A Charge-transfer Complex Between Riboflavin and Hydroquinone: Crystal Structure

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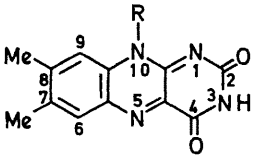
Summary The molecular complex between riboflavin dihydrobromide and hydroquinone is of the charge-transfer type but the interaction does not appear to involve a specific site on the flavin, it being inferred that the association nevertheless influences the CO(4)–N(5) region of the acceptor.

SUGGESTIONS that riboflavin, (I), as FMN or FAD, is involved in charge-transfer interactions in mitochondrial electron transport has prompted us to examine the crystal structure of a possible model for such processes. At the same time we hoped to further investigate the environment of the CO(4)–N(5) region of riboflavin and its significance in flavin binding.[1]

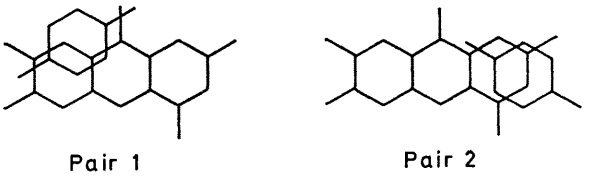


(I) R = D-ribityl

Very unstable, black, crystals of a riboflavin hydrobromide–hydroquinone compound were grown from a 6N-HBr solution containing an excess of diol. Crystals were mounted in capillaries containing mother liquor and two which showed least internal disorder were used for *X*-ray data collection by photographic methods: monoclinic; $a = 20{\cdot}55$, $b = 13{\cdot}69$, $c = 10{\cdot}18$Å, $\beta = 91°09'$; space group $P2_1$; $Z = 4$. Present refinement by block diagonal procedures stands at $R = 0{\cdot}151$.

Four bromide ions, two molecules of riboflavin (doubly protonated), and two molecules of hydroquinone make up the asymmetric unit, bond lengths and angles agreeing with expected values within the present limits of error. The molecules are associated in pairs by what are clearly charge-transfer interactions. The separations between mean planes are 3·35 for Pair 1 and 3·28Å for Pair 2 (Figure). In illustrating the possibility of a donor–acceptor complex as suggested for flavin co-enzymes the crystal structure supports the similar interference drawn from the 10-methylisoalloxazine–naphthalene-2,7-diol interaction.[2] It does not, however, support the detailed conclusion drawn in this latter instance. The donor–acceptor pairs overlap in a different manner (Figure) and neither overlaps any of the atoms N(5), C(6), C(8), N(10) of the flavin nucleus which are in the region of the lowest empty orbital,[3] although the hydroquinone lies close to C(8) and N(10) in Pair 1. We infer that any section of the nucleus may be involved in a charge-transfer association, depending on the exact geometry of its partner and that this is possibly a biological requirement.

In a further departure from the situation in 10-methylisoalloxazine–naphthalene-2,7-diol none of the bromide ions interacts with a flavin nucleus, two of them being hydrogen-bonded to ribityl groups and two to hydroquinone molecules. The four nitrogen atoms of each riboflavin are clearly involved in hydrogen bonding since all are within 2·8—3·1Å of oxygen atoms. A survey of all such short interactions further indicates that one hydrogen atom is available for each hydrogen bond in the solid if it be assumed that both N(1) and N(5) are protonated. This agrees with earlier findings for N(1)[2,4] but does point to a new situation at N(5).



FIGURE

Neither riboflavin hydrobromide monohydrate[4] (from 6N-HBr) nor 10-methylisoalloxazine hydrobromide–naphthalene-2,7-diol (from conc. HBr) is protonated at N(5) although it has been suggested that the CO(4)–N(5) chelate site will nearly always contain a positive ion or dipole. We infer that the formation of the dihydrobromide (from 6N-HBr) which occurs in the present instance reflects the increased basicity of N(5), and that this is a likely consequence of electronic transfer from the donor to the flavin nucleus. Thus the ability of the chelate site to hold a positive dipole, already demonstrated,[2] and the ability of N(5) to accept a proton under suitable conditions, as presently inferred, is in line with the mode of reduction of riboflavin.[4] It would also seem to support suggestions that charge transfer, *e.g.* between flavin and NADPH, is important in some functions of the co-enzyme.[5]

Each riboflavin molecule is hydrogen-bonded to two others by two sets of "base pairs," NH(3) · · · · · CO(4′), NH(3′) · · · · · CO(4) and NH^+(1) · · · · · CO(2′), NH^+(1′) · · · · · CO(2), the respective distances being 2·78, 2·80, 2·96, and 2·83Å. Further hydrogen bonds link ribityl chains to bromide ions and hydroquinone molecules. A search of "difference" maps reveals no evidence for the presence of water molecules.

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