in ratio in solution did not improve the yield beyond 42%.[8]

Apparently in reactions on the polymer, at sufficiently high ratios the majority of enolizable ester groups (separated from each other by the polymer lattice) have some nonenolizable ester moieties in their close vicinity.

In order to confirm the mechanism proposed in Scheme II, namely the interaction of ester groups within the same polymer bead, equal amounts of two different batches of polymer, each containing a different ester, were mixed and treated with tritylllithium for 10 min. One batch contained *p*-chlorobenzoate groups (1 mmol/g), the other 3-phenylpropionate (0.1 mmol/g). Upon cleavage and work-up as described above, no ketones whatsoever could be detected (tlc), the only products being unreacted starting acids. This result indicates that the condensations described are truly intrapolymeric and that no mechanism such as cleavage followed by condensation is involved.[11]

Acknowledgment. Stimulating discussions with C. Yaroslavsky and B. Amit are gratefully acknowledged.

(8) The mixed condensation of aliphatic with aromatic esters is well documented in the literature.[9] Though in some cases good yields of the condensation product are reported, they do not usually exceed 60%.[10] Self-condensation of the aliphatic ester is often difficult to avoid.

(9) C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, **1**, 266 (1942).

(10) E. E. Royals, J. C. Hoppe, A. D. Jordan, Jr., and A. G. Robinson III, *J. Amer. Chem. Soc.*, 73, 5857 (1951); E. E. Royals and D. G. Turpin, *ibid.*, 76, 5452 (1954).

(11) Preliminary attempts to react polymer-bound acid **2** with an excess of a *soluble* ester of 4 have as yet been unsuccessful.

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Preequilibrium Complex Formation and Nucleophilic Addition (and Its Position) As Factors in Flavin-Catalyzed Oxidations

Sir:

Two-electron hydrogen transfer in flavin-catalyzed biological oxidation reactions can be envisaged as involving a hydride ion plus a proton or, alternatively, two protons plus two electrons.[1a] Recent reviews[1a,b] have centered attention on the possible universality of the latter process in which flavin–substrate adduct formation is involved (*e.g.*, eq 1). Although alkaline hydrolysis opens some isoalloxazines at the 10a position,[2] covalent adducts at the 4a position are known from photochemical oxidative decarboxylation[3] and the latter position has been proposed[1a,b,4] as the reactive electrophilic center in nonphotochemical (dark) reactions (*e.g.*, eq 1).

Since an alternative mechanism involving a charge-transfer complex[5,6] has been suggested for oxidation

(1) (a) G. A. Hamilton, *Progr. Bioorg. Chem.*, **1**, 83 (1971); (b) P. Hemmerich, *Vitam. Horm.*, **28**, 467 (1970).

(2) D. E. Guttman and T. E. Platek, *J. Pharm. Sci.*, **56**, 1423 (1967).

(3) W. H. Walker, P. Hemmerich, and V. Massey, *Eur. J. Biochem.*, **13**, 258 (1970).

(4) L. E. Brown and G. A. Hamilton, *J. Amer. Chem. Soc.*, **92**, 7225 (1970).

(5) I. Isenberg, S. L. Baird, and A. Szent-Györgyi, *Proc. Nat. Acad. Sci. U. S.*, 47, 245 (1961).

(6) E. M. Kosower (in "Flavins and Flavoproteins," E. C. Slater, Ed., Elsevier, New York, N. Y., 1965, p 1) has pointed out that the evidence offered in support of such a complex is questionable.

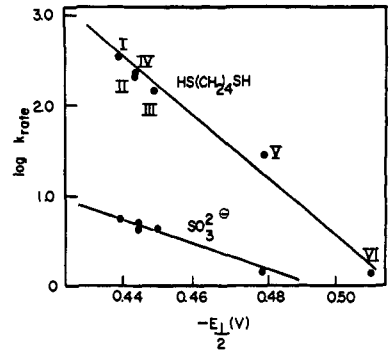
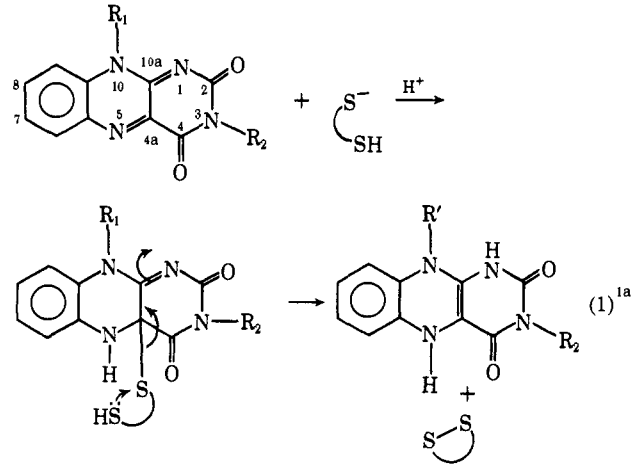


Figure 1. Linear free-energy correlations with polarographic half-wave potentials of rates of reaction of isoalloxazines I–VI with 1,4-butanedithiol and sulfite ion.

of NADH by flavins, we have set about to determine the importance of preequilibrium complex formation as well as the steric availability of the 4a and 10a positions to the dark reactions of flavins. To this end,



reactions of isoalloxazines I–VI (see Table I) have been investigated.[7] Molecular models of I show that (i)

Table I

	R_1	R_2
I	2,6-$(CH_3)_2C_6H_3$	CH_3
II	2-$CH_3C_6H_4$	CH_3
III	C_6H_5	CH_3
IV	CH_3	CH_3, 7-Cl
V	CH_3	CH_3
VI	CH_3	H, 7,8-$(CH_3)_2$

approach to the 10a position is hindered above and below the plane of the isoalloxazine ring by the *o*-methyl substituents, and (ii) formation of a face-to-face complex involving that portion of the isoalloxazine ring adjacent to the 10 position is hindered. Both of these steric effects decrease in the order I > II > III > IV = V = VI. In order to assess the effectiveness of the blocking of the 10a position in I, its hydrolysis was investigated (pH 10.5–13.75; eq 2). The first step of the reaction is reversible and I can be regenerated (anaerobic) in 100% yield on acidification of the kinetic

(7) Compounds I–V were synthesized by standard methods, starting with *o*-fluoronitrobenzenes; see J. P. Lambooy, *Heterocycl. Compounds*, **9**, 136, 148 (1967). VI was a gift from Dr. H. A. Harbury.

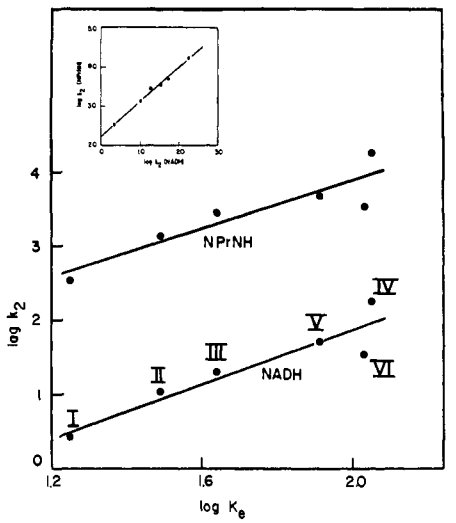
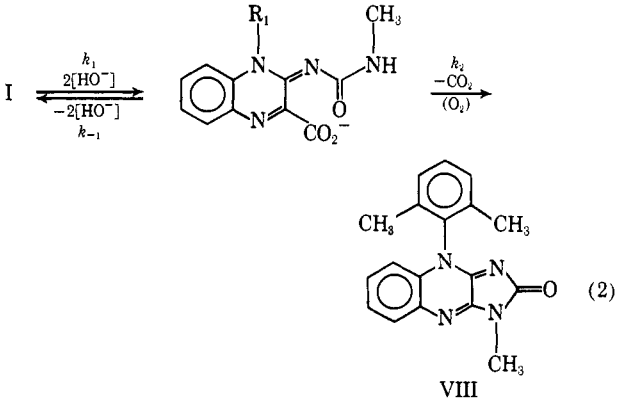


Figure 2. Linear free-energy correlations of rates of reduction of isoalloxazines I–VI by NPrNH and NADH with equilibrium constants for the formation of complexes of I–VI with tryptophan. The inset is a plot of log k_{rate} for NPrNH *vs.* log k_{rate} for NADH.

solution after the appropriate time interval. Compound VIII[8] does not yield I in acid. These results establish that the usual HO^- attack at the 10a position is effectively blocked in I and redirected to the 4 position.[9]



The rates of reaction of compounds I–VI (dark, anaerobic, solvent water containing 5 vol % DMF) with four reagents have been determined: (a) sulfite[10] (pH 7.10, 29.9°); (b) 1,4-butanedithiol[11] (pH 8.98, 29.9°); (c) NADH[12] (pH 7.65, 29.9°); and (d) *N*-propyl-1,4-dihydronicotinamide[13] (NPrNH) (pH 7.71, 29.75°). Plots (Figure 1) of log k_{rate} *vs.* the polarographic half-wave potentials ($E_{1/2}$) determined for I–VI (pH 8.97, 30°, reference, saturated calomel electrode) reveal a linear free-energy relationship for both sulfite and 1,4-butanedithiol. Since steric hindrance at the 10a position does not bring about negative rate deviations we are assured that *nucleophilic addition does not occur at the 10a position.*[14,15]

For NADH and NPrNH, plots of the log of the second-order rate constants *vs.* $E_{1/2}$ exhibit increasing negative deviation in the order III < II < I (plot not shown). If the best straight line is drawn through the points for IV, V, and VI, the rate constant for I exhibits a negative deviation of *ca.* 150-fold. These results suggest that either reduction of the isoalloxazine is initiated at the hindered 10a position or that face-to-face complexing is important. Plots of log k_{rate} for both NADH and NPrNH *vs.* log of the complexing constants K_e (determined by fluorescence quenching[16]) of I–VI (pH 7.85; solvent H_2O–5 vol % DMF) for tryptophan (Figure 2) and β-resorcylic acid were found to be linear. From this result it is clear that kinetically important preequilibrium *complex formation takes place between flavins and the dihydronicotinamide ring system.* A plot of log k_{rate}^{NADH} *vs.* log k_{rate}^{NPrNH} (insert to Figure 2) is of slope 0.9 and intercept 2.23 indicating that NADH and NPrNH possess essentially equal sensitivity to the electronic and steric alterations in going from I to VI but that the rate constants for NPrNH exceed those for NADH about 100-fold. That the second-order rate constant ($K_e k_r$ of eq 3) is less for

$$\text{flavin} + \text{dihydronicotinamide} \overset{K_e}{\rightleftharpoons} \text{complex} \xrightarrow{k_r} \text{product} \quad (3)$$

NADH than for NPrNH may find partial explanation in the decreased availability of flavin for complexing with the dihydronicotinamide ring of NADH owing to competitive (but nonproductive) complexing by the adenine moiety. Relatively strong intermolecular[16] and intramolecular[17] complexing of adenine with flavins is known.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

(8) VIII was isolated by neutralization of an anaerobic hydrolysis reaction followed by solvent extraction and chromatography on silica gel and alumina: nmr singlets at δ 1.97 (6 H) and 3.51 (3 H) as well as between 6.8 and 8.1 (7 H); mass spectrum, parent peak *m/e* 304; calcd 304. *Anal.* Calcd: C, 71.05; H, 5.26; N, 18.24. Found: C, 70.83; H, 5.05; N, 18.37.

(9) HO^- attack at the 4a position would be hydrolytically nonproductive[1a] so these results should not be construed to indicate the 4 position to be more electrophilic than the 4a position.

(10) F. Muller and V. Massey, *J. Biol. Chem.*, **214**, 4007 (1969).

(11) I. M. Gascoigne and G. K. Radda, *Biochim. Biophys. Acta*, **131**, 498 (1967).

(12) J. L. Fox and G. Tollin, *Biochemistry*, **5**, 3865 (1966).

(13) C. H. Suelter and D. E. Metzler, *Biochim. Biophys. Acta*, 44, 23 (1960).

(14) F. Muller and V. Massey[10] provide evidence for the final position of sulfite to be at N-5.

(15) Contrary to the suggestions of Gascoigne and Radda[11] thiol anion generated *via* specific base catalysis is the reactive species.

(16) G. R. Penzer and G. K. Radda, *Quart. Rev., Chem. Soc.*, **21**, 43 (1967).

(17) D. B. McCormick, "Molecular Associations in Biology," Academic Press, New York, N. Y., 1968, p 377.

(18) Postdoctoral Fellows of the Department of Chemistry, University of California at Santa Barbara.

(19) A portion of this material to be submitted by S. Smith in fulfillment of the requirement for the Ph.D. in Chemistry, University of California, Santa Barbara.

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Intramolecular Quenching of the Excited Singlets of Phenyl ω-Dialkylaminoalkyl Ketones. Singlet State Type II Photoelimination of α-Dimethylaminoacetophenone

Sir:

Phenyl ketones undergo intersystem crossing so rapidly[1,2] that it is generally assumed that they do so

(1) R. M. Hochstrasser, *Accounts Chem. Res.*, **1**, 266 (1968).