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MICELLAR CATALYSIS OF CN^--ASSISTED ISOALLOXAZINE(FLAVIN ANALOGUE) OXIDATION OF ALDEHYDES TO CARBOXYLIC ACIDS

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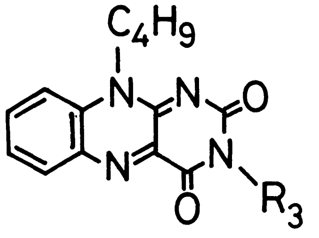
Facile isoalloxazine oxidation of aldehydes to carboxylic acids was achieved in the presence of a cationic micelle and CN^- ion. The formation of a carbanion intermediate was proposed on the basis of the kinetic examinations. The role of the cationic micelle and CN^- ion was discussed.

Flavin oxidation of carbanions has been of much concern in connection with enzymatic oxidation-reduction reactions.[1-3] Nonenzymatic oxidation of nitroalkane carbanions by isoalloxazines(flavin analogues) is remarkably facilitated in the presence of a cationic micelle.[4] This finding may be applied to oxidation of other carbanions, leading to new synthetic procedures.

At an early date of the century, Lapworth[5,6] clarified the essential features of the benzoin condensation. The reaction involves a carbanion intermediate, Ph-$\bar{C}$(CN)(OH). If flavin can oxidize the carbanion to PhCOCN which is readily hydrolyzed to PhCOOH, an aldehyde will be oxidized to the corresponding carboxylic acid with the aid of CN^- ion. The reaction is analogous to the action of aldehyde oxidase which is presumed to require FAD as cofactor.[7] We wish to describe that the facile conversion of aldehydes to carboxylic acids can be achieved by the catalytic action of CN^- and flavin.

Isoalloxazines employed are 3-methyl-10-butylisoalloxazine(I)[8] and 3-hexadecyl-10-butylisoalloxazine(II).[4]



(I) $R_3=CH_3$-

(II) $R_3=C_{16}H_{33}$-

All the kinetic measurements were carried out anaerobically(N_2) at 30 ± 0.1°C at pH 10.5(0.05 M KCN and 0.005 M H_3BO_3) unless otherwise stated. Disappearance of the isoalloxazines was followed at λ_{max}(433 nm for I and 440 nm for II).

Figure 1 shows the time-dependence of the absorption of isoalloxazine I in the presence of p-chlorobenzaldehyde, CN^-, and CTAB(hexadecyltrimethylammonium bromide) at a concentration above the critical micelle concentration.[9] The disappearance of I was found to be zeroth-order up to 95% reaction. Introduction

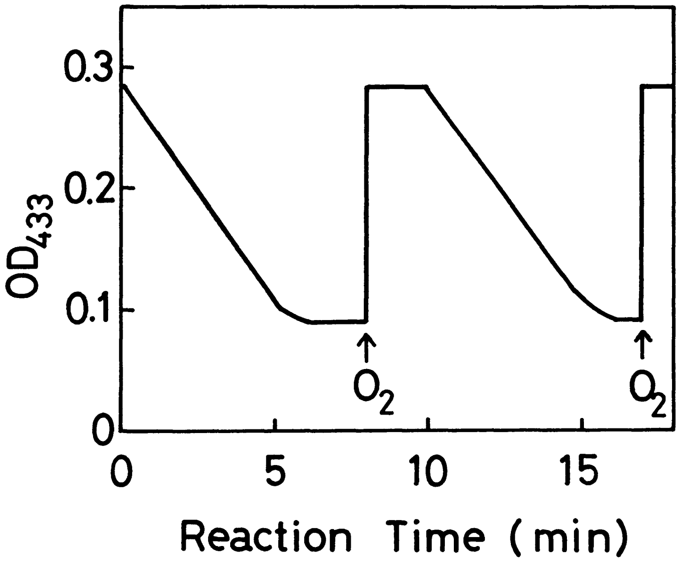


Fig. 1. Time-dependence of absorbance of I. [CTAB]=1.0 x 10^{-2} M, [I]=2.0 x 10^{-5} M, [p-Cl-C_6H_4CHO]=5.0 x 10^{-3} M.

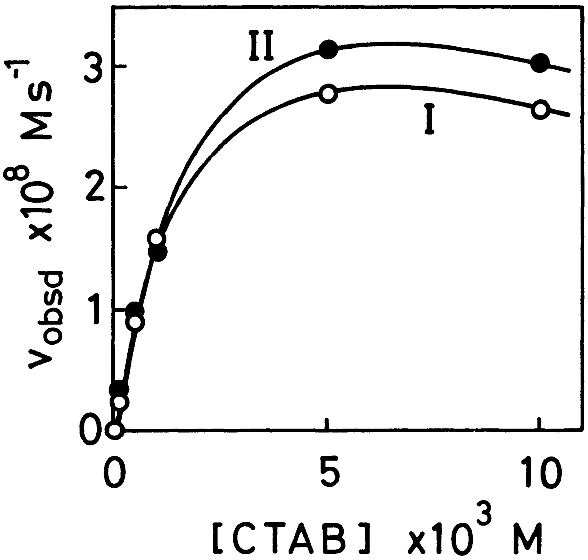
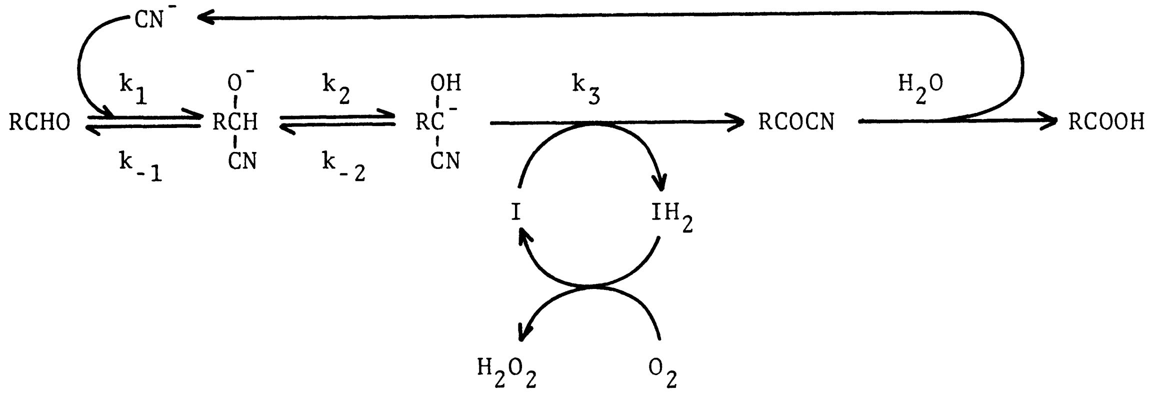


Fig. 2. v_{obsd} vs. [CTAB]. [I]=[II]=2.0 x 10^{-5} M, [p-Cl-C_6H_4CHO]=5.0 x 10^{-3} M.

of oxygen into the final reaction mixture regenerated I quantitatively, and after several minutes the zeroth-order disappearance of I started again. The reaction rate(i.e., slope of the zeroth-order disappearance) was first-order in CN^- and in p-chlorobenzaldehyde([CN^-]=0.01-0.05 M,[p-Cl-C_6H_4CHO]=(2-15) x 10^{-3} M). When the reaction was carried out on a preparative scale under anaerobic conditions, p-chlorobenzoic acid was isolated in 98% yield. Under aerobic conditions, the isolated amount of p-chlorobenzoic acid reached more than 300%. These observations afford the following reaction scheme(R=p-Cl-C_6H_4-).



The oxidation of benzaldehyde in the micellar system showed similar zeroth-order behavior for up to 90% reaction. In the nonmicellar system, the disappearance kinetics of I changed from zeroth-order to first-order during the course of the reaction(at 70% completion for p-chlorobenzaldehyde and at 20% completion

Table 1. The micellar effect on the oxidation of aldehydes[a)]

Aldehyde		k_2K ($\times 10^6$ $M^{-1}s^{-1}$)		
	M	None	I + CTAB	II + CTAB
p-Cl-C_6H_4CHO	0.005	0.49 (100%)	107 (100%)	126 (100%)
C_6H_5CHO	0.020	0.10 (100%)[b)]	25.3 (100%)	16.8 (100%)
C_3H_7CHO	0.034	0.01 (12%)	0.23 (4%)	0.57 (47%)
HCHO	0.10	<0.001 (0%)	<0.001 (0%)	0.04 (12%)

[a)] pH 10.5([KCN]=0.05 M, $[H_3BO_3]$=0.005 M), [CTAB]=1.0 x 10^{-2} M. The value in parenthesis indicates the percentage of reduced isoalloxazine.
[b)] 10 vol% acetonitrile.

for benzaldehyde). The fact that the reaction rate is zeroth-order in I in the initial stage is consistent with the rate-limiting deprotonation of $RCH(CN)O^-$(k_2) followed by rapid oxidation of $R\bar{C}(OH)(CN)$ by I(k_3).[10)] On the other hand, the first-order kinetics indicate that oxidation process(k_3) is involved in the rate-limiting step. These kinetic results imply that the CTAB micelle accelerates the oxidation step more efficiently than the deprotonation step.

The micellar effect was evaluated by analyzing the zeroth-order, initial stage of the reaction. The reaction rate(v_{obsd}) for the zeroth-order disappearance of I can be expressed by Eq. 1,[10)]

$$v_{obsd} = k_2K[CN^-][RCHO]/(1 + K[CN^-]) \quad (1)$$

where $K=k_1/k_{-1}$. Since v_{obsd} was first-order in CN^- and RCHO, $1 \gg K[CN^-]$ is assumed under the experimental conditions. The reaction rates are thus considered in term of k_2K.

The reaction rate is plotted against the concentration of CTAB in Fig. 2. The reaction was very slow in the nonmicellar system(k_2K=4.9 x 10^{-7} $M^{-1}s^{-1}$ for p-chlorobenzaldehyde). The reaction rate rised rapidly with increasing CTAB concentration, and the rate augmentation of about 300-fold was observed at the optimal CTAB concentration(5 x 10^{-3} M). The micellar effect was essentially the same for the two isoalloxazines. The result is contrasting to the oxidation of nitroethane carbanion in which the reaction did not proceed with I under comparable conditions.[4)] Probably, it is a prerequisite to the facile oxidation that either isoalloxazine or substrate is hydrophobic enough to be tightly associated with the CTAB micelle. Thus, $R\bar{C}(OH)(CN)$, more hydrophobic than nitroethane carbanion, is readily oxidized by I.

The oxidation of several aldehydes is summarized in Table 1. Benzaldehyde was converted to benzoinc acid quantitatively,[12)] but the rate was somewhat smaller than that of p-chlorobenzaldehyde. This is compatible with the claim that the rate-limiting step in the early stage of the reaction is deprotonation of $RCH(CN)O^-$.

Aliphatic aldehydes were hardly oxidized by I in the nonmicellar system. Instead, slow hydrolysis of isoalloxazine ring was observed. The oxidation became possible upon the addition of micellar CTAB, although reduction and hydrolysis of isoalloxazines occurred competitively.12) It was difficult to judge the reaction order due to the competing hydrolysis reaction. The reaction rates were tentatively estimated by multiplying the total disappearance rate of isoalloxazine by the factor of reduced isoalloxazine which could be determined by oxygen reoxidation of reduced isoalloxazines(indicated in the parenthesis in Table 1). Table 1 indicates that isoalloxazine II is very effective in the oxidation of aliphatic aldehydes. Since II is quite insoluble by itself in aqueous solutions,13) the oxidation must occur mainly in the micellar phase.

In conclusion, the present study demonstrated that the combination of CN^- with a cationic micelle facilitates the flavin oxidation of aldehydes efficiently. The rate acceleration is attributable to (1) the enhanced local concentration of CN^- onto the micellar phase, (2) the micellar environment which facilitates the deprotonation,14,15) and (3) the enhanced reactivity of carbanions in the micellar phase.

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