Preparation and Oxygenation of (Flavonolato)copper Isoindoline Complexes with Relevance to Quercetin Dioxygenase

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Mesitylcopper reacts with flavonol (flaH) in the presence of 1,3-bis(2-pyridylimino)isoindoline (indH) to yield the diamagnetic complex Cu^I(fla)(indH), which on reaction with molecular oxygen undergoes oxidative splitting of the C2−C3 bond of the pyranone ring of the flavonolate ligand to give Cu^I(indH)(*O*-bs) (*O*-bs = *O*-benzoylsalicylate) (orthorhombic, $P\bar{1}$, $a = 8.048(7)$ Å, $b = 8.969(9)$ Å, $c = 19.240(2)$ Å, $\alpha = 85.69°$, $\beta = 80.24(7)°$, $\gamma = 77.87(7)°$, $V = 1337(2)$ Å^3, $Z = 2$) and carbon monoxide. The reaction of $[Cu^I(CH_3CN)_4]ClO_4$, flaH, and indH with dioxygen at room temperature affords the paramagnetic complex $[Cu^{II}$(fla)(indH)]ClO_4 ($\mu = 2.10\ \mu_B$), and after elimination of $HClO_4$, Cu^{II}(fla)(ind) (orthorhombic, P_{bca}, $a = 8.888(2)$ Å, $b = 19.169(7)$ Å, $c = 33.614(10)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 5727(3)$ Å^3, $Z = 8$) with $\mu = 1.86\ \mu_B$ is formed. The latter undergoes cleavage of the pyranone ring on oxygenation at 80 °C to give Cu^{II}(ind)(*O*-bs) ($\mu = 1.87\ \mu_B$, ν(CO) = 1742 cm^{-1}, and ν(CO$_2$) = 1581, 1387 cm^{-1}) and carbon monoxide. Cu^{II}(fla)(ind) and $[Cu^{II}$(fla)(indH)]ClO_4 serve as good catalysts for the oxygenation of flavonol to *O*-benzoylsalicylic acid.

Introduction

Quercetin 2,3-dioxygenase is a widely occurring copper(II)-containing metalloenzyme in plants that catalyzes the reaction of dioxygen with quercetin (**1a**) to yield a depside (**2a**; carboxylic acid ester) and carbon monoxide (eq 1).[2−6] Very few
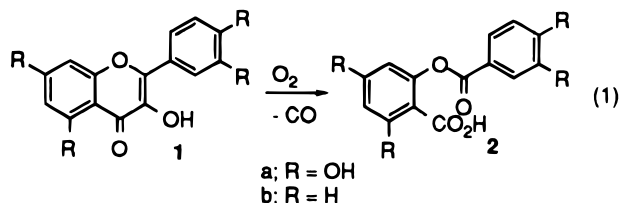
data on the enzyme itself are available in the literature, but model studies have been carried out on a few systems with copper[7−9] and other metals.[10,11] These studies focused mainly on flavonol (**1b**, flaH) or on compounds with motifs resembling

the hydroxypyranone ring. Ruthenium[12] and cobalt[13] complexes of 1,3-bis(2-pyridylimino)isoindoline (**3**, indH) were used as
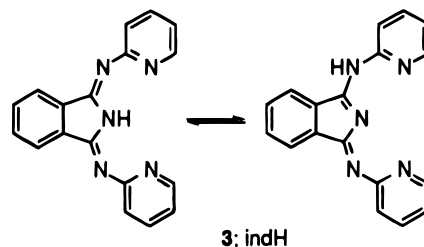
catalysts in various oxygenation reactions. These data and our interest in (flavonolato)copper complexes as possible models for the active site of quercetin 2,3-dioxygenase[14−16] prompted us to synthesize a number of compounds with 3-hydroxyflavones. Copper(I) and copper(II) flavonolate complexes without any ligand and with simple P- and N-containing ligands were prepared and successfully used in the oxygenation of flavonol.[17−21] As an extension of this work to tridentate N-ligands, we report

(1) (a) Hungarian Academy of Sciences. (b) University of Veszprém. (c) Universität Heidelberg.
(2) Westlake, D. W.; Talbot, G.; Blakely, E. R.; Simpson, F. J. *Can J. Microbiol.* **1959**, *5*, 62.
(3) Simpson, F. J.; Talbot, G.; Westlake, D. W. S. *Biochem. Biophys. Res. Commun.* **1959**, *2*, 621.
(4) Hattori, S.; Noguchi, I. *Nature* **1959**, *184*, 1145.
(5) Sakamoto, H. *Seikagu (J. Jpn. Biochem. Soc.)* **1963**, *35*, 633.
(6) Oka, T.; Simpson, F. J.; Krishnamurty, H. G. *Can. J. Microbiol.* **1977**, *16*, 493.
(7) Utaka, M.; Hojo, M.; Fujii, Y.; Takeda, A. *Chem. Lett.* **1984**, 634.
(8) Utaka, M.; Takeda, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1824.
(9) Balogh-Hergovich, É.; Speier, G. *J. Mol. Catal.* **1992**, *71*, 1.
(10) Nishinaga, A.; Tojo, T.; Matsuura, T. *J. Chem. Soc., Chem. Commun.* **1974**, 896.
(11) Nishinaga, A.; Kuwashige, T.; Tsutsui, T.; Mashino, T.; Maruyama, K. *J. Chem. Soc., Dalton Trans.* **1994**, 805.

(12) Gagné, R. R.; Marks, D. N. *Inorg. Chem.* **1984**, *23*, 65.
(13) Tolman, C. A.; Druliner, J. D.; Krusic, P. J.; Nappa, M. J.; Seidel, W. C.; Williams, I. D.; Ittel, S. D. *J. Mol. Catal.* **1988**, *48*, 129.
(14) Makasheva, E.; Golovkina, N. T. *Zh. Obsch. Khim.* **1973**, *43*, 1640.
(15) Thomson, M.; Williams, C. R. *Anal. Chim. Acta* **1976**, *85*, 375.
(16) Takamura, K.; Ito, M. *Chem. Pharm. Bull.* **1977**, *25*, 3218.
(17) Speier, G.; Fülöp, V.; Párkányi, L. *J. Chem. Soc., Chem. Commun.* **1990**, 512.
(18) Balogh-Hergovich, É.; Speier, G.; Argay, G. *J. Chem. Soc., Chem. Commun.* **1991**, 551.
(19) Balogh-Hergovich, É.; Kaizer, J.; Speier, G. *Inorg. Chim. Acta* **1997**, *256*, 9.
(20) Lippai, I.; Speier, G.; Huttner, G.; Zsolnai, L. *Chem. Commun.* **1997**, 741.
(21) Lippai, I.; Speier, G. *J. Mol. Catal.* **1998**, *130*, 139.

here the preparation and characterization of several copper(I) and copper(II) flavonolate complexes with the ligand 1,3-bis-(2-pyridylimino)isoindoline and its deprotonated form and their oxygenations to the corresponding copper depside (*O*-benzoyl-salicylic acid, *O*-bs) complexes. The crystal structures of a copper(II) flavonolate complex with indH and that of an (*O*-benzoylsalicylato)copper(I) complex are also reported.

Experimental Section

Materials. Solvents used for the reactions were purified by literature methods[22] and stored under argon. 3-Hydroxyflavone,[23] 1,3-bis(2-pyridylimino)isoindoline,[24] *O*-benzoylsalicylic acid,[25] mesitylcopper-(I),[26] and [$Cu^I(CH_3CN)_4$]ClO_4[27] were prepared by literature methods. Conventional Schlenk-type inert gas techniques were used.[28]

Physical Measurements. Electronic spectra were recorded with a Shimadzu UV-160 spectrometer. Infrared spectra were obtained for Nujol mulls using a Specord IR-75 (Carl Zeiss) spectrometer. Magnetic susceptibilities were determined at room temperature on a Bruker B-E 10B8 magnetic balance. EPR spectra were obtained with a JEOL JES-FE3X spectrometer. Microanalyses were carried out by the Microanalytical Service of the University of Veszprém. GC analyses were performed on an HP 5830A gas chromatograph equipped with a flame ionization detector and a CP SIL8CB column. GC-MS measurements were recorded on an HP 5890 II, 5971 GC-MSD gas chromatograph at 75 eV.

Syntheses of the Complexes. (a) [Cu^{II}(fla)(indH)]ClO_4 (4). [$Cu^I(CH_3CN)_4$]ClO_4 (0.328 g, 1 mmol), flavonol (0.238 g, 1 mmol), and indH (0.300 g, 1 mmol) were dissolved in 60 mL of acetonitrile, and the mixture was stirred under an atmosphere of O_2 for 4 h. A green precipitate formed, which was filtered off, washed with ether, and dried under vacuum. It was identified as [Cu^{II}(fla)(indH)]ClO_4. Yield: 90%. Mp: 265–267 °C. IR (Nujol): 3276, 3209, 1661, 1632, 1562, 1107, 611 cm^{-1}. UV–vis (MeCN), λ_{max}/nm: 240, 306, 334, 417, 440, 631, 797. Anal. Calcd for $C_{33}H_{22}N_5O_7CuCl$: C, 56.65; H, 3.17; N, 10.01. Found: C, 56.24; H, 3.06; N, 9.62. $\mu = 2.10\ \mu_B$. Recrystallization of [Cu^{II}(fla)(indH)]ClO_4 from acetonitrile gave green crystals of Cu^{II}(fla)-(ind).

(b) Cu^I(fla)(indH) (5). [Cu^I(mes)]$_5$ (0.183 g, 0.2 mmol), flavonol (0.238 g, 1 mmol), and indH (0.300 g, 1 mmol) were dissolved in 60 mL of acetonitrile, and the mixture was stirred under an atmosphere of argon for 8 h. A brown precipitate formed, which was filtered off, washed with ether, and dried under vacuum. It was identified as Cu^I-(fla)(indH). Yield: 88%. Mp: >300 °C. IR (Nujol): 1654, 1627, 1580, 1009 cm^{-1}. UV–vis (DMF), λ_{max}/nm (ϵ/M^{-1} cm^{-1}): 277 (5754), 418 (5248), 447 (9333). Anal. Calcd for $C_{33}H_{22}N_5O_3Cu$: C, 66.04; H, 3.69; N, 11.67. Found: C, 65.82; H, 3.59; N, 11.48.

(c) Cu^{II}(fla)(ind) (6). [Cu^I(mes)]$_5$ (0.183 g, 0.2 mmol), flavonol (0.238 g, 1 mmol), and indH (0.300 g, 1 mmol) were dissolved in 60 mL of dichloromethane, and the mixture was stirred under an atmosphere of O_2 for 4 h. The solution was initially brown, but it became green after approximately 5 min and a green solid deposited. The solid was filtered off, washed with ether, and dried under vacuum. Yield: 85%. The filtrate gave a small quantity of green crystals of Cu^{II}(fla)(ind) on standing overnight, which were, however, unsuitable for crystallographic characterization. Mp: 306–308 °C. $\mu = 1.86\ \mu_B$. IR (Nujol): 1636, 1574, 1001 cm^{-1}. UV–vis (MeCN), λ_{max}/nm (ϵ/M^{-1} cm^{-1}): 307 (16 785), 334 (17 103), 415 (14 698), 444 sh (9073), 631 (152). Anal. Calcd for $C_{33}H_{21}N_5O_3Cu$: C, 66.16; H, 3.53; N, 11.69.

Found: C, 65.84; H, 3.64; N, 11.46. Recrystallization from acetonitrile gave green crystals of Cu^{II}(fla)(ind)·CH_3CN. The acetonitrile solution produced crystals suitable for X-ray analysis upon standing at room temperature for a few days.

(d) Cu^I(indH)(*O*-bs) (7). [Cu^I(mes)]$_5$ (0.183 g, 0.2 mmol), *O*-benzoylsalicylic acid (0.242 g, 1 mmol), and indH (0.300 g, 1 mmol) were dissolved in 60 mL of acetonitrile, and the mixture was stirred under an atmosphere of Ar for 4 h. A small quantity of a brown precipitate formed, which was filtered off, and the filtrate was allowed to stand at room temperature for 2 days. Brown crystals formed, which were filtered off, washed with ether, and dried under vacuum. The product was identified as Cu^I(indH)(*O*-bs). Yield: 72%. The filtrate produced crystals suitable for X-ray analysis upon standing at room temperature for a few days. Mp: 275 °C dec. IR (Nujol): 1666, 1634, 1741, 1578, 1380, 1009 cm^{-1}. UV–vis (DMF), λ_{max}/nm (ϵ/M^{-1} cm^{-1}): 272 (10 965), 309 (10 471), 334 (10 471), 421 sh (10 965), 447 (9333). Anal. Calcd for $C_{32}H_{22}N_5O_4Cu$: C, 63.62; H, 3.67; N, 11.59. Found: C, 63.34; H, 3.54; N, 11.22.

(e) Cu^{II}(ind)(*O*-bs) (8). Method A. [Cu^I(mes)]$_5$ (0.183 g, 0.2 mmol), *O*-benzoylsalicylic acid (0.242 g, 1 mmol), and indH (0.300 g, 1 mmol) were dissolved in 50 mL of acetonitrile, and the mixture was stirred under an atmosphere of O_2 for 3 h. A green precipitate formed, which was filtered off, washed with ether, and dried under vacuum. It was identified as Cu^{II}(ind)(*O*-bs). Yield: 85%. Mp: 253 °C. $\mu = 1.87\ \mu_B$. IR (Nujol): 1742, 1636, 1581, 1387 cm^{-1}. Anal. Calcd for $C_{32}H_{21}N_5O_4$-Cu: C, 63.73; H, 3.51; N, 11.61. Found: C, 63.45; H, 3.57; N, 11.36. UV–vis (DMF), λ_{max}/nm (ϵ/M^{-1} cm^{-1}): 309 (912), 333 (955), 417 (1096), 440 (891.3), 816 (14). Attempts to obtain suitable single crystals of Cu^{II}(ind)(*O*-bs) for X-ray analysis failed.

Method B. Cu^{II}(fla)(ind) (0.30 g, 0.5 mmol) in acetonitrile (30 mL) was treated with dioxygen (0.1 MPa) at 80 °C for 30 h. The green precipitate was filtered off, washed with acetonitrile, and dried under vacuum (0.39 g, 65%).

Method C. Cu^I(fla)(indH) (0.30 g, 0.5 mmol) in acetonitrile (25 mL) was treated with dioxygen (0.1 MPa) at 80 °C for 25 h. The green precipitate was filtered off, washed with acetonitrile, and dried under vacuum (0.30 g, 50%).

Crystallographic Data Collections and Refinements of the Structures. (a) Cu^{II}(fla)(ind)·CH_3CN (6·CH_3CN). The diffraction intensities of an approximately 0.30 × 0.30 × 0.30 mm crystal were collected with graphite-monochromatized Mo Kα radiation using a Siemens (Nicolet Syntex) R3m/V diffractometer and the ω-scan technique. A total of 4378 reflections were collected, of which 4378 (R_{int} = 0.000) were considered unique and 2397 were considered observed ($I > 2\sigma(I)$). An experimental absorption correction was applied (φ scan; $\Delta\varphi = 10°$), and the data were corrected for Lorentz and polarization effects. The cell parameters were obtained from the least-squares refinement of the setting angles of 25 carefully centered reflections with 2θ in the range 4.4–47.6°.

The structure was solved by direct methods. Final cycles of refinement converged with discrepancy indices of $R = 0.0878$ and $R_w = 0.1495$. Form factors were taken from the usual sources.[29] All calculations were performed with SHELXL93[30] and SHELXS86[31] crystallographic software packages.

A summary of the crystal data and X-ray experimental details is given in Table 1.

(b) Cu^I(indH)(*O*-bs) (7). The diffraction intensities of an approximately 0.20 × 0.40 × 0.40 mm crystal were collected with graphite-monochromatized Mo Kα radiation using a Siemens (Nicolet Syntex) R3m/V diffractometer and the ω-scan technique. A total of 4530 reflections were collected, of which 4171 (R_{int} = 0.0335) were considered unique and 3207 were considered observed ($I > 2\sigma(I)$). An experimental absorption correction was applied (φ scan), and the data were corrected for Lorentz and polarization effects. The cell parameters

(22) Perrin, D. D.; Armarego, W. L.; Perrin, W. L. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: New York, 1990.
(23) Nishinaga, A.; Tojo, T.; Tomita, H.; Matsuura, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2511.
(24) Siegl, W. O. *J. Org. Chem.* **1977**, *42*, 1872.
(25) Einhorn, A.; Rothlauf, L.; Seuffert, R. *Chem. Ber.* **1911**, *44*, 3309.
(26) Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981**, *46*, 192.
(27) Hathaway, B. J.; Holah, D. G.; Postlethwaite, J. D. *J. Chem. Soc.* **1961**, 3215.
(28) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-sensitive Compounds*; John Wiley & Sons: New York, 1986.

(29) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, U.K., 1974; Vol. 4.
(30) Sheldrick, G. M. SHELXL93: Program for Crystal Structure Refinement. University of Göttingen, 1993.
(31) Sheldrick, G. M. SHELXS86: Program for Crystal Structure Solution. University of Göttingen, 1990.

Table 1. Crystallographic Data for Cu^{II}(fla)(ind)·CH$_3$CN and Cu^I(indH)(*O*-bs)

	Cu^{II}(fla)(ind)·CH$_3$CN	Cu^I(indH)(*O*-bs)
empirical formula	C$_{35}$H$_{24}$N$_6$O$_3$Cu	C$_{32}$H$_{22}$N$_5$O$_4$Cu
fw	640.14	604.9
color	green	green
space group	*Pbca*	*P*$\bar{1}$
a (Å)	8.888(2)	8.048(7)
b (Å)	19.169(7)	8.969(9)
c (Å)	33.614(10)	19.24(2)
α (deg)	90	85.69(8)
β (deg)	90	80.24(7)
γ (deg)	90	77.87(7)
V (Å^3)	5727(3)	1337(2)
Z	8	2
T (K)	295	293(2)
$\lambda_{Mo\ K\alpha}$ (Å)	0.710 73	0.710 73
D_{calcd} (g cm^{-3})	1.485	1.500
μ (mm^{-1})	0.812	0.866
R	0.0878	0.0393
R_w (F^2)	0.1842	0.1158
GOF (F^2)	1.238	1.221

were obtained from the least-squares refinement of the setting angles of 25 carefully centered reflections with 2θ in the range 4.3−48.0°.

The structure was solved by direct methods. Final cycles of refinement converged with discrepancy indices of $R = 0.0393$ and $R_w = 0.1109$. Form factors were taken from the usual sources.[29] All calculations were performed with SHELXL93[30] and SHELXS86[31] crystallographic software packages.

A summary of the crystal data and X-ray experimental details is given in Table 1.

Reactions of Flavonol with Dioxygen in the Presence of Copper Flavonolate Complexes. In a typical procedure flavonol (0.119 g, 0.5 mmol) was added, to a solution of Cu^{II}(ind)(fla) (0.06 g, 0.1 mmol) in DMF (20 mL), and the mixture was stirred under dioxygen at 100 °C for 8 h. GC analyses were performed to determine the conversion of the substrate (C$_{16}$ standard), and GC of the solution after treatment with an ether solution of diazomethane gave the methylated products. These were identified by comparison of their mass spectra with reference spectra.[32]

The catalytic reactions were also followed by electronic spectroscopy in the range 500−200 nm. In these experiments, the copper complex and flavonol were dissolved under an argon atmosphere in DMF and the solution was heated to 120 °C. The argon was then replaced with dioxygen, and consumption of flavonol was analyzed periodically at 344 nm.

Results and Discussion

Reaction of Flavonol, [Cu^I(CH$_3$CN)$_4$]ClO$_4$, and 1,3-Bis-(2-pyridylimino)isoindoline in Acetonitrile under an Atmosphere of Dioxygen. The reaction of molar quantities of [Cu^I(CH$_3$CN)$_4$]ClO$_4$, indH, and flavonol in acetonitrile with dioxygen at room temperature yields the complex [Cu^{II}(fla)-(indH)]ClO$_4$. Recrystallization results in loss of HClO$_4$ from the complex, but its structure is clear from its analytical data and spectroscopic properties. In the infrared spectrum, two strong absorptions at 1632 and 1661 cm^{-1} can be found, which are characteristic of a coordinated nondeprotonated isoindoline ligand.[12] Additional bands observed at 1107 and 611 cm^{-1} are associated with the perchlorate ion. The strong absorption at 1562 cm^{-1} can be assigned to ν(CO) of the flavonolate ligand. The decrease of ca. 40 cm^{-1} for the ν(CO) band compared to that of the flavonol [ν(CO) 1602 cm^{-1}] is due to chelation and formation of a stable five-membered ring.[32] Room-temperature magnetic measurements yield a value of 2.10 μ_B/copper,

consistent with a copper(II) complex. The solid-state EPR spectrum is axial with $g_\perp = 2.136$ and $g_{||} = 2.353$ ($A_{||} = 139.6 \times 10^{-4}$ cm^{-1}). These results and the analytical data suggest that the complex can be formulated as [Cu^{II}(fla)(indH)]-ClO$_4$ (**4**), with a square pyramidal Cu(II) center.

Reaction of Flavonol, [Cu^I(mes)]$_5$, and 1,3-Bis(2-pyridyl-imino)isoindoline in Acetonitrile under an Atmosphere of Ar. The reaction of molar quantities of [Cu^I(mes)]$_5$, indH, and flavonol in acetonitrile under argon at room temperature produces a diamagnetic compound. The infrared spectrum of the product shows strong bands at 1654, 1627, and 1009 cm^{-1}, characteristic of the nondeprotonated ligand. The coordination of flavonol is supported by ν(CO) at 1580 cm^{-1}. These results and the analytical data suggest that the complex is Cu^I(fla)-(indH) (**5**).

Characterization of Cu^{II}(fla)(ind) (6). Attempted recrystallization of [Cu^{II}(fla)(indH)]ClO$_4$ from acetonitrile in air results in large prismatic crystals. Crystallographic characterization indicates that the crystals are Cu^{II}(fla)(ind)·CH$_3$CN. This complex can also be prepared by the reaction of [Cu^I(mes)]$_5$, flavonol, and indH in dichloromethane under dioxygen. Characteristic changes in the IR spectrum indicate that the complex contains the deprotonated isoindoline ligand (absence of a strong band at 1100 cm^{-1} and absorptions in the range 1600−1660 cm^{-1}). Complexes with deprotonated isoindoline ligands exhibit a weak band above 1600 cm^{-1}.[12] The IR band for ν(CO) of the flavonolate ligand lies at 1574 cm^{-1}. In the electronic spectrum of the complex, a d−d absorption at 631 nm can be found. Higher energy bands at 414 and 444 nm are associated with charge-transfer transitions. The electronic spectrum complex **4** in acetonitrile shows two d−d transitions, suggesting the presence of two different copper(II) complexes. The band of the complex [Cu^{II}(fla)(indH)]ClO$_4$ is at 797 nm. The higher energy band (631 nm) is associated with the d−d absorption of the Cu^{II}(fla)(ind) complex. The solid-state EPR spectrum is axial with $g_\perp = 2.0999$ and $g_{||} = 2.277$. The room-temperature magnetic moment (1.86 μ_B) is consistent with this structure.

The structure of **6**·CH$_3$CN is shown in Figure 1, and bond distances and bond angles relevant to the copper coordination sphere are given in Table 2.

The geometry around copper(II) may be best described as trigonally distorted square pyramidal, since it is on the borderline between trigonal bipyramidal and square pyramidal due to a τ value of 0.50. For perfect square pyramidal and trigonal bipyramidal geometries, the values of τ are zero and unity respectively, τ being an index of the degree of trigonality within the structural continuum between square pyramidal and trigonal bipyramidal geometries.[33] Two nitrogen atoms of the tridentate ligand (indH) (Cu−N1 2.039(6), Cu−N5 2.031(7) Å) and one oxygen atom of the flavonolate ligand (Cu−O2 2.206(5) Å) occupy basal positions. The other oxygen atom of the flavonolate (Cu−O1 1.942(5) Å) and one nitrogen of the isoindoline ligand (Cu−N3 1.903(6) Å) are in apical positions. The Cu−N distances involving the pyridine nitrogen atoms, N1 and N5, are significantly longer than that involving the pyrrole nitrogen atom, N3. The same pattern of bond lengths was observed in Ni(II)[34] and Mo(II)[35] complexes of the isoindoline ligand. The Cu−O and Cu−N bond lengths are otherwise comparable to

(32) Bellamy, L. M. *Ultrarot-Spektrum und chemische Konstitution*; Dr. Dietrich Steinkopff Verlag: Darmstadt, Germany, 1966; p 12.

(33) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Vershoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349.

(34) Lether, R. J.; Zhang, W.; Bensimon, C.; Crutchley, R. J. *Inorg. Chim. Acta* **1993**, *210*, 183.

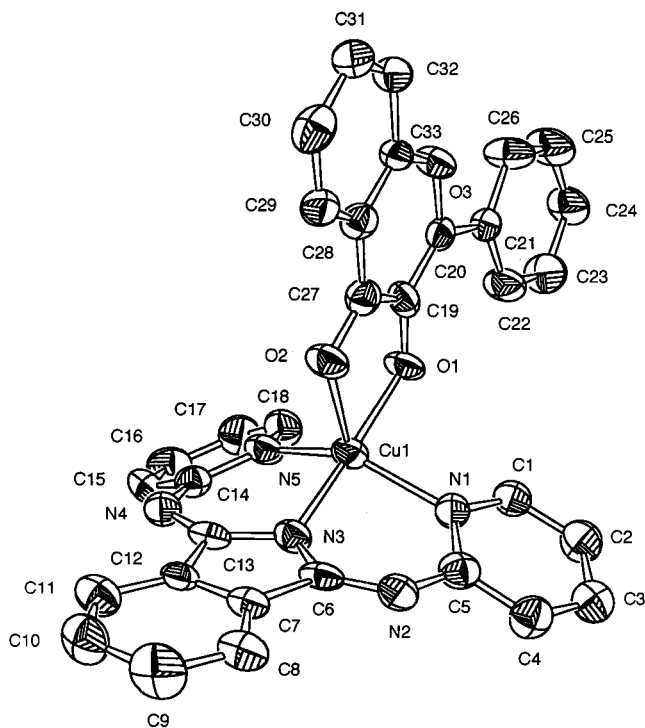(35) Baird, D. M.; Shih, K. Y.; Welch, J. H.; Bereman, R. D. *Polyhedron* **1989**, *8*, 2359.

Figure 1. Molecular structure of Cu^{II}(fla)(ind)·CH$_3$CN (**6**·CH$_3$CN).

Table 2. Selected Bond Lengths (Å) and Angles (deg) for Cu^{II}(ind)(fla)·CH$_3$CN

Bond Lengths			
Cu1−N3	1.903(6)	C6−N3	1.375(10)
Cu1−O1	1.942(5)	C13−N4	1.281(9)
Cu1−N5	2.031(7)	C13−N3	1.381(9)
Cu1−N1	2.039(6)	N4−C14	1.394(10)
Cu1−O2	2.206(5)	C14−N5	1.357(9)
N1−C5	1.332(10)	C18−N5	1.350(10)
N1−C1	1.347(10)	O1−C19	1.322(8)
C5−N2	1.397(9)	O19−C27	1.437(10)
N2−C6	1.297(10)	O2−C27	1.273(8)

Angles			
N3−Cu1−O1	174.6(2)	C5−N1−Cu1	124.5(6)
N3−Cu1−N5	88.0(3)	C1−N1−Cu1	115.4(6)
O1−Cu1−N5	94.0(2)	C6−N3−Cu1	121.8(5)
N3−Cu1−N1	87.8(3)	C13−N3−Cu1	120.7(5)
O1−Cu1−N1	93.4(2)	C18−N5−Cu1	117.5(6)
N5−Cu1−N1	144.5(3)	C14−N5−Cu1	124.8(6)
N3−Cu1−O2	94.0(2)	C19−O1−Cu1	114.5(4)
O1−Cu1−O2	80.6(2)	O1−C19−C27	118.1(7)
N5−Cu1−O2	109.0(2)	C27−O2−Cu1	107.0(5)
N1−Cu1−O2	106.5(2)	O2−C27−C19	119.7(7)

those reported previously for related systems.[36,37] The EPR spectrum is consistent with a square pyramidal Cu(II) ion. This means that the copper(II) ion has a $d_{x^2-y^2}$ ground state with $g_\parallel \gg g_\perp > 2.0$.[38] This is the most common ground state of copper(II) compounds. Even coordination compounds with high symmetries show distortions (Jahn−Teller effect), approaching approximately planar geometries. A trigonal symmetry would just weaken a planar ligand field, and this would lead to a d_{z^2} ground state. However, this is not the case for **6**.

Characterization of Cu^I(indH)(*O*-bs) (7). The reaction of molar quantities of [Cu^I(mes)]$_5$, *O*-bsH, and indH in acetonitrile

(36) Gagne, R. R.; Gall, R. S.; Lisensky, G. C.; Marsh, R. E.; Speltz, L. M. *Inorg. Chem.* **1979**, *18*, 771.
(37) Addison, A. W.; Burke, P. J.; Henrick, K. *Inorg. Chem.* **1982**, *21*, 60.
(38) Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, U.K., 1987; Vol. 5, pp 663−673.
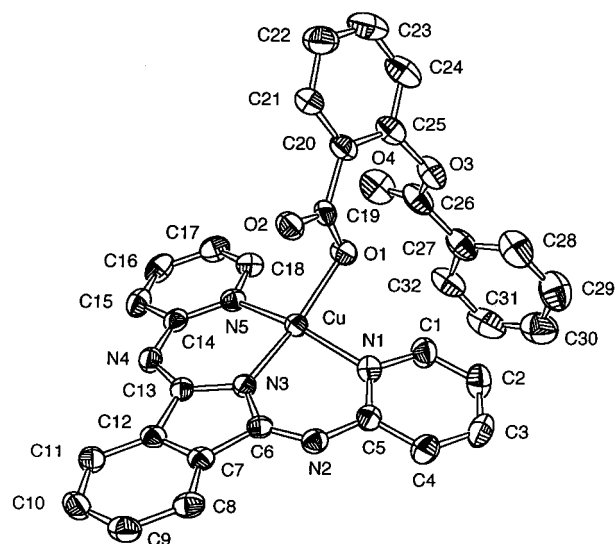
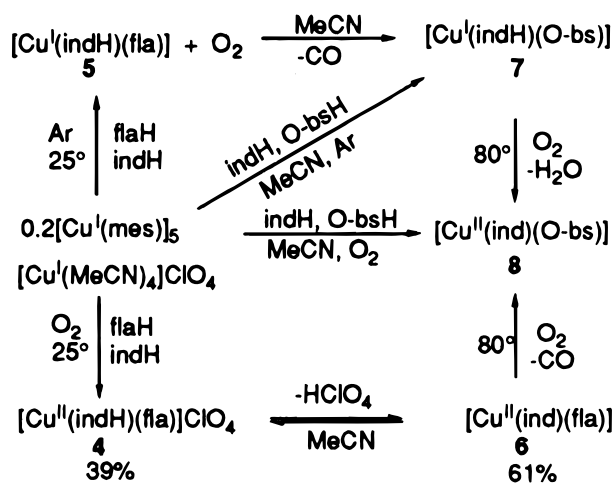**Figure 2.** Molecular structure of Cu^I(indH)(*O*-bs) (**7**).

Table 3. Selected Bond Lengths (Å) and Angles (deg) for Cu^I(indH)(*O*-bs)

Bond Lengths			
Cu−N3	1.881(3)	C6−N3	1.381(4)
Cu−O1	1.973(3)	N3−C13	1.384(4)
Cu−N1	2.003(3)	C13−N4	1.287(4)
Cu−N5	2.014(3)	N4−C14	1.387(4)
N1−C5	1.349(4)	C14−N5	1.367(4)
N1−C1	1.365(4)	C18−N5	1.354(4)
C5−N2	1.386(4)	O1−C19	1.277(3)
N2−C6	1.290(4)	C19−O2	1.234(4)

Angles			
N3−Cu−O1	165.86(9)	C1−N1−Cu	116.6(2)
N3−Cu−N1	90.19(13)	C6−N3−Cu	124.8(2)
O1−Cu−N1	91.92(12)	C13−N3−Cu	125.5(2)
N3−Cu−N5	90.79(13)	C18−N5−Cu	117.1(2)
O1−Cu−N5	91.94(12)	C14−N5−Cu	124.8(2)
N1−Cu−N5	160.15(10)	C19−O1−Cu	103.0(2)
C5−N1−Cu	124.9(2)	O2−C19−O1	123.0(3)

under argon at room temperature yields the diamagnetic complex Cu^I(indH)(*O*-bs). The infrared spectrum of this complex has two strong absorptions at 1634 and 1666 cm^{-1} and a third absorption at 1009 cm^{-1}, all of which are characteristic of a coordinated nondeprotonated isoindoline ligand. The IR band for ν(CO) of the *O*-benzoylsalicylate ligand is at 1741 cm^{-1}, and the ν(CO$_2$) absorptions are at 1578 and 1380 cm^{-1}.

The structure of **7** is shown in Figure 2, and bond distances and angles relevant to the copper coordination sphere are given in Table 3. The coordination about the copper ion is square planar, the copper being coordinated to three nitrogen atoms of the tridentate indH ligand and to one oxygen atom of the monodentate carboxylate group. The copper−nitrogen bond distances are similar to the values obtained for complex **6**. The copper−oxygen bond distance [Cu−O1 1.973(3) Å] is very close to that found in Cu^{II}(*O*-bs)$_2$(py)$_3$ [Cu−O1 1.971 Å].[39] In Cu^I(*O*-bs)(PPh$_3$)$_2$[40] and [Cu^{II}(idpaH)(*O*-bs)]ClO$_4$,[41] the Cu−O distances are longer [Cu−O1 2.148(2), 1.995(5) Å; Cu−O2 2.280(2), 2.344(6) Å]; however, in these cases, the *O*-benzoyl-salicylato ligand is bidentate. From the crystallographic data, it

(39) Balogh-Hergovich, É.; Kaizer, J.; Speier, G.; Argay, G.; Párkányi, L. *J. Chem. Soc., Dalton Trans.* **1999**, 3847.
(40) Balogh-Hergovich, É.; Kaizer, J.; Speier, G.; Fülöp, V.; Párkányi, L. *Inorg. Chem.* **1999**, *38*, 3787.
(41) Balogh-Hergovich, É.; Kaizer, J.; Speier, G.; Huttner, G.; Zsolnai, L. *Inorg. Chim. Acta* **2000**, *304*, 72.

Scheme 1

Scheme 2

Table 4. Data for the Oxygenations of Flavonol Catalyzed by (Flavonolato)copper Isoindoline Complexes (in DMF)

complex	time (h)	T (°C)	conv[a] (%)	products yields (%)[a]			
				2	**9**	**10**	**11**
$[Cu^{II}(fla)(indH)]ClO_4$ (**4**)	8	100	21		50	4	46
$Cu^{II}(fla)(ind)$ (**6**)	8	100	17	12	44	11	33
$Cu^{II}(fla)(ind)$ (**6**)	4	120	42	4	48	25	23
$Cu^{II}(fla)(ind)$ (**6**)	8	120	69	1	49	22	27

[a] Determined by GLC.

Figure 3. Concentration−time profiles for the catalytic oxygenation of flavonol: ○, $[Cu^{II}(fla)(indH)]ClO_4$ (**4**); +, $Cu^{II}(fla)(ind)$ (**6**). Conditions: $[Cu]_0 = 1.0 \times 10^{-4}$ M, $[flaH]_0 = 7.0 \times 10^{-4}$ M, $[O_2] = 7.7 \times 10^{-3}$ M, 120 °C, DMF.

is clear that the Cu−O bond distances do not depend on the oxidation state of copper. In cases of monodentate carboxylate coordination, the Cu−O bond lengths are shorter (1.971−1.973 Å), while those of bidentate coordination are longer (1.995−2.344 Å).

Reaction of Cu^{II}(fla)(ind) with Dioxygen. Upon the reaction of Cu^{II}(fla)(ind) (**6**) or $[Cu^I(indH)(O\text{-}bs)]$ (**7**) with dioxygen in acetonitrile at 80 °C, $Cu^{II}(ind)(O\text{-}bs)$ (**8**) is obtained (Scheme 1). This complex can also prepared by the reaction of $[Cu^I(mes)]_5$, O-bsH, and indH in acetonitrile under dioxygen. Characteristic changes in the IR spectrum indicate that the complex contains a deprotonated isoindoline ligand (absence of strong band at 1100 cm^{-1} and absorptions in the range 1600−1660 cm^{-1}). The IR band for $\nu(CO)$ of the benzoylsalicylate ligand is at 1742 cm^{-1}, and the $\nu(CO_2)$ bands are at 1581 and 1378 cm^{-1}. The electronic spectrum of the complex shows a d−d absorption at 816 nm. Higher energy bands at 440 and 417 nm are associated with charge-transfer transitions. In the solid state, the compound exhibits an axial EPR spectrum with $g_\perp = 2.060$ and $g_\parallel = 2.2133$, which would be consistent with a square pyramidal stereochemistry around the copper(II) ion. The room-temperature magnetic susceptibility is 1.87 μ_B. These results and the analytical data suggest that the complex can be unambiguously formulated as $Cu^{II}(ind)(O\text{-}bs)$ (**8**). Attempts to oxygenate **6** and **7** at low temperatures failed because the reactions were too slow to be completed in reasonable times.

Oxygenations of Flavonol Catalyzed by Cu^{II}(fla)(ind) and $[Cu^{II}$(fla)(indH)]ClO$_4$. We extended the stoichiometric oxygenation reactions of the (flavonolato)copper isoindoline complexes to catalytic processes to determine whether they would be good catalysts for oxygenation reactions. The catalytic reactions of flavonol with the complexes Cu^{II}(fla)(ind) (**6**) and $[Cu^{II}(fla)(indH)]ClO_4$ (**4**) were carried out according to Scheme 2 in DMF between 100 and 120 °C and at atmospheric dioxygen pressure. The flavonol:catalyst ratios were chosen to be (5−7):1, and the reaction products were identified by GC-MS after methylation of product **2** and its hydrolysates **9**−**11**. The quantitative evaluation of the products of the reactions is compiled in Table 4. The data show that, at higher temperatures, the yields are higher and the initial product **2** is to a large extent hydrolyzed during the reaction and workup.

Preliminary kinetic measurements for the copper flavonolate catalyzed oxygenation of flavonol in DMF at 120 °C and constant dioxygen pressure based on measuring the flaH concentration by UV−vis spectroscopy at 344 nm resulted in the concentration−time profiles shown in Figure 3. Plotting the
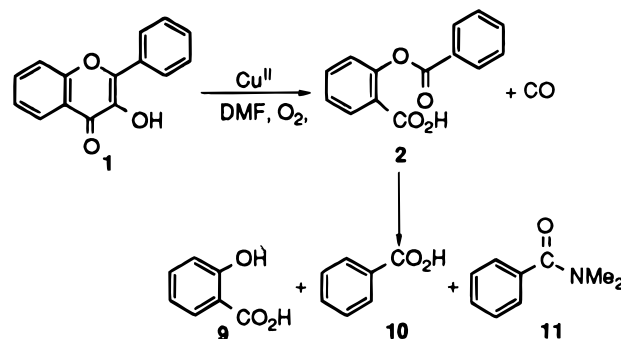
log [flaH] values against time resulted in a straight line consistent with the pseudo-first-order rate law $-d[flaH]/dt = k'[flaH]$, where $k' = k_3[O_2][Cu]$ and the k' values for Cu^{II}(fla)-(ind) and $[Cu^{II}(fla)(indH)]ClO_4$ are 6.64×10^{-5} and 3.68×10^{-5} s^{-1}, respectively. Attempts to carry out the oxygenation reactions at room temperature to isolate possible peroxidic intermediates failed.

Conclusion

In summary, it can be said that the relatively rigid tridentate ligation of the isoindoline ligands (indH and ind$^-$) to copper(I) and copper(II) flavonolate complexes can have considerable variability in structure and reactivity. In the reactions of the flavonolate complexes with dioxygen, an oxidative ring splitting of the pyranone ring of flavonol takes place under rather severe conditions (high temperature), mimicking the quercetinase enzyme reaction. However, attempts to isolate the dioxygen adducts of the flavonolato complexes failed. The complexes $[Cu^{II}(fla)(indH)]ClO_4$ (**4**) and Cu^{II}(fla)(ind) (**6**) do catalyze the oxygenation of flavonol in DMF to O-benzoylsalicylic acid (**2**)

Scheme 3
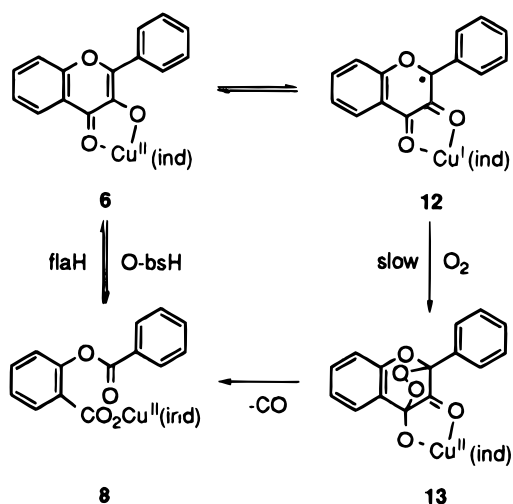
and the hydrolysates salicylic acid (**9**), benzoic acid (**10**), and dimethylbenzamide (**11**) with good yields, just mimicking the enzyme reaction. The pseudo-first-order rate constant in the case of **6** is almost 2 times larger than that for the reaction of **4**. This is probably due to the larger π-releasing ability of ind$^-$ compared to indH. The stoichiometric oxygenation and catalytic cycle of the oxygenation of flavonol catalyzed by **6** can be interpreted as shown in Scheme 3. We assume a redox role for copper, and because of valence isomerism, the copper(I)

flavonoxyl radical complex **12** is formed. **12** has two redox-active sites, the flavonoxyl radical ligand and Cu(I), which can react with dioxygen in a slow step to form the *endo*-peroxide **13**. This then breaks down rapidly to the (*O*-benzoylsalicylato)-copper(II) complex **8** and CO. *O*-Benzoylsalicylate is then displaced by the flavonol to give **6** in a reversible step. In the stoichiometric reactions, the end product **8** is formed. The role of copper(II) seems to be to accept an electron from the flavonolate ligand to generate redox-active copper(I) and the flavonoxyl radical. However, it is also possible that the role of the copper is just to deprotonate flavonol, because the flavono-late ion can also react with dioxygen at comparable reaction rates.[42] Further work is in progress to isolate and detect intermediates in such oxygenation reactions and to clarify the role of copper(II) to better understand the mechanism of this unique reaction.

(42) Barhács, L.; Kaizer, J.; Speier, G. *J. Org. Chem.* **2000**, *65*, 3449.