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MICELLE ENHANCED OXIDATION OF AMINES BY COENZYME PQQ

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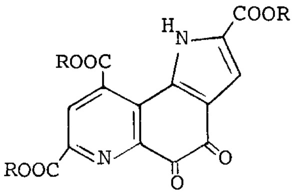
Summary: Nonenzymatic oxidation of amines with the coenzyme PQQ is enhanced by a cationic surfactant to give the corresponding carbonyl compounds, suggesting that the micelle presents a good environment for oxidation with PQQ. The similar reaction is applicable to alcohols though an efficiency is not so high.

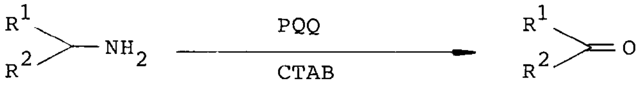
Several types of an alcohol dehydrogenase which is neither NAD nor flavin dependent have been found to contain a unique low molecular weight prosthetic group.[1] This coenzyme (PQQ or methoxatin) was assigned the pyrroloquinoline quinone structure 1 on the basis of an X-ray crystallographic analysis.[2] The properties of PQQ are being disclosed[3] and few enzymological studies have been reported.[4a,b,c] The mechanistic role of the coenzyme PQQ in oxidation process, however, remains obscure.[4] In this paper we wish to demonstrate that oxidation of amines with PQQ is facilitated by micelle.



1: PQQ, R=H

2: PQQTME, R=Me

Treatment of cyclohexylamine with PQQ in an aqueous solution (pH 10.7) at room temperature under air gave cyclohexanone (22% yield based on 1) as a sole isolable product. The presence of hexadecyltrimethylammonium bromide (CTAB, 2x10^{-2} M) in the system drastically enhanced the oxidation reaction, and the yield increased to 386%. This enhancement is assumed to be attributed to micelle formation[5] because an effective oxidation occurred above its cmc.



The hydrolysis of the trimethyl ester of PQQ (2, PQQTME), a key intermediate in a total synthesis, requires tedious experiments.[6] It was found to be easily realized on treatment of PQQTME with 0.05 M Na_2CO_3 or NaOH at room temperature for 12 h, which was ascertained by the UV spectra.[7] In addition, use of thus obtained PQQ in the presence of CTAB (pH 9.0) led to the formation of cyclohexanone in 406% yield. These findings make it possible to generate PQQ in situ from 2 under mild conditions. The generated PQQ was used in the following experiments.

It should be noted that the present oxidation reaction was strongly influenced by pH of a starting aqueous solution (adjusted by adding 0.5 N HCl). Oxidation was most accelerated (778%) when pH was around 7-8. Cyclohexanone was produced in only 152% yield at the higher pH 12. In the case of lowering pH to 1.6, the oxidation reaction was depressed completely.

Hexadecylpyridinium bromide (CPyB) which is expected to form a cationic micelle also promoted the oxidation reaction efficiently, as shown in Table 1. On the other hand, sodium dodecyl sulfate (SDS) and polyoxyethylene dodecanol ether (Brij-35) did not serve well as micellar catalysts, resulting in that the anionic and nonionic micelles did not provide a good environment for the oxidation of cyclohexylamine with PQQ at the present reaction conditions.

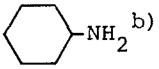
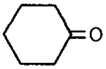
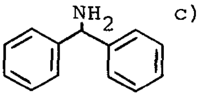
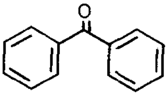
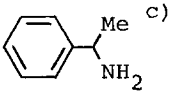
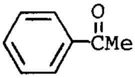
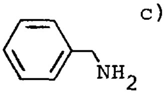
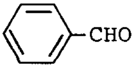
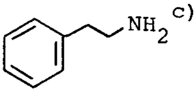
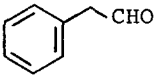
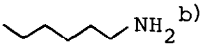
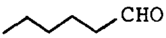
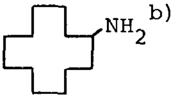
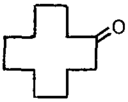
The present methodology was applied to oxidation of various amines. The results are summarized in Table 1. An efficient catalytic process was formed in the reaction of benzylamine derivatives such as benzhydrylamine, α-phenethylamine, and benzylamine. The further oxidized product, benzoic acid, was not detected in the last case. Compared with these amines, oxidations of β-phenethylamine and hexylamine were found to be difficult, but aliphatic amines having a long alkyl chain (cyclododecylamine and dodecylamine) were subjected to facile oxidation to give the corresponding carbonyl compounds in good yields, respectively. This acceleration might be explained by the formation of a mixed micelle.

The mechanism of regeneration of an active species is uncertain though semiquinone is suggested to participate in the oxidation reaction.[4a,b,c] Oxygen is considered to play an important role because the reaction under nitrogen atmosphere converted benzylamine to benzaldehyde in a poor yield.

Oxidation of alcohols to carbonyl compounds was carried out by treatment with the generated PQQ and CTAB in an aqueous solution (pH 7.3) under air. The conversion, however, was not so high as exemplified in oxidation of benzyl alcohol into benzaldehyde (62% yield).

Enhancement of oxidation reactions with PQQ in the micellar environment is assumed to be correlated with enzymatic reactions. Further investigation including clarification of the cationic micellar effect on the present oxidation is being in progress now.

Table 1. Oxidation of Amines with the Generated PQQ in the Presence of CTAB[a]

Amine	Initial pH	Final pH	Product	Yield (%)[g]
 [b]	6.6	9.1		778
	6.6[d]	8.8		466
	7.0[e]	8.8		trace
	6.7[f]	9.0		trace
 [c]	7.0	8.4		4176
 [c]	6.7	8.5		852
 [c]	7.2	7.0		1852
 [c]	7.3	8.9		18
 [b]	6.8	8.2		47
 [b]	6.7	7.4		359
 [b]	7.3	8.0		1568

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a) After quantitative hydrolysis of PQQTME (0.025 mmol) to PQQ in an aqueous alkaline solution (12.5 ml), an amine (2.5 mmol) and CTAB (0.25 mmol) were added unless otherwise stated. The initial pH was adjusted with 0.5 N HCl, and the reaction was carried out at room temperature under air for 24h.

b) PQQTME was hydrolyzed with 0.05 M Na_2CO_3.

c) PQQTME was hydrolyzed with 0.05 M NaOH.

d) CPyB (0.25 mmol) was used instead of CTAB.

e) SDS (0.25 mmol) was used instead of CTAB.

f) Brij-35 (0.25 mmol) was used instead of CTAB.

g) Yields were determined by glc based on PQQTME.

Acknowledgement

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5 The cmc value ($1.0\text{-}1.3\times10^{-4}$ M) of CTAB under the conditions employed was determined from its surfacetension-concentration curve.

6 PQQ (1) and PQQTME (2) were prepared according to the reported method: E. J. Corey and A. Tramontano, J. Am. Chem. Soc., 103, 5599 (1981). The other routes for their syntheses have been reported independently: J. A. Gainor and S. M. Weinreb, J. Org. Chem., 47, 2833 (1982); J. B. Hendrickson and J. G. deVries, ibid., 47, 1148 (1982).

7 The generated PQQ showed the absorption maximum at 248 nm.[3]

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