Tetrahedron Letters Vol. 21, pp 2543 - 2546
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0040-4039/80/0622-2543$02.00/0

FACILE OXIDATION OF ALDEHYDES AND α-KETO ACIDS AS CATALYZED BY FLAVIN AND THIAZOLIUM ION

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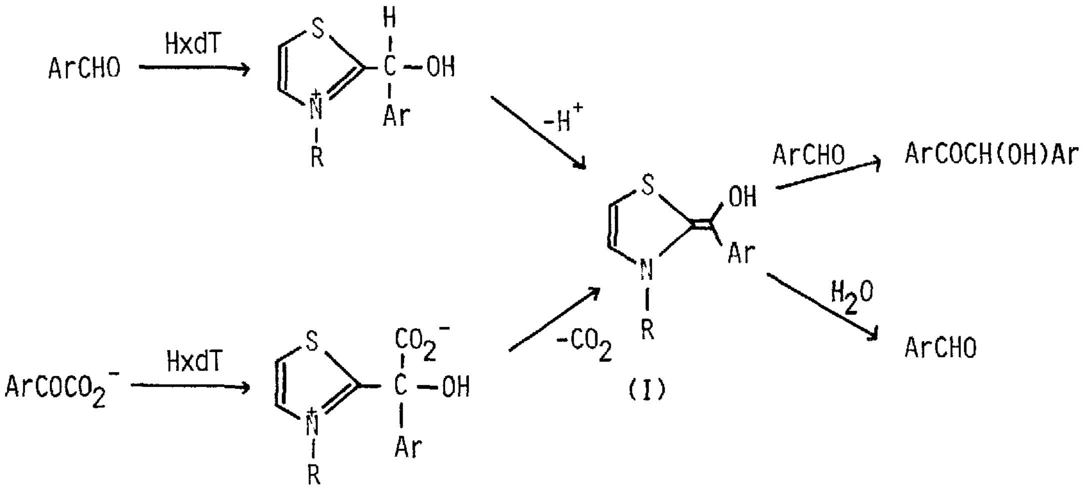
Oxidation of aldehydes and α-keto acids to carboxylic acids ocurrs readily in the presence of a flavin, thiazolium ion, and cationic micelles, the reaction involving trapping by the flavin of the intermediate formed from the substrate-thiazolium adducts through deprotonation or decarboxylation.

Some flavin-dependent enzymes employ a carbanion intermediate during the oxidation by flavin of bound substrates.[1,2) The concept can be applied readily to organic chemistry as "flavin-trapping" of a transient carbanion intermediate.[3,4) By this method, we can divert a reaction sequence from, for example, condensation reaction to oxidation reaction. A successful example is seen in the benzoin condensation, the intermediary carbanion of which can be trapped oxidatively by flavin.[3)

Pyruvate dehydrogenase (E. coli) catalyzes the conversion of pyruvic acid to acetic acid and requires FAD and thiamine pyrophosphate (TPP) as cofactors.[5) It occurred to us that the decarboxylated intermediate from the adduct of TPP and pyruvic acid, which is equivalent to the deprotonated intermediate from the adduct of TPP and acetaldehyde, may be trapped oxidatively by flavin. In fact, the imtermediate produced by the enzyme can be oxidized by a strong electron-acceptor such as $K_3Fe(CN)_6$.[6) We wish to report herein that, in the non-enzymatic system, flavin readily oxidizes the intermediates with the aid of a cationic micelle. This is the first nonenzymatic example for the synergistic catalysis of flavin coenzyme and TPP coenzyme.

We have used 3-methyltetra-O-acetylriboflavin (MeFl) and N-hexadecylthiazolium bromide (HxdT). As has been reported by Tagaki et al.,[7) the cationic micelle of thiazolium salts catalyzes the acyloin condensation of aldehydes. We also confirmed that, in the absence of MeFl, HxdT mixed with a cationic micelle (CTAB, 10 mM) catalyzes the conversion of 4-chlorobenzaldehyde to 4,4'-dichlorobenzoin and 4,4'-dichlorobenzil (Table 1). Similarly, 4-chlorobenzoylformic acid was converted to 4-chlorobenzaldehyde, although the reaction was much slower than the condensation of the aldehyde. These results are rationalized by a reaction sequence in Scheme 1 (Ar = 4-Cl-C_6H_4 and R = $C_{16}H_{33}$).



Scheme 1

4,4'-Dichlorobenzil and a trace of 4-chlorobenzoic acid were attributed to air oxidation of 4,4'-dichlorobenzoin and 4-chlorobenzaldehyde (or (I)), respectively. Based on the previous informations on the TPP catalysis,[8)] we can assign (I) to the key intermediate. On the other hand, the formation of 4,4'-dichlorobenzoin and 4-chlorobenzaldehyde was markedly inhibited on the addition of MeFl, and 4-chlorobenzoic acid became the main product (Table 1). The result clearly indicates that the intermediate (I) is trapped oxidatively by MeFl.

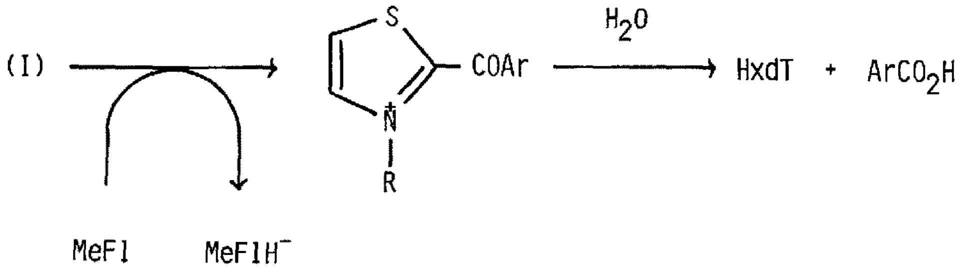
Kinetic measurements were carried out at 30°C under anaerobic conditions by following the decrease in the absorption band of MeFl at 448 nm. A typical reaction condition is: $[\mathrm{MeFl}] = 5.00 \times 10^{-5}$ M, $[\mathrm{HxdT}] = 5.00 \times 10^{-4}$ M, $[\mathrm{CTAB}] = 1.00 \times 10^{-2}$ M, [substrate] = 0.01 M, and pH 7.5 with 0.02 M phosphate. The results are summarized as follows: (i) the oxidation of aldehydes and α-keto acids is zero-order with respect to MeFl and first-order with respect to substrates and HxdT, and the apparent second-order rate constants ($k_{2,\mathrm{app}} = v_{\mathrm{obs}} / [\mathrm{substrate}][\mathrm{HxdT}]$) are, for example, $1.74 \times 10^{-2}\ \mathrm{M}^{-1}\ \mathrm{sec}^{-1}$ for 4-chlorobenzaldehyde and $1 \times 10^{-5}\ \mathrm{M}^{-1}\ \mathrm{sec}^{-1}$ for 4-chlorobenzoylformic acid, (ii) the substrate with electron-withdrawing substituent(s) is oxidized more easily: for example, the order of the reactivity for a series of aldehyde substrates is 2,4-dichlorobenzaldehyde > 4-chlorobenzaldehyde > benzaldehyde > 1-octylaldehyde > 1-butyraldehyde > formaldehyde, (iii) HxdT can be replaced by polyanionic TPP, but the reaction hardly proceeds when HxdT is replaced by more hydrophilic N-benzylthiazolium bromide, and (iv) the cationic micellar environment is indispensable to the reaction.

Table 1. Product Analysis for the Flavin Oxidation of 4-Chlorobenzaldehyde and 4-Chlorobenzoylformic Acid[a)]

Condition(mM)			Product(%)			
Substrate	HxdT	MeFl	$ArCO_2H$	ArCOCH(OH)Ar	ArCOCOAr	S[b)]
ArCHO						
50	1	0	< 0.4	37	47	5
5	1	5	63	0	0	0
ArCOCHO						
5	1	0	0	3	0	71
5	1	1	8	< 1	0	63

a) 30°C, 1 day, pH 8.0 with 0.05 M phosphate, [CTAB] = 10 mM. The product was analyzed by high-pressure liquid chromatography. Ar = $4\text{-}ClC_6H_4\text{-}$.

b) Recovered substrate.



Scheme 2

There are several precedents for the zero-order behavior in flavin-mediated reactions, the proposed mechanisms for which commonly involve the rate-limiting formation of reactive species followed by the immediate oxidatic by flavin.[1)] Therefore, the deprotonation and the decarboxylation to afford (I) are assigned to the rate-limiting step, and the oxidation of (I) in Scheme 2 occurs as a fast trapping step. The substituent effect is not incompatible with this conclusion. The rates were accelerated when the reaction system involves the micelle-bound thiazolium ion and/or the hydrophobic substrate(see the reactivity order for aliphatic aldehydes). This suggests, together with the above conclusion, that the CTAB micelle as catalyst plays two different roles: (i) enhancement of the adduct concentration and (ii) the facilitation of the rate-limiting steps. 2-Acylthiazolium ions thus produced are readily hydrolyzed to corresponding carboxylic acids in aqueous solution.[9)]

A similar oxidation has been found for the FAD plus TPP system in the presence of the CTAB micelle. This implicates that the cationic micelle well provides the apoenzyme-like reaction field. The detailed kinetic results will be published as a full manuscript.[10)]

In conclusion, the present study demonstrated that micelle-bound thiazolium ion facilitates the flavin oxidation of aldehydes and α-keto acids. The finding is important not only from a biochemical viewpoint but also as a new synthetic procedure.

The authors thank Professor M. Koike(Nagasaki University School of Medicine) for helpful discussions.

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(Received in Japan 1 April 1980)