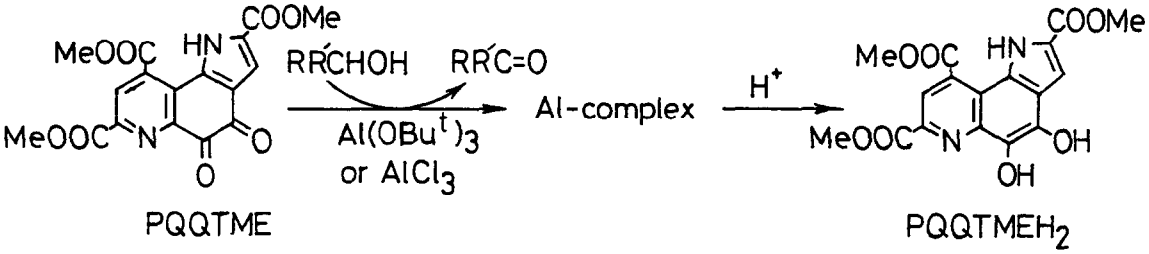
Tetrahedron Letters,Vol.26,No.35,pp 4225-4228,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

# BIOMIMETIC OXIDATION OF ALCOHOLS BY COENZYME PQQ-TRIMETHYL ESTER

Shinobu ITOH, Minae MURE, Yoshiki OHSHIRO,* and Toshio AGAWA
Department of Applied Chemistry, Faculty of Engineering, Osaka University,
Yamada-oka 2-1, Suita, Osaka 565, Japan

Oxidation of alcohols to corresponding carbonyl compounds by coenzyme PQQ-trimethyl ester was performed in the presence of aluminum t-butoxide or aluminum chloride under anaerobic conditions. Reduced PQQTME ($PQQTMEH_2$) was obtained by acidification of an aluminum complex of reduced PQQTME which was isolated in the reaction.

Biomimetic oxidation reaction of alcohols is of current and potent interest and several types of coenzyme models (flavin or $NAD^+$ analogues) have been investigated for this purpose. In addition to the NAD(P)-dependent and flavoprotein dehydrogenases, it has become clear that there is another class, the so called quinoprotein, in which PQQ is involved as the coenzyme.[1] We have already demonstrated non-enzymatic oxidation reaction of amines, amino acids, and thiols by coenzyme PQQ.[2] However, PQQ alone was not efficient enough to oxidize alcohols because of its relatively low oxidation potential.[3] In this paper, we wish to demonstrate the oxidation of alcohols with PQQ-trimethyl ester mediated by aluminum t-butoxide or aluminum chloride.




In this study, we used PQQTME[4] as a model of coenzyme PQQ. The oxidation of benzyl alcohol (10-fold excess over PQQTME) with PQQTME was carried out in THF or acetonitrile under anaerobic conditions (in a Thunberg vessel), but the

reaction did not proceed within a week. The presence of aluminum t-butoxide (3 equivalents to PQQTME) in the system drastically enhanced the reactivity in oxidation, and benzaldehyde was obtained in 77 % yield based on PQQTME after 24 hours. Aluminum chloride was also effective for the reaction, where acetonitrile was favorable as a solvent. When the reaction was carried out at 52°C, the yield went up to 99 %. α-Phenethyl alcohol, 2-octanol, and cyclohexanol were also converted into corresponding carbonyl compounds under the same conditions, but benzhydrol was not so reactive because of its steric hindrance (Table).

Table. Oxidation of alcohols with PQQTME.[a)]

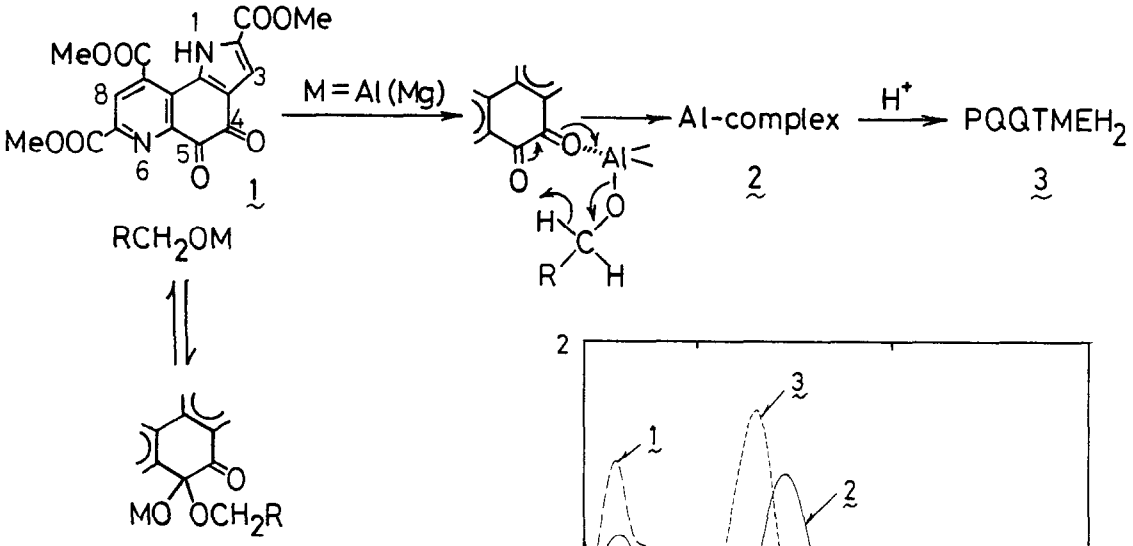
| Alcohol | Aluminum Salt | Solvent | Time (h) | Temp. | Yield (%)[b)] |
|---|---|---|---|---|---|
| $PhCH_2OH$ | $Al(OBu^t)_3$ | THF | 24 | rt | 77 |
| | $Al(OBu^t)_3$ | $CH_3CN$ | 24 | rt | 77 |
| | $AlCl_3$ | $CH_3CN$ | 24 | rt | 76 |
| | $AlCl_3$ | $CH_3CN$ | 9 | 52°C | 99 |
| | $AlCl_3$ | THF | 24 | rt | 11 |
| | $AlCl_3$ | $CH_2Cl_2$ | 24 | rt | trace |
| $PhCH(OH)CH_3$ | $AlCl_3$ | $CH_3CN$ | 9 | 52°C | 64 |
| $Ph_2CHOH$ | $AlCl_3$ | $CH_3CN$ | 9 | 52°C | 13 |
| 2-octanol | $AlCl_3$ | $CH_3CN$ | 9 | 52°C | 92 |
| cyclohexanol | $AlCl_3$ | $CH_3CN$ | 9 | 52°C | 44 |

a) PQQTME (0.025 mmol), Aluminum salt (0.083 mmol), Alcohol (0.25 mmol), Solvent (10 ml), under anaerobic conditions.
b) Yields were determined by GLC based on PQQTME.

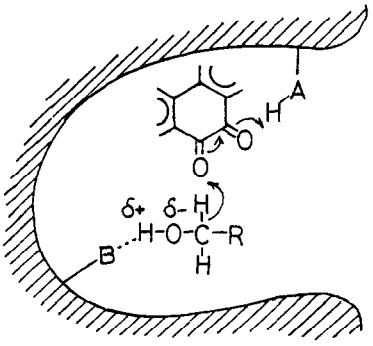
An aluminum complex of reduced PQQTME precipitated in the course of the reaction of benzyl alcohol with PQQTME in the presence of $AlCl_3$ in acetonitrile. The absorption spectrum of the complex (2 in Figure) resembled to that of $PQQTMEH^-$ and $^1H$-NMR in $CD_3CN$ showed the large upfield shifts of the signals of 3-H and 8-H (δ 6.56 and 8.30) compared to those of PQQTME (δ 7.50 and 8.92) or $PQQTMEH_2$ (δ 7.53 and 8.71).[5] Furthermore, the complex was converted to $PQQTMEH_2$ (3 in Figure) by acidification in an aqueous solution (1N HCl-acetonitrile-dimethyl sulfoxide; 5 : 4.5 : 0.5). From these results, it is assumed that aluminum coordinates mainly to the quinol group.

Benzyloxymagnesium bromide[6] was also oxidized with PQQTME in THF to give benzaldehyde in 51 % yield. Lithium or potassium benzyl oxide,[7] however, was

not oxidized by PQQTME under the same conditions. So we considered the reaction mechanism is an Oppenauer type one as follows.[8] An aluminum alkoxide formed from an alcohol and aluminum t-butoxide (or aluminum chloride) in situ interacts with more electron rich quinone carbonyl oxygen (C-4) of PQQTME and withdraws electrons as a Lewis acid to accelerate abstraction of net hydride from the benzyl position by the quinone (Scheme 1). A lithium or potassium alkoxide was considered to attack C-5 quinone carbonyl carbon of PQQTME, while Duine and his coworkers reported the C-5 adduct of methanol on PQQ.[9] Coordination of counter cation (Al or Mg) to the quinone carbonyl as a Lewis acid is




Scheme 1.




Scheme 2.

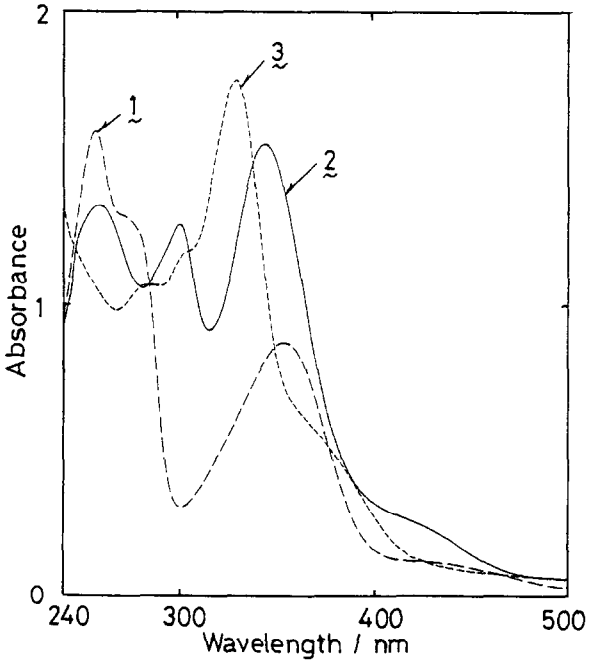



Figure. Absorption spectra of PQQTME (1) in MeCN, Al-complex of reduced PQQTME (2) in MeCN-DMSO (9:1), and $PQQTMEH_2$ (3) in 0.1 N HCl-MeCN-DMSO (5:4.5:0.5).

important to proceed the oxidation reaction.

The mechanism of the oxidation of alcohols by PQQ in enzymatic systems is not known, but this result suggests that enzymatic oxidation of alcohols by PQQ proceeds with the aid of concerted general acid-base catalysis in the active site as shown in Scheme 2. The present result is a first example of non-enzymatic oxidation of alcohols by a PQQ model.

References


1. S. A. Salisbury, H. S. Forrest, W. B. T. Cruse, and O. Kennard, Nature (London), 280, 843 (1979) ; J. A. Duine and J. Frank, Jzn., Trends Biochem. Sic., 6, 278 (1981).
2. Y. Ohshiro, S. Itoh, K. Kurokawa, J. Kato, T. Hirao, and T. Agawa, Tetrahedron Lett., 24, 3465 (1983) ; S. Itoh, N. Kato, Y. Ohshiro, and T. Agawa, ibid, 25, 4753 (1984) ; S. Itoh, N. Kato, Y. Ohshiro, and T. Agawa, Chem. Lett., 1985, 135.
3. J. A. Duine, J. Frank, Jzn., and P. E. J. Verwiel, Eur. J. Biochem., 118, 395 (1981).
4. E. J. Corey and A. Tramontano, J. Am. Chem. Soc., 103, 5599 (1981).
5. An authentic sample of $PQQTMEH_2$ was prepared by the reaction of PQQTME with several reductants such as thiophenol, phenylhydrazine, sodium borohydride, and 1-benzyl-1,4-dihydronicotinamide (BNAH), and was identified by spectral data. A dissociation of a proton from $PQQTMEH_2$ ($PQQTMEH_2 \rightleftharpoons PQQTMEH^- + H^+$) was observed spectrophotometrically in anaerobic aqueous solutions (pKa = 9.0).
6. Benzyloxymagnesium bromide was prepared from benzyl alcohol and phenylmagnesium bromide in THF under anaerobic conditions.
7. Lithium and potassium benzyl oxides were generated in situ by the reaction of benzyl alcohol with n-butyllithium and potassium t-butoxide, respectively.
8. It is well known that a quinone can be used as a hydrogen acceptor in the Oppenauer oxidation of alcohol. [C. Djerassi, in "Organic Reactions" Vol.6, Eds. R. Adams et al., Wiley, New York, 1951, p207]
9. R. H. Dekker, J. A. Duine, J. Frank, Jzn., P. E. J. Verwiel, and J. Westerling, Eur. J. Biochem., 125, 69 (1982).


(Received in Japan 18 May 1985)