X-Ray Crystal Structure of the 7,8-Dimethylisoalloxazine-10-acetic Acid–Tryptamine Complex. A Model for Flavin–Indole Charge-transfer Complexes

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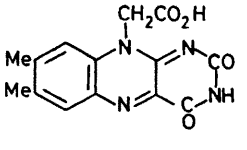
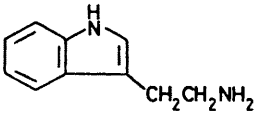
Summary The structure of the molecular complex 7,8-dimethylisoalloxazine-10-acetic acid–tryptamine tetrahydrate has been determined by *X*-ray crystallography; it is of the charge-transfer type and suggests that tryptophan residues may be significant in flavin–protein binding in the flavoproteins.

ACCORDING to various spectral investigations,[1] it has been established that the tryptophan residues of apoenzymes have an important role in the development of the enzymatic function of flavoproteins and can form charge-transfer complexes with flavin coenzymes; this may be regarded as a fundamental interaction necessary for the recognition between the apoenzyme and coenzyme.[2] Little is known about the binding site and mode of either molecule.

To increase our knowledge of flavin–indole interactions, we have determined the crystal structure of the title complex, which is the first model of a flavin–indole charge-transfer complex to be investigated directly at the molecular level.



(1)



(2)

7,8-Dimethylisoalloxazine-10-acetic acid (DIA) (**1**) was synthesized according to the previously described method.[3] The addition of an equimolar amount of tryptamine (TPA) (**2**) to an aqueous suspension of DIA increased the solubility of the DIA and caused the colour to change from yellow to dark red, with the appearance of a charge-transfer band at 460—600 nm (λ_{max} 512 nm). The dark red crystals obtained from the aqueous solution consisted of a 1:1 (DIA–TPA) complex and contained four water molecules per complex.

Crystal data: $C_{24}H_{32}N_6O_8$, $M = 532{\cdot}54$, monoclinic, space group $P2_1/c$, $a = 18{\cdot}618(4)$, $b = 7{\cdot}008(1)$, $c = 19{\cdot}469(6)$ Å, $\beta = 100{\cdot}63(3)°$, $U = 2496{\cdot}62$ Å^3, $D_m = 1{\cdot}383$ g cm^{-3}, $D_c = 1{\cdot}417$ g cm^{-3}, $Z = 4$.† The structure was solved by a combination of a Patterson vector search and direct methods (program 'MULTAN'[4]), and refined by least-squares to $R = 0{\cdot}11$ using 1795 independent reflections.

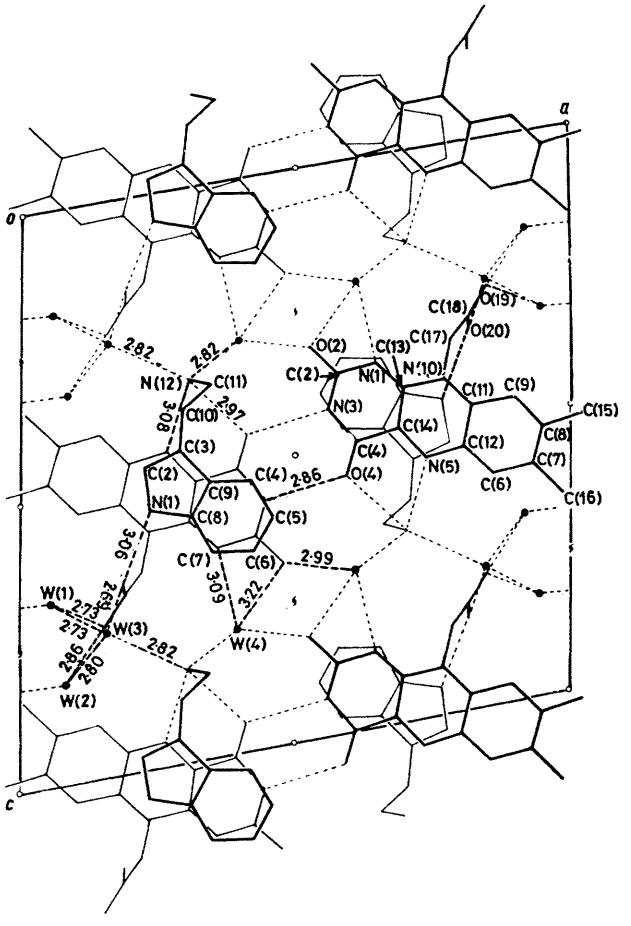


FIGURE 1. Stacking and hydrogen-bonding diagram with the atomic numbering, shown as a projection on to (010). Dashed lines represent possible hydrogen bonds and short contacts [W(4) - - - O(2) and N(12) - - - O(4)]. E.s.d.s of the interatomic distances are 0·02 Å.

As shown in Figure 1, the DIA molecule forms a dimer with two hydrogen bonds [N(3) - - - O(4′), 2·86(2) Å] around a centre of symmetry. Alternate DIA and TPA molecules are stacked in the *b*-direction and surrounded by water molecules, which stabilize the molecular packing by hydrogen bond formation. All the hydrogen atoms attached to the nitrogen atoms and those of the water molecules participate in the hydrogen bonds [2·69(2)—3·09(2) Å]. The 'chelate sites' of the isoalloxazine ring, N(1)–O(2) and O(4)–N(5), are occupied by water [W(4)] and by the amino group [N(12)] of the TPA molecule respectively, as in metal–flavin complexes.[5]

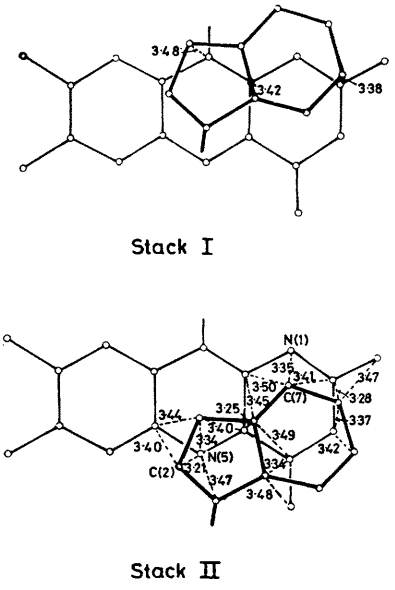


FIGURE 2. The observed overlapping modes and orientations of the isoalloxazine and indole groups, with interatomic distances less than 3·5 Å, viewed perpendicular to the isoalloxazine plane. E.s.d.s of the distances are 0·01—0·02 Å.

As shown in Figure 2, there are two types of overlap between the isoalloxazine and indole rings in the complex crystal (stacks I and II). It is interesting that the benzene ring of the indole group lies above the uracil ring of the isoalloxazine group, and that the pyrrole ring lies above the pyrazine ring, with some of the interatomic distances being shorter than normal van der Waals separation (3·4 Å). The stacked rings are almost parallel to each other (dihedral angle, 2·8° for both pairs), and the separation between mean planes is 3·40 Å for stack I and 3·23 Å for stack II, suggesting partial charge-transfer from the indole group to the lowest unoccupied orbital of the isoalloxazine group in the ground state. These stacking forces also imply that the tryptophan residues are important for the binding between flavins and apoenzymes in flavoproteins.

In stack II particularly, the strong interactions between C(2) (TPA) and N(5) (DIA) [3·21(2) Å] and C(7) and N(1) [3·35(2) Å] could play an important role in raising the proton-accepting ability of N(1) and N(5) during the reduction of flavins, and it may reflect the reductive role of tryptophan residues in flavoproteins.

† The atomic co-ordinates for this work are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

On the other hand, it may be that the mutual orientations of the stacked rings in the complex molecule depend mainly on the strength of coulombic interactions, because the unusually short contacts between the stacked rings occur between two atoms capable of forming electron-rich–electron-deficient pairs.[6]

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