Flavin-mediated Oxidative Decarboxylation of *p*-Chlorobenzoylformic Acid Assisted by Cyanide Ion and Cationic Micelles

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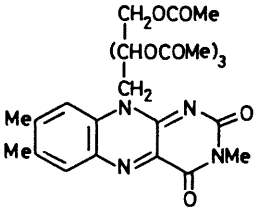
Summary Oxidative decarboxylation of *p*-chlorobenzoylformic acid to *p*-chlorobenzoic acid occurs readily in the presence of a flavin, cyanide ion, and cationic micelles, the reaction involving trapping by the flavin of the carbanion intermediate formed from the cyanide-adduct.

IT has been proposed that some flavin-dependent enzymes such as amino-acid oxidase and lactate oxidase employ a carbanion intermediate during the oxidation by flavin of bound substrates.[1,2] This proposition is also supported by model studies in non-enzymatic systems.[3] Application of this concept to organic chemistry should be interesting, since carbanion intermediates are proposed for a number of organic reactions.[4] We here demonstrate the trapping by the flavin of the transient carbanion intermediate formed by the cyanide ion-assisted decarboxylation of an α-keto acid.



(1)

We have used 3-methyltetra-*O*-acetylriboflavin (**1**),[5] and the oxidation of *p*-chlorobenzoylformic acid was carried out aerobically in an aqueous medium at 50 °C for 2 days in the dark in the presence or absence of (**1**), KCN, or CTAB. Neutralisation with aqueous HCl precipitated *p*-chlorobenzoic acid which was filtered off. The filtrate was extracted with chloroform and analysed by high-speed liquid chromatography. The yields in the Table are the sum of the precipitated and extracted material.

TABLE. Product analysis for the oxidative decarboxylation of *p*-chlorobenzoylformic acid[a]

[(**1**)]/ mM	[KCN]/ mM	[CTAB]/ mM	% Yields[b] $ArCO_2H$	ArCH(OH)-C(:O)Ar	ArC(:O)-C(:O)Ar
0·179	0	0	0	0	0
0·179	0	2·0	0	0	0
0	7·5	0	3·0	16·0	0
0·179	7·5	0	29·6	2·3	0·1
0	7·5	2·0	47·0	0·2	0·1
0·179	7·5	2·0	57·0	0·1	0·1

[a] $[p\text{-}ClC_6H_4COCO_2H] = 2{\cdot}5 \times 10^{-3}$ M. [b] Ar = p-ClC_6H_4.

The Table shows: (i) the presence of the cyanide ion is a primary prerequisite for the oxidation to occur, (ii) as noticed by Franzen and Fikentscher,[6] the main product in the absence of (**1**) and CTAB (hexadecyltrimethylammonium bromide) is *pp'*-dichlorobenzoin, whereas the formation of the benzoin condensation products is markedly inhibited on the addition of (**1**) or CTAB and *p*-chlorobenzoic acid becomes the main product, (iii) molecular oxygen acts as an efficient oxidising agent only in the presence of CTAB, and (iv) the highest yield of *p*-chlorobenzoic acid is obtained in the presence of both (**1**) and CTAB. The reaction was unaffected by the addition of anionic (sodium dodecyl sulphate) and non-ionic (Brij-35) surfactants above their critical micelle concentrations.

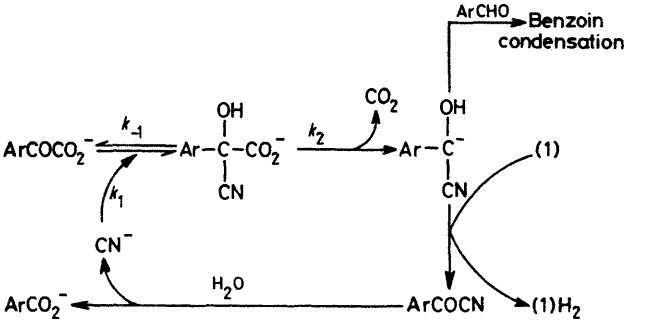
Kinetic measurements at 50 °C under anaerobic conditions established that (i) the oxidation of *p*-chlorobenzoylformic acid [monitored by the disappearance of (**1**)] in the presence of CTAB micelles is zero-order in (**1**) for up to 95% reaction and first-order in cyanide ion and *p*-chlorobenzoylformic acid, (ii) plots of the apparent second-order rate constant ($k_2' = v_{obs}/[CN^-][p\text{-}ClC_6H_4COCO_2H]$) *vs.* concentration of CTAB show typical sigmoid curves, and (iii) the maximum rate constant ($2{\cdot}75 \times 10^{-4}$ l mol^{-1} s^{-1}) observed at [CTAB] = $9{\cdot}75 \times 10^{-3}$ M is greater by more than three orders of magnitude than that in the non-micellar system ($k_2' = 10^{-7}$ l mol^{-1} s^{-1}).

These observations can be explained by the reactions in the Scheme (Ar = *p*-ClC_6H_4). The zero-order disappearance of (**1**) is rationalised in terms of rate-limiting decarboxylation (k_2) of the cyanide ion-adduct followed by rapid oxidation of the transient carbanion by (**1**). The rate equation for the Scheme is given by equation (1), where

$$v_{obs} = k_2K[CN^-][ArCOCO_2^-]/(1 + K[CN^-]) \quad (1)$$

$K = k_1/k_{-1}$. Since v_{obs} was first-order in CN^- and $ArCOCO_2^-$, $K[CN^-] << 1$ is assumed under these conditions (*i.e.*, $k_2' = k_2K$).

The Scheme indicates that the cyanide ion acts as a catalyst to facilitate the decarboxylation which yields the carbanion intermediate. The marked rate acceleration is attributed to (i) enhanced local concentration of cyanide ion on the cationic micellar surface, (ii) easy decarboxylation in the cationic micellar environment as seen in the decarboxylation of the 6-nitrobenzisoxazole-3-carboxylate ion catalysed by cationic micelles and related aggregates,[7,8] and (iii) activation of the carbanion by micellar hydrophobic environments.[9]



SCHEME

A similar oxidative decarboxylation has been found for benzoylformic acid and pyruvic acid. To the best of our knowledge, this is the first example of a non-enzymatic oxidative decarboxylation mediated by a flavin coenzyme.

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