Geometry of Metal–Flavin Interactions: the Crystal Structure of Bis-(10-methylisoalloxazine)copper(II) Perchlorate Tetrahydrate

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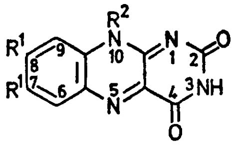
Summary An octahedral copper(II) complex of 10-methylisoalloxazine is characterized by strong flavin–copper bonding in the flavin primary chelate site [Cu–H_2O = 1·939(7); Cu–O(4) = 2·029(7); and Cu–N(5) = 2·415(7) Å] serving as a model for enzymic metal–flavin complexes as well as controverting earlier suggestions that quinonoid flavin forms complexes only with metals which are capable of one-electron oxidation.

Many flavoproteins contain metals as additional prosthetic groups,[1] notably non-heme iron and molybdenum. Early studies[2] of flavin–metal interactions indicated that only the semiquinoid form of flavin had appreciable general affinity for metals and the air-stable quinonoid flavin (I) formed complexes only with metals capable of one-electron oxidation such as Cu^I, Fe^{II}, Ag^I, *etc.* Several flavin-silver complexes recently prepared[3,4] reveal two chelate sites, a primary site involving O(4) and N(5) originally predicted by Bamberg and Hemmerich[5] which generally shows stronger binding, and a secondary site involving N(1) and O(2). Objections to these silver salts as models for possible enzymic complexes include the relatively low stereoselectivity of Ag^+ (although the flavin co-ordination is in fact fairly regular) and the moderately weak binding found (Ag–N $\geqslant$ 2·28 Å, Ag–O $\geqslant$ 2·38 Å).



(I)

The copper complex reported here is undoubtedly a better model for flavin interactions with transition metals and in addition it demonstrates the possibility of strong complex formation with an essentially non-oxidizable ion.

A warm, nearly saturated aqueous solution of copper(II) perchlorate was added to a hot saturated solution of 10-methylisoalloxazine in formic acid. Upon slow cooling orange crystals formed. The copper(II) tetrafluoroborate salt is isomorphous.[6] Preliminary Weissenberg photography showed the crystals to be monoclinic, elongated on *a*, with systematic absences *h*0*l* for *l* even and 0*k*0 for *k* odd.

Crystal data: $C_{11}H_8N_4O_2$, 0·5 $Cu(ClO_4)_2$, $2H_2O$, $M = 395{\cdot}4$; space group $P2_1/c$; $a = 8{\cdot}439(8)$, $b = 12{\cdot}208(12)$, $c = 15{\cdot}37(2)$ Å, $\beta = 111{\cdot}08(5)°$; $U = 1477$ Å; $D_c = 1{\cdot}78$ g cm^{-3} for $Z = 4$; $D_m = 1{\cdot}79$ g cm^{-3}; λ (Mo-K_α) = 0·7107 Å.

1910 independent reflections ($I > 2\,\sigma_I$) to $2\theta = 47°$ were measured by 2θ scans on a Picker four-circle, card-controlled diffractometer with a scintillation detector and Zr-filtered Mo-K_α radiation and no absorption correction has been applied.

The structure was solved by Patterson and Fourier techniques and refined to a current *R* 10·4% by least-squares with copper and the perchlorate group assigned ellipsoidal thermal parameters and the remainder of the molecule isotropic.

The copper ion occupies a centre of symmetry with co-ordination as shown in the Figure. One independent water molecule is co-ordinated to copper and the other probably hydrogen bonded to N(1) [3·05(1) Å] and/or O(2) [2·98(1) Å] of the flavin. The flavin N(3) is hydrogen bonded to a perchlorate oxygen atom [2·84(1) Å]. In contrast to the silver complexes where bonding is moderately strong at best, the bonding here is characteristic of strong interaction. Octahedral copper(II) nearly always has four strongly bound ligand atoms and two more weakly bound, the latter at distances ranging from 0·5 to 0·7 Å greater than for similar strongly bound atoms. Short distances (1·93—2·06 Å) and long ones (2·4—2·9 Å) are expected for both nitrogen and oxygen.[7]

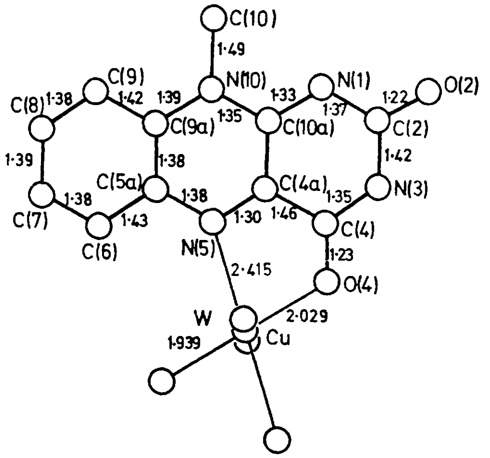


FIGURE. *Co-ordination about the copper, and ligand bond distances. Standard deviations are* 0·007 Å *for bonds to copper and ca.* 0·01 Å *for the remainder.*

It is unusual for an aromatic chelate to provide the distant ligands in a copper(II) complex, but closer approach of N(5) to copper is prevented by a short van der Waals contact (*ca.* 2·6 Å) between O(4) and the C(6) hydrogen atom of the centrosymmetrically related molecule. As in the silver salts and not surprisingly in this case, there seem to be no changes in the ligand geometry upon co-ordination.[4]

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[1] H. R. Mahler and E. H. Cordes, 'Biological Chemistry,' 2nd edn., Harper and Row, New York, 1971, p. 655.

[2] P. Hemmerich, F. Müller, and A. Ehrenberg, in 'Oxidases and Related Redox Systems,' eds. T. E. King, H. S. Mason, and M. Morrison, vol. I, Wiley, New York, 1965, p. 157.

[3] C. J. Fritchie, jun., G. D. Sproul, and T. D. Wade, IX International Congress of Crystallography, Kyoto, Japan, 1972, Abstract III-45.

[4] C. J. Fritchie, jun., *J. Biol. Chem.*, 1972, in the press.

[5] P. Bamberg and P. Hemmerich, *Helv. Chim. Acta*, 1961, **44**, 1001.

[6] W. T. Garland and C. J. Fritchie, jun., unpublished work.

[7] A. M. Mathieson and H. K. Welsh, *Acta Cryst.*, 1953, **5**, 599; Y. Komiyama and E. C. Lingafelter, *ibid.*, 1965, **17**, 1145; H. C. Freeman and J. E. W. L. Smith, *ibid.*, 1966, **20**, 153; R. W. G. Wyckoff, 'Crystal Structures,' vol III, 2nd edn., Wiley, New York, 1965, p. 716; S. C. Abrahams and E. Prince, *J. Chem. Phys.*, 1962, **36**, 50.