Photo-addition Reactions in the Benzenoid Subnucleus of Flavoquinones

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By photochemical attack on flavin cations, compounds substituted in the benzenoid subnucleus have been prepared. Water and alcohols can be added in this way and under certain conditions the alcoholic groups of the flavin side chain are involved. Structures and properties of photo-products are described.

It has been shown by TE NIJENHUIS and BERENDS that the benzenoid (or better: o-quinoid) subnucleus of alloxazines can be attacked photochemically. We found that with flavins the reaction products bear a hydroxyl group either in the 6 or in the 9 position of the benzenoid nucleus. The reactive species is the protonated flavin, the rate of the reaction has an optimum at pH 0-1. At still lower pH dynamic proton quenching decreases the rate. The fastest reaction is given by formylmethylflavin (1) which is fully protonated at pH 1 (pK = 3.5) and by 1,10-substituted flavinium salts (Scheme 1, No. 1 and 2).

The reaction involves water addition either at the 6,7- or at the 8,9-position and subsequent oxidation of the hydrate as Scheme I shows. Experiments done in D2O with formylmethylflavin showed that the remaining aromatic proton in the reaction products was not exchanged against deuterium, which proved the absence of 6,9-addition.

The very stable cyclic hemiacetals (2) are formed during the photolysis of N(10)-2'-carbonyl flavins via the addition of the 9-OH group to the carbonyl function, thus forming cyclic acetals. All these compounds, i.e. alcohols or cyclic acetals show UV-spectra with a characteristic absorption centered at 405 nm: the hydroxylated compounds are completely non-fluorescent, the cyclic acetals show only a weak brownish-red fluorescence.

In methanolic sulfuric acid, methanol adds to the benzenoid subnucleus yielding 9-methoxy compounds exclusively. The hydroxyl groups (irrespective of being in the 6 or in the 9-position) show a relatively low pK around 7 owing to the electron deficiency of the flavoquinone nucleus. UV-spectra of 9-hydroxy-3-methyl lumiflavin are given in Fig. 1. An unequivocal assignment of the position of the hydroxyl groups can be made by chelate formation with copper(II) perchlorate in acetate buffer at pH 6 or in acetone. In the case of 6-substitution metal chelates of the structure 3 can be formed, which is not possible in the case of 9-substituted compounds. As an example the proof of structure for hydroxylated
1,10-ethano-flavinium perchlorates is given in Fig. 2. Only the spectrum of the 6-hydroxylated compound changes, due to chelate formation, whereas the spectra of the unsubstituted and of the 9-hydroxylated compound remain unchanged. UV-spectra of flavin metal complexes have been described by Hemmerich and Lauterwein.}

Flavins with a 2'-hydroxy group in the side chain (4) undergo photoreactions as shown in Scheme II.

Scheme II. Photoreactions of flavins with a 2'-OH group in the side chain.

The 2'-OH group adds to the protonated flavin nucleus in the way alcohols do, to give cyclic ethers (6). The reaction is slow, because protonation (4, 5 pK 0.5) occurs at a pH where dynamic proton quenching becomes predominant. The cyclic ethers (6) are also found as photolysis products of neutral flavins (6) in the presence of divalent anions (4).

The neutral flavin (4) undergoes fast photolysis to lumichrome (10) or oxidation of the 2'-CHOH group to the corresponding carbonyl function (4, 7) by intramolecular hydrogen abstraction. The thus formed carbonyl compounds are protonated in a pH region (pK 1 - 3.5) where proton quenching occurs to a lesser extent and undergo fast hydroxylation and acetal formation. The carbonyl compound 7 (R = CH₃) is quite stable to further lumichrome decay, which shows that oxidation of the 2'-CHOH group is not the first step in photolytic lumichrome formation.

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