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# OXIDATIVE DECARBOXYLATION OF α-AMINO ACIDS WITH COENZYME PQQ

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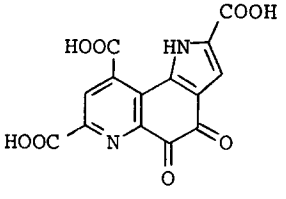
Summary: Oxidative decarboxylation of α-phenylglycine with coenzyme PQQ was performed catalytically in the presence of CTAB under mild conditions to give benzaldehyde and benzoic acid.

PQQ (Methoxatin) has been noted as a novel coenzyme of several types of alcohol and amine dehydrogenases, and a few enzymological studies have been reported.[1] In particular, the role of coenzyme PQQ of methylamine dehydrogenase is of great interest since a copper containing amine oxidase has been considered as a PQQ-containing enzyme, quinoprotein.[2] The mechanistic role of PQQ in the dehydrogenation process, however, has not been defined. In the preliminary paper, we demonstrated the catalytic oxidation of amines with coenzyme PQQ in the presence of cationic micelle.[3] This oxidation reaction was the first example of the nonenzymatic oxidation of amines to carbonyl compounds by PQQ.

On the other hand, oxidation of amino acids is very important process in cellular metabolism, and flavin and pyridoxal coenzymes play important roles in such reactions. Therefore, the reaction of amino acids with PQQ is very interesting from the viewpoint of biomimetic reaction. In this paper, we wish to report the catalytic oxidative decarboxylation reaction of amino acids with coenzyme PQQ.

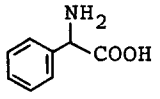
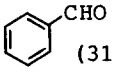
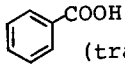
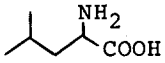
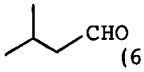
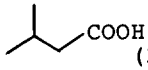
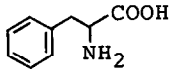
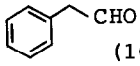
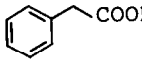
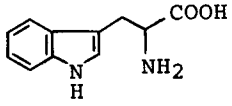



PQQ : 4,5-dihydro-4,5-dioxo-1H-pyrrolo [2,3-f]quinoline-2,7,9-tricarboxylic acid

Treatment of α-phenylglycine with a catalytic amount of PQQ[4] in aqueous solution (pH 7.13) in the presence of CTAB (cetyltrimethylammonium bromide) gave benzaldehyde (3265%) and benzoic acid (171%) without formation of α-keto acid, benzoylformic acid. Benzoic acid must have been formed by autoxidation of benzaldehyde. The reaction was carried out at 30°C under aerobic condition, and the yields were determined by GLC based on PQQ. The reaction was infulenced

by the pH of the starting aqueous solution, and was accelerated remarkably at around pH 7. Leucine, phenylalanine, and tryptophan were also converted into the corresponding aldehydes and carboxylic acids, though the conversions were not so high as compared with the case of α-phenylglycine. The results are summarized in Table 1.

Table 1. Oxidative Decarboxylation of α-Amino Acids with coenzyme PQQ in the presence of CTAB.[a)]

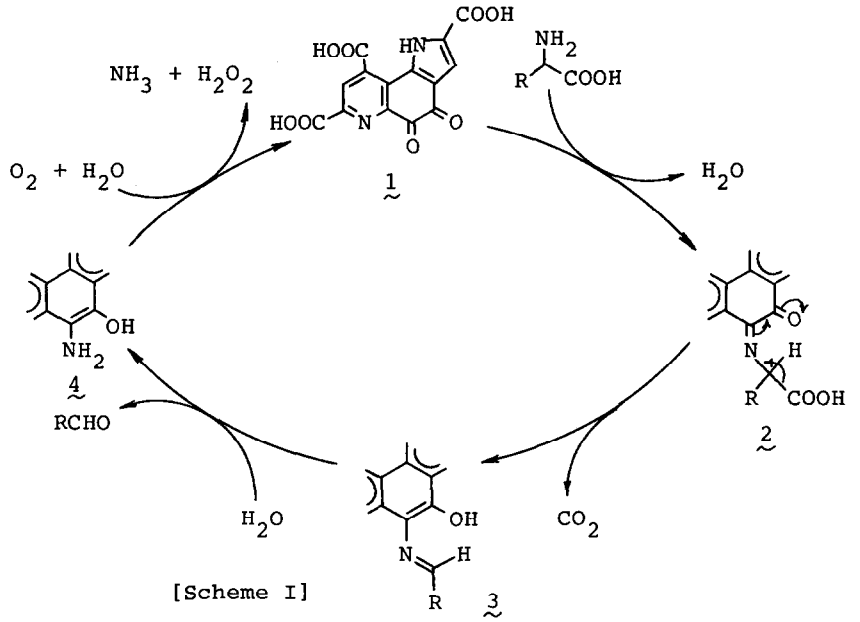
| Amino Acid | Initial pH | Final pH | Product (Yield, %)[c)] | |
|---|---|---|---|---|
|  | 2.10 | 2.41 |  (313) |  (trace) |
| | 7.13 | 8.82 | (3265) | (171) |
| | 9.86 | 9.14 | (2699) | (100) |
| | 13.40[b)] | 12.99 | (182) | (62) |
|  | 7.22 | 6.07 |  (62)[d)] |  (333)[d)] |
|  | 7.21 | 8.28 |  (16) |  (20) |
|  | 7.20 | 8.58 |  (37)[d)] | |

a) After quantitative hydrolysis of PQQTME (PQQ-trimethyl ester, 0.025 mmol) to PQQ in 0.05M $Na_2CO_3$ aqueous solution (10 ml), an amino acid (2.5 mmol) and CTAB (0.25 mmol) were added. The initial pH was adjusted with 0.5N HCl, and the reaction was carried out at 30°C under aerobic condition for 24h.
b) The initial pH was adjusted with NaOH.
c) Yields were determined by GLC based on PQQ.
d) Yields were determined by $^1$H-NMR based on PQQ.

Under the same conditions, benzoylformic acid and N-methylphenylglycine were not converted to benzaldehyde. These results indicate that an α-keto acid was not produced in the course of the reaction, and the oxidizable amino group of amino acids should be unsubstituted one. This oxidative decarboxylation reaction seems to be similar to the Strecker degradation in which α-amino acids are converted into corresponding aldehydes by treating with a carbonyl compound.[5]

The reaction mechanism of the oxidative decarboxylation of α-amino acids

with PQQ is assumed as shown in Scheme I. In the first step, the ketimine 2 is formed between the amino group of the amino acid and one of the quinone carbonyl (C-5) of PQQ 1, and the ketimine 2 releases carbon dioxide to generate aldimine 3 accompanied by double bond migration. Successive hydrolysis gives the corresponding aldehyde and reduced type of PQQ, the o-hydroxyaniline derivative 4, which is considered to be oxidized easily by oxygen to reproduce PQQ 1.




[Scheme I]

It is well known that the quinone carbonyl group of PQQ is easily attacked by nucleophiles such as amines, alcohols and hydroxide ion to form a covalent adduct,[1c] and Grigg and Thianpatanagul clarified that the imine formed between an amino acid and a carbonyl compound undergoes decarboxylation via the zwitterionic intermediate.[6] Eckert and Bruice also reported that phenanthrolinequinones oxidize an amine via the adduct of the amine to the quinone followed by α-proton migration catalyzed by base.[7] From these points of view, the assumed mechanism seems to be reasonable. Generation of hydrogen peroxide in the course of the reaction was confirmed by the oxidative decarboxylation of benzoylformic acid which was added to the starting reaction mixture. It is known that α-keto acids are converted into corresponding carboxylic acids with hydrogen peroxide[8] but not with PQQ itself (vide ante).

As isatin and alloxan are known to decompose α-amino acids in an aqueous solution at relatively high temperature,[5] we examined the catalytic activities of isatin and alloxan in the neutral aqueous solution at 30°C in the presence of CTAB to compare with that of PQQ, but their catalytic activities were extremely low. The catalytic activitiy of 1,7-phenanthrolinequinone as a PQQ analog was also examined under the same conditions, but its activity was not so high (Table 2). So special enphasis is to be laid on the fact that PQQ would be an excellent autorecycling catalysis for the Strecker degradation. Further study is in progress now.

Table 2. Oxidative Decarboxylation of α-Phenylglycine with Isatin, Alloxan, and 1,7-Phenanthrolinequinone[a)]

| Carbonyl Compound | Initial pH | Final pH | Yield (%)[b)] | |
|---|---|---|---|---|
| | | | PhCHO | PhCOOH |
| Isatin | 7.49 | 7.30 | 97 | 11 |
| Alloxan | 7.05 | 8.50 | trace | 0 |
| 1,7-Phenanthrolinequinone | 7.90 | 8.90 | 163 | 65 |

a) The reaction was carried out at 30°C under aerobic condition for 24h by using a carbonyl compound (0.025 mmol), α-phenylglycine (2.5 mmol), and CTAB (0.25 mmol) in aqueous solution (11 ml). The initial pH was adjusted with 0.05M $Na_2CO_3$ and 0.5N HCl.
b) Yields were determined by GLC based on carbonyl compounds.

Acknowledgement

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