cm^{-1}. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 271 (52481), 294 (17783), 331 (2042), 694 (115) nm. μ_B = 2.06. $C_{38}H_{25}ClCuN_4O_8$ (764.6): calcd. C 59.70, H 3.29, N 7.33; found C 58.62, H 2.98, N 7.21. The complex was also prepared by stirring (0.76 g, 1 mmol) Cu(fla)(phen)$_2$]ClO$_4$ in acetonitrile (30 mL) at room temperature under dioxygen (0.1 MPa) for 25 h (0.61 g, 80%).

Oxygenation of Cu(L)(fla)$_2$ (7a−d, 8−9): In a typical experiment, [Cu(phen)(fla)$_2$] (**7a**) (0.57 g, 0.8 mmol) in DMF (50 cm^3) was treated with dioxygen (0.1 MPa) until dioxygen uptake ceased at 80 °C. The dioxygen uptake was measured by a gas-volumetric method. The GC-MS analyses of the reaction mixture, after treatment with dilute HCl solution (10%) and ethereal diazomethane showed the presence of methyl benzoate: *m*/*z* (%) = 136 (23) [M$^+$], 105 (100), 77 (87); coumaronedione: *m*/*z* (%) = 148 (3) [M$^+$], 120 (100), 92 (59), 64 (22), 63 (14); and methyl 2-hydroxyphenylglyoxylate: *m*/*z* (%) = 180 (7) [M$^+$], 121 (100), 93 (11), 65 (11). Addition of excess Et$_2$O resulted in the deposition of [Cu(phen)(2HOpg)$_2$] (**14**) as a green microcrystalline solid: Yield 0.20 g (43%). M.p. 204 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3037 w, 1616 vs, 1575 vs, 1516 s, 1462 m, 1423 s, 1375 m, 1346 m, 1326 m, 1265 w, 1213 vs, 1158 s, 1110 m, 1039 vw, 908 w, 858 vs, 785 s, 752 m, 733 s, 688 m, 629 w, 575 m. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 273 (42213), 398 (5262) nm. μ_B = 1.91. $C_{28}H_{18}CuN_2O_8$ (574.0): calcd. C 58.59, H 3.16, N 4.88; found C 57.89, H 3.33, N 5.12.

Cu(bpy)(2HOpg)$_2$ (15): Yield 0.18 g (41%). M.p. 176 °C. IR (KBr): $\tilde{\nu}$ = 3057 w, 1618 vs, 1577 vs, 1550 s, 1516 s, 1496 s, 1448 m, 1428 s, 1387 m, 1352 w, 1326 m, 1258 w, 1217 vs, 1156 s, 1041 w, 770 vs, 668 m, 629 w, 573 m. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 268 (29960), 305 (46121) nm. μ_B = 1.94. $C_{26}H_{18}CuN_2O_8$ (550.0): calcd. C 56.78, H 3.30, N 5.09, found C 56.49, H 3.16, N 5.12.

Cu(TMEDA)(2HOpg)$_2$ (16): Yield 0.12 g (30%). M.p 195 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3126 vw, 3084 vw, 3068 vw, 3045 vw, 2871 vw, 2827 vw, 1616 vs, 1571 vs, 1519 s, 1478 w, 1465 w, 1445 s, 1421 s, 1407 m, 1362 m, 1320 m, 1258 m, 1207 s, 1147 s, 1084 vw, 1062 w, 1035 m, 990 w, 913 w, 861 m, 845 w, 769 s, 758 s, 745 s, 735 m, 720 m, 671 m, 558 m. UV/Vis (DMF): λ_{max} (ε/L mol^{-1} cm^{-1}) = 266 (14207), 302 (19828), 349 (7650) nm. μ_B = 1.91. $C_{22}H_{26}CuN_2O_8$ (510.0): calcd. C 51.81, H 5.14, N 5.49; found C 52.23, H 4.95, N 5.57.

X-ray Data Collection: Crystal data for [Cu(*O*-bs)(phen)$_2$]ClO$_4$·1.5 CH$_2$Cl$_2$: crystal dimensions 0.20 × 0.25 × 0.30 mm, triclinic, space group $P\bar{1}$, a = 10.499(3) Å, b = 12.556(4) Å, c = 17.094(5) Å, α = 72.69(2), β = 89.35(2), γ = 69.19(2)°, V = 1999.7(10) Å^3, Z = 2, $\rho_{calcd.}$ = 1.481 g·cm^{-3}, 2 Θ_{max} = 48.0°, radiation Mo-K_α (λ = 0.71073 Å), ω-scan, T = 200 K. Of the 6861 measured reflections, 6160 were independent, and 4838 observed for $I > 2\sigma(I)$. Lorentz and polarisation factors and experimental absorption correction (ψ scan, μ = 0.870 mm^{-1}). Data were collected with a Siemens (Nicolet Syntex) R3m/V diffractometer and the structure was solved by direct methods and refined by full-matrix least-squares techniques against F^2 (SHELXL-93,[23] SHELXS-86[24]), hydrogen atoms located geometrically, R_1 = 0.0962, ωR_2 = 0.2614 (all data) for 540 parameters, min/max residual electron density = −0.642/1.448 e Å^{-3}. CCDC-179746 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Physical Measurements: Electronic spectra were recorded with a Shimadzu UV-160 (Carl Zeiss) spectrometer, infrared spectra with a Specord IR-75 (Carl Zeiss) spectrometer. Magnetic susceptibilities were determined at room temperature with a Bruker B-E 10B8 magnetic balance. GC analyses were performed with an HP 5830A gas chromatograph equipped with a flame ionization detector and a CP SIL8CB column. GC-MS measurements were recorded with an HP 5890 II, 5971 GC/MSD at 75 eV.

Kinetic Measurements: Reactions of copper flavonolate complexes with O$_2$ were performed in DMF solutions. In a typical experiment Cu^{II}(phen)(fla)$_2$ was dissolved under argon in a thermostatically controlled reaction vessel with an inlet for taking samples with a syringe, and connected to a mercury manometer to maintain a constant pressure. The solution was then heated to the appropriate temperature, a sample was taken by syringe, and the initial concentration of Cu^{II}(phen)(fla)$_2$ was determined by UV/Vis spectroscopy measuring the absorbance of the reaction mixture at 432 nm (63 658) {λ_{max} of a typical band of Cu^{II}(phen)(fla)$_2$}. The argon was then replaced by dioxygen, and the consumption of Cu^{II}(phen)(fla)$_2$ was analysed periodically (ca. every 10 min). Experimental conditions are summarised in Table 1. The temperature was determined with an accuracy of ±0.5 °C and the pressure of dioxygen with an accuracy of ±0.5%. The O$_2$ concentration was calculated from literature data,[25] taking into account the partial pressure of DMF[26] and assuming the validity of Dalton's law.

Supporting Information: Kinetic data and diagrams for the oxygenations are available (see also footnote on the first page of this article).

Acknowledgments

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