Synthesis and Characterization of Dimethyl 9,10-Dihydro-9,10-dioxobenzo[*f*]quinoline-2,4-dicarboxylate. Effect of the Pyrrole Nucleus on the Reactivity of Coenzyme PQQ

Shinobu Itoh, Yoshifumi Fukui, Shigenobu Haranou, Masaki Ogino, Mitsuo Komatsu, and Yoshiki Ohshiro*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamada-oka 2-1, Suita, Osaka 565, Japan

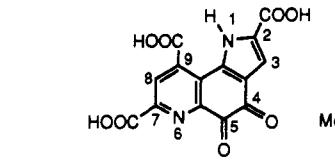
Received January 23, 1992

Dimethyl 9,10-dihydro-9,10-dioxobenzo[*f*]quinoline-2,4-dicarboxylate (4) was synthesized, and its physical and chemical properties were compared to those of the trimethyl ester of PQQ (PQQTME, 2) and the 1-methyl derivative (3). The synthesis of 4 was accomplished by a Doebner–von Miller-type annulation between 3-amino-2-naphthol and dimethyl 2-oxoglutaconate and a subsequent oxidation with Fremy's salt. The electronic effect of the pyrrole nucleus of coenzyme PQQ (1) was examined by comparing the reactivity of 4 to that of 2 and 3 in the acetone adduct formation reaction, the redox reaction with phenylhydrazine, and the aerobic autorecycling oxidation of benzylamine. The significant role of the pyrrole nucleus in conducting the intramolecular general base catalysis in the amine oxidation is discussed.

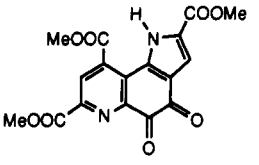
Introduction

Since PQQ (1) was first reported to be a prosthetic group of methanol dehydrogenase from methylotrophic bacteria,[1] several non-flavin- and non-nicrotinamide-dependent dehydrogenases have been reported to contain PQQ. These enzymes are known as quinoproteins.[2] PQQ has been also demonstrated to act as an efficient electron-transfer catalyst in the non-enzymatic oxidation of biologically important substances such as amines,[3] amino acids,[4] thiols,[5] glucose,[6] and NADH.[7] In addition to such chemical and enzymological interest, the pharmaceutical activities[8,9] and the nutritional importance[10] of PQQ itself have recently received much attention in various research fields.

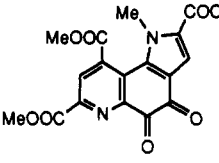
PQQ (1) has a unique heterocyclic *o*-quinone structure. The *o*-quinone ring, the active site, is condensed with an electron-withdrawing pyridine nucleus and also with an electron-donating pyrrole. Therefore, the electronic nature of the *o*-quinone moiety of PQQ is different from that of simple *o*-quinone compounds. Despite the fact that the effect of the substituents has been investigated by means of several PQQ derivatives,[11-13] little attention has been focused on the structural importance of the *pyrroloquinolinequinone* skeleton. In order to explore this issue, we synthesized and characterized the 6-deaza derivative of coenzyme PQQ, methyl 4,5-dihydro-4,5-dioxobenz[*g*]indole-2-carboxylate (5), and investigated the effect of the peri pyridine nitrogen on the physical and chemical properties.[14] Thus, in this study, *benzoquinolinequinone* derivative 4 was synthesized, and its physical and chemical properties were investigated in order to determine the effect of the pyrrole nucleus. The trimethyl ester of PQQ (2) and its 1-methyl derivative (3) were employed as reference compounds.



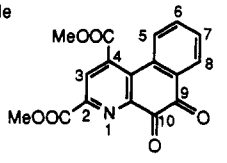
1 PQQ



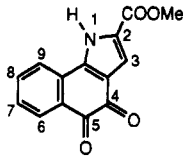
2



3



4



5

Results and Discussion

Synthesis of Benzoquinolinequinone 4. A Doebner–von Miller-type annulation was used to construct the benzo[*f*]quinoline skeleton having carbomethoxy groups at the 2- and 4-positions (Scheme I). This method was also used for the total synthesis of PQQ.[15] Treatment of 3-amino-2-naphthol with 1.5 equiv of dimethyl 2-oxoglutaconate and a catalytic amount of PTS in refluxing CH_2Cl_2 for 17 h gave benzoquinoline derivative 6 in 28% isolated yield. Oxidation of 6 with Fremy's salt produced

(1) Salisbury, S. A.; Forrest, H. S.; Cruse, W. B. T.; Kennard, O. *Nature (London)* **1979**, *280*, 843.
(2) *PQQ and Quinoproteins, Proceedings of the First International Symposium on PQQ and Quinoproteins*; Jongejan, J. A., Duine, J. A., Eds.; Kluwer Academic Publisher: Dordrecht, The Netherlands, 1989.
(3) (a) Ohshiro, Y.; Itoh, S.; Kurokawa, K.; Kato, J.; Hirao, T.; Agawa, T. *Tetrahedron Lett.* **1983**, *24*, 3465. (b) Itoh, S.; Kitamura, Y.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1907. (c) Mure, M.; Itoh, S.; Ohshiro, Y. *Chem. Lett.* **1989**, 1491. (d) Mure, M.; Itoh, S.; Ohshiro, Y. *Tetrahedron Lett.* **1989**, *30*, 6875.
(4) (a) Itoh, S.; Kato, N.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1984**, *25*, 4753. (b) Mure, M.; Suzuki, A.; Itoh, S.; Ohshiro, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 1608.
(5) (a) Itoh, S.; Kato, N.; Ohshiro, Y.; Agawa, T. *Chem. Lett.* **1985**, 135. (b) Itoh, S.; Kato, N.; Mure, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 420.
(6) Itoh, S.; Mure, M.; Ohshiro, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1580.
(7) (a) Itoh, S.; Kinugawa, M.; Mita, N.; Ohshiro, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 694. (b) Itoh, S.; Mita, N.; Ohshiro, Y. *Chem. Lett.* **1990**, 1949.
(8) Watanabe, A.; Hobara, N.; Tsuji, T. *Curr. Ther. Res.* **1988**, *44*, 896.
(9) Nishigori, H.; Yasunaga, M.; Mizumura, M.; Lee, J. W.; Iwatsuru, M. *Life Sci.* **1989**, *45*, 593.
(10) Killgore, J.; Smidt, C.; Duich, L.; Romero-Chapman, N.; Tinker, D.; Reiser, K.; Melko, M.; Hyde, D.; Rucker, R. B. *Science* **1989**, *245*, 850.
(11) (a) Sleath, P. R.; Noar, J. B.; Eberlein, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 3328. (b) Noar, J. B.; Rodriguez, E. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 7198. (c) Noar, J. B.; Bruice, T. C. *J. Org. Chem.* **1987**, *52*, 1942. (d) Rodriguez, E. J.; Bruice, T. C.; Edmondson, D. E. *J. Am. Chem. Soc.* **1987**, *109*, 532. (e) Rodriguez, E. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 7947.
(12) (a) Itoh, S.; Kato, J.; Inoue, T.; Kitamura, Y.; Komatsu, M.; Ohshiro, Y. *Synthesis* **1987**, 1067. (b) Itoh, S.; Inoue, T.; Fukui, Y.; Huang, X.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* **1990**, 1675.
(13) Shinagawa, E.; Matsushita, K.; Nonobe, M.; Adachi, O.; Ameyama, M.; Ohshiro, Y.; Itoh, S.; Kitamura, Y. *Biochem. Biophys. Res. Commun.* **1986**, *139*, 1279.
(14) Itoh, S.; Fukui, Y.; Ogino, M.; Haranou, S.; Komatsu, M.; Ohshiro, Y. *J. Org. Chem.* **1992**, *57*, 2788.
(15) Corey, E. J.; Tramontano, A. *J. Am. Chem. Soc.* **1981**, *103*, 5599.

0022-3263/92/1957-4452$03.00/0

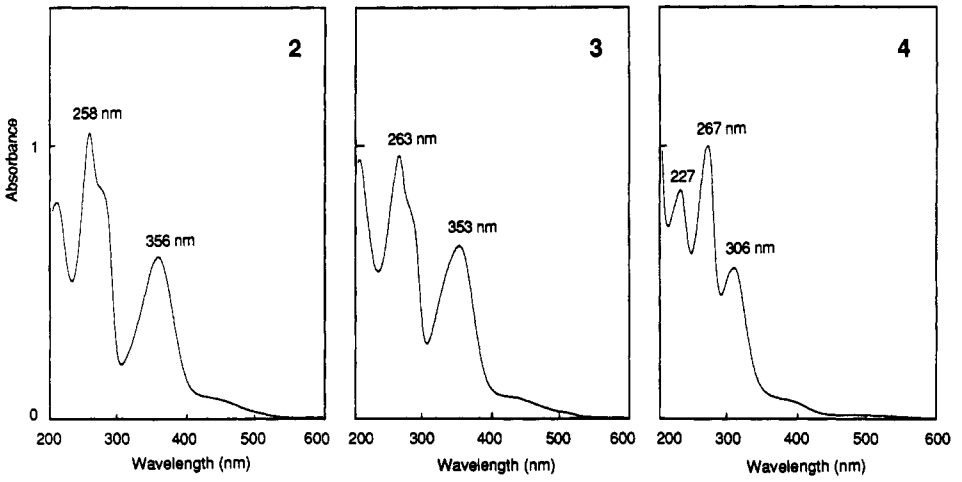


Figure 1. UV-visible spectra of 2, 3, and 4 in acetonitrile (4.0×10^{-5} M).

Scheme I

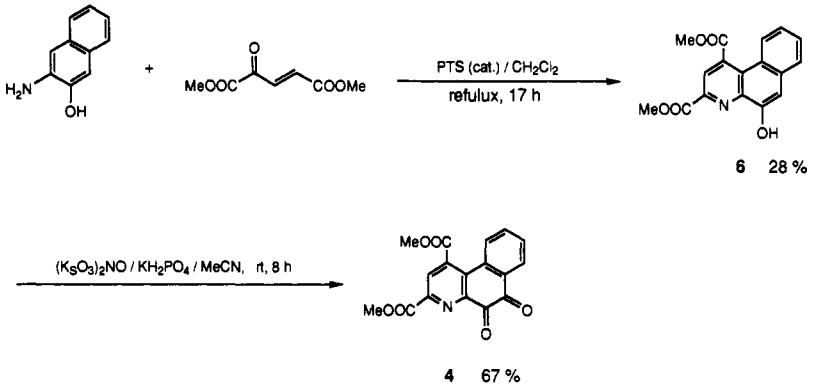


Table I. Comparison of Physical Properties of 2, 3, and 4

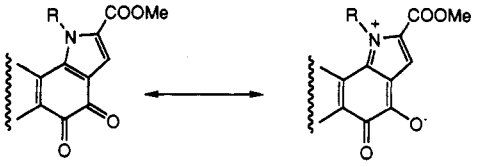
		2	3	4
^{13}C NMR	C-4 (C-9)	173.5[a]	173.7	177.9[c]
(ppm, DMSO-d_6)	C-5 (C-10)	177.2[b]	177.9	176.5[d]
IR, quinonoid $\nu_{C=O}$ (cm^{-1})		1686	1684	1692
E_m[e] Q_{ox}/Q_{sem} (E_{m1})		-[f]	-476	-423
Q_{sem}/Q_{red} (E_{m2})		-[f]	-785	-813

[a] Doublet, $^3J_{CH}$ = 1.4 Hz. [b] Singlet. [c] Doublet of doublets, $^3J_{CH}$ = 4.1 Hz, $^4J_{CH}$ = 1.5 Hz. [d] Singlet. [e] $E_m = {}^1/_2(E_{ap} + E_{cp})$ (midpoint potential), vs SCE in CH_3CN containing 0.1 M tetrabutylammonium perchlorate, scan rate = 10 mV/s. [f] A complicated voltammogram was obtained; cathodic peaks at -280, -735, -915, and -1465 mV vs SCE, anodic peaks at 70, -350, -660, and -1312 mV vs SCE.

the expected benzoquinolinequinone 4 in 67% yield. Acetone is usually used as a cosolvent in the Fremy's salt oxidation; however, in this case, acetonitrile is recommended as the cosolvent because 4 is easily converted into acetone adduct 9 when acetone is used (vide infra).

Physical Properties. Some of the physical properties of 2, 3, and 4 are summarized in Table I. ^{13}C-NMR signals for the quinonoid carbonyl carbons were assigned by means of the ^{1}H–^{13}C coupling patterns ($^3J_{CH}$ and $^4J_{CH}$ indicated in the footnote of Table I). It is interesting to note that the C-9 signal of 4 shifts about 4.5 ppm downfield compared to the C-4 carbonyl carbon signals of 2 and 3, but the chemical shifts of C-10 of 4 and C-5 of 2 and 3 are essentially the same. The IR absorption (1692 cm^{-1}) of the quinonoid carbonyl stretching of 4 is a little higher than that of 2 and 3 (1686 and 1684 cm^{-1}, respectively). These spectroscopic data suggest that in *pyrroloquinolinequinone* molecules such as 2 and 3, there is a relatively large resonance interaction between the pyrrole ring and the quinone function as illustrated in Scheme II. Figure 1 shows the UV-vis spectra of the quinones in acetonitrile. The quinonoid n-π^* transition of 2 and 3 appears at longer wavelength than that of 4 (2 and 3, 400–530 nm; 4, 350–420 nm). This absorption shift may also reflect the resonance effect of the pyrrole ring in 2 and 3. In other words, conjugation between the quinone function and the pyrrole ring in 2 and 3 is stronger than that between the quinone function and the benzene ring in 4.

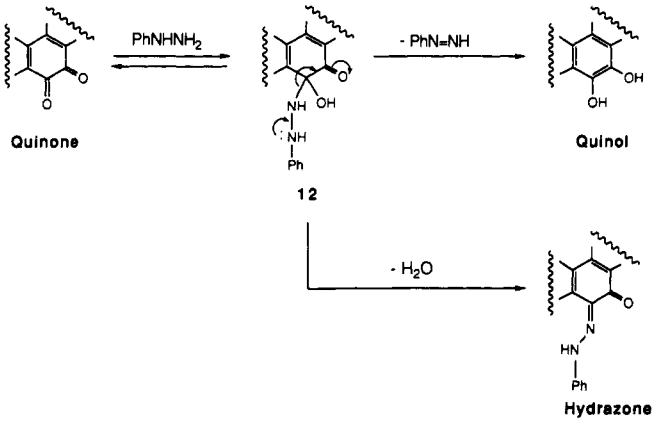
Scheme II



The one-electron redox potentials of the quinones were determined by cyclic voltammetry in an acetonitrile solution. In the case of 3 and 4, two reversible redox peaks for quinone/semiquinone and semiquinone/quinol couples (E_{m1} and E_{m2}) were observed at around -450 and -800 mV vs SCE, respectively. However, as has been already reported,[16] 2 gave a somewhat complicated voltammogram. The complexity has been attributed to the formation of several complexes of the semiquinone with the quinone and of the semiquinone with itself during the electrochemical processes.[16] But the present results suggest that the acid–base equilibrium of the pyrrole proton, which may take place during the electrochemical processes, is responsible for the complexity of the voltammogram.[17] In

(16) Eckert, T. S.; Bruice, T. C.; Gainor, J. A.; Weinreb, S. M. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 2533.

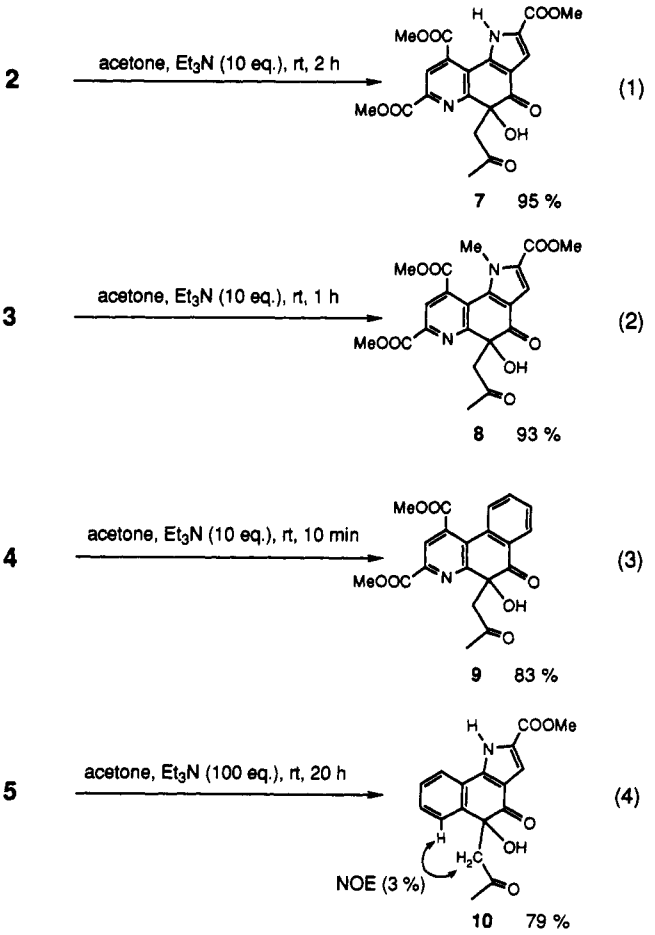
Scheme III



fact, model compounds such as **5**, which have a pyrrole proton, also gave a similar complex voltammogram. The semiquinone formation constant K, defined as K = [semiquinone]^2/[quinone][quinol], can be evaluated from the value of $\Delta E_m = E_{m1} - E_{m2}$ by the equation $K = \exp[(F/RT)(\Delta E_m)]$. The K values for **3** and **4** were calculated to be 1.67×10^5 and 3.91×10^6, respectively. These results indicate that the pyrrole nucleus decreases E_{m1} by about 50 mV and destabilizes the semiquinone to some extent. The electron-releasing nature of the pyrrole nucleus may be responsible for this electronic effect. In an aqueous solution, accurate redox potentials of **3** and **4** could not be determined because **3** and **4** are strongly adsorbed on the electrode surface.

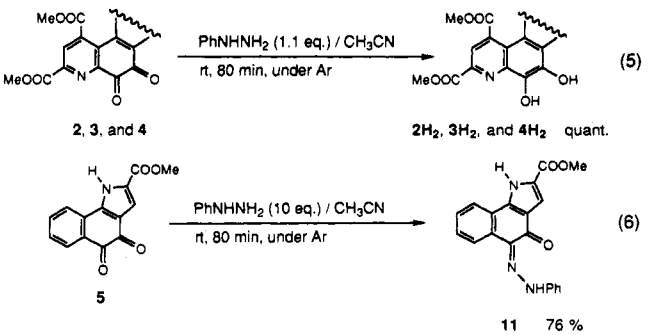
Acetone Adduct Formation. Nucleophilic addition to the quinonoid carbonyl carbon has been proposed as a key step in the oxidation reactions of amines, amino acids, hydrazines, and thiols by PQQ.[5,18,19] The reactivity of the quinones toward nucleophiles was evaluated in the reaction with acetone enolate. Compounds **2** and **5** have been already demonstrated to form stable aldol-type adducts **7** and **10**, respectively (eqs 1 and 4).[14] Compounds **3** and **4** also gave similar adducts **8** and **9** almost quantitatively (eqs 2 and 3). It has been demonstrated that the nucleophile adds to **3** and **4** at C-5 by measuring the NOE on the methylene protons of the acetonyl chain of each adduct. An NOE of about 3% was detected only between the methylene protons and the aromatic proton at the 6-position of **10**, but no such effect between the methylene protons and any aromatic protons was detected in **7**.[14] In a similar manner, acetone was determined to have added to **8** and **9** at C-5 and C-10, respectively. No NOE was detected between the methylene protons and either H-3 of **8** or H-8 of **9**. If the addition had occurred at C-4 in **8** and C-9 in **9**, an NOE should have been detected between the methylene protons and those aromatic protons. In the case of **8**, the addition position was further confirmed by comparing the chemical shifts of H-3 and H-8 to those of **3**. In the C-5 acetone adduct, H-8 shifts upfield more than H-3 does (**3**: H-3, δ = 7.59, H-8, 8.63; **8**: H-3, 7.48, H-8, 8.39 ppm in $CDCl_3$). A similar phenomenon has been reported for acetone adduct **7**.[14]

It is interesting to note that the reactivity of benzoquinolinequinone **4** is much higher than that of the others; the order of reactivity was **4** ≫ **3** > **2** ≫ **5**. Considering the electron-withdrawing nature of the pyridine nucleus



having two methyl ester groups and the electron-releasing nature of the pyrrole nucleus, the C-5 addition of acetone (C-10 in the case of **9**) and the above order of the reactivity are very reasonable. Differences between the reactivity of **2** and **3** suggest that dissociation of the pyrrole proton of **2** under the basic conditions decreases the reactivity of the quinone.

Reaction with Phenylhydrazine. Studies on the reactions between PQQ and hydrazines have provided important information not only for enzymological studies of quinoprotein inhibition but also for mechanistic investigation of amine oxidation by PQQ.[14,18] Therefore, the reaction of the model compounds with phenylhydrazine was also examined. As in the case of **2**,[14] quinones **3** and **4** were quantitatively reduced to the corresponding quinols, $\mathbf{3H_2}$ and $\mathbf{4H_2}$, respectively (eq 5).



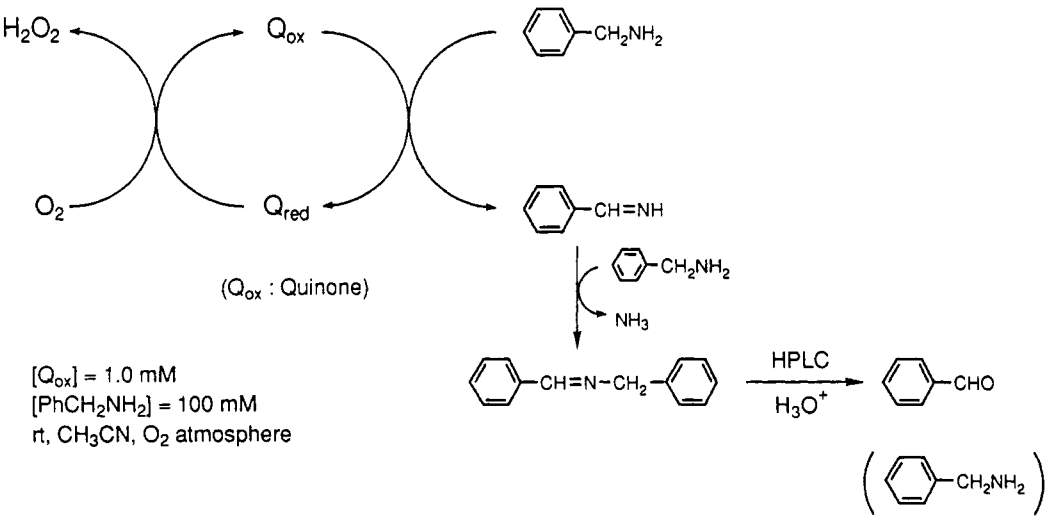
For the reaction of PQQ and hydrazines, we have already proposed an ionic mechanism that involves a carbinolamine-type intermediate **12** as illustrated in Scheme III.[18] The efficient quinol formation has been explained by the electron-withdrawing effect of the pyridine nucleus having two ester groups. The pyridine nucleus may facilitate the

(17) Details about the electrochemistry of **2** and its analogues in organic solvents will be reported elsewhere.

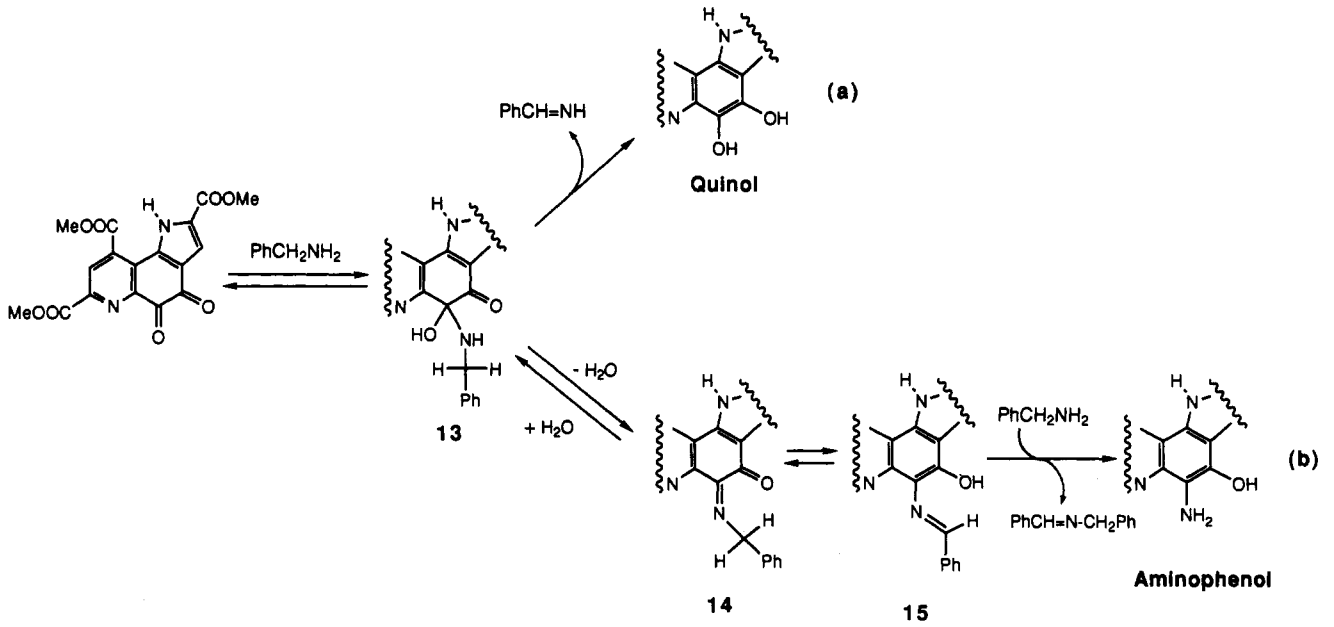
(18) Mure, M.; Nii, K.; Inoue, T.; Itoh, S.; Ohshiro, Y. *J. Chem. Soc., Perkin Trans 2* **1990**, 315.

(19) (a) Itoh, S.; Mure, M.; Ogino, M.; Ohshiro, Y. *J. Org. Chem.* **1991**, *56*, 6857. (b) Ohshiro, Y.; Itoh, S. *Bioorg. Chem.* **1991**, *19*, 169.

Scheme IV



Scheme V



nucleophilic addition of the hydrazine to the quinone and stabilize the carbinolamine-type intermediate thus formed through intramolecular hydrogen bonding between the peri pyridine nitrogen and the hydrazino NH group. The electron-withdrawing effect of the pyridine ring might also accelerate the electron migration from the hydrazino nitrogen to the quinone. Therefore the redox reaction is the predominant pathway in **2**, **3**, and **4**. The formation of the hydrazone **11** from **5** (eq 6) has been attributed to the lack of the electronic effects of the peri pyridine nitrogen.[14]

Aerobic Oxidation of Benzylamine. The pyrroloquinolinequinone derivatives have been demonstrated to act as very efficient turnover catalysts in the aerobic oxidation of amines (Scheme IV).[3,19] In the preceding study on compound **5**, we reported that such catalytic activity is completely lost when the peri pyridine nitrogen is removed from the pyrroloquinolinequinone molecule.[14] In this study, the effect of the pyrrole nucleus on the catalytic oxidation of benzylamine in acetonitrile was investigated. Figure 2 shows the time course of the aerobic oxidation of benzylamine, which was obtained by monitoring the formation of benzaldehyde by HPLC. Interestingly, even replacement of the pyrrole proton by a methyl group drastically depressed the catalytic activity, and in the case of **4**, no catalytic reaction proceeded within 100 min.

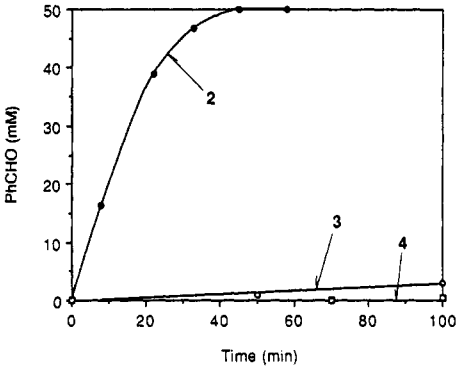
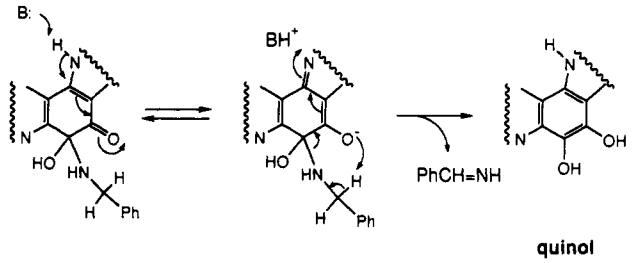


Figure 2. Time course of the oxidation of benzylamine (100 mM) in the presence of **2**, **3**, or **4** (1.0 mM) at room temperature in CH_3CN under O_2 atmosphere.

An ionic mechanism that involves carbinolamine intermediate **13** has been proposed for the oxidation of benzylamine by **2**; direct α-deprotonation of **13** (path a) and the transamination reaction (path b) occur competitively to give the quinol and the aminophenol, respectively (Scheme V).[19a] In the case of **2**, quinol **$2H_2$** was the major

Scheme VI



product.[19a] The efficiency of quinol formation has been attributed to the existence of *intramolecular general base catalysis* as depicted in Scheme VI. However, such an intramolecular general base catalysis could not be expected in the case of **3** and **4**. Therefore the transamination (path b) becomes the major pathway. In fact, **3** was converted mainly into the aminophenol product, and the reactivity of **3** was 2 orders of magnitude lower than that of **2**.[19a] The very low catalytic activity of **3** and **4** could be attributed to the deactivation of the quinones that may take place via imine intermediates such as **14** and **15** during the course of the reaction.

PQQ, or a closely related compound, used to be regarded as the second organic cofactor of mammalian copper-containing amine oxidases and bacterial methylamine dehydrogenase.[20] But, recently, it has been revealed that the newly discovered redox cofactors TOPA quinone[21] and tryptophan tryptophylquinone (TTQ)[22] are involved in bovine serum amine oxidase and methylamine dehydrogenase, respectively. However, our results clearly demonstrate that *the pyrroloquinolinequinone skeleton of coenzyme PQQ is essential for efficient amine oxidation in vitro*. Comparison of the chemical properties of these new cofactors with those of PQQ will undoubtedly provide another interesting avenue for research.

Experimental Section

The trimethyl ester of PQQ (**2**)[15] and its 1-methyl derivative (**3**)[12a] were prepared by the reported methods. When purification was necessary, the chemicals used in this study were purified by the standard methods.[23] Melting points are uncorrected. Redox potentials of the quinones were measured by cyclic voltammetry in anhydrous acetonitrile containing 0.1 M tetrabutylammonium perchlorate by means of a GC working electrode, a Pt auxiliary electrode, and an SCE as the reference.

Dimethyl 10-Hydroxybenzo[*f*]quinoline-2,4-dicarboxylate (6). A CH_2Cl_2 solution (160 mL) of 2-amino-3-naphthol (1.50 g, 9.43 mmol), dimethyl 2-oxoglutaconate (2.45 g, 14.2 mmol), and a catalytic amount of *p*-toluenesulfonic acid was allowed to reflux for 17 h under N_2. Evaporation of the solvent gave a brown residue from which **6** was isolateed as a yellow solid in 28% yield by flash chromatography on SiO_2 ($CHCl_3$): mp 163–165 °C dec; IR (KBr) 3404 (OH), 1728 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 4.09 (3 H, s, $COOCH_3$), 4.11 (3 H, s, $COOCH_3$), 7.47 (1 H, dt, J = 1.8, 7.9 Hz, H-7), 7.48 (1 H, s, H-9), 7.64 (1 H, ddd, J = 1.1, 7.9, 8.8 Hz, H-6), 7.84 (1 H, dd, J = 1.1, 7.9 Hz, H-8, an NOE of 6.5% was detected when H-9 was irradiated), 8.11 (1 H, br d, J = 8.8 Hz, H-5, the long-range coupling with H-7 (J = 1.8 Hz) is not clear), 8.36 (1 H, s, H-3), 8.6 (1 H, br s, OH); MS (EI) m/z 311 (M^+). Anal. Calcd for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.54; H, 4.18; N, 4.43.

Dimethyl 9,10-Dihydro-9,10-dioxobenzo[*f*]quinoline-2,4-dicarboxylate (4). To a solution of **6** (100 mg, 0.322 mmol) in CH_3CN (20 mL) at 0–5 °C was added an aqueous solution (20 mL) containing Fremy's salt (350 mg, 1.30 mmol) and KH_2PO_4 (169 mg, 1.24 mmol). The mixture was stirred at room temperature for 8 h and extracted with $CHCl_3$ (50 mL × 4). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was washed with ether and recrystallized from benzene to give **4** as a yellow solid in 67% yield: mp 217–219 °C dec; IR (KBr) 1718 (ester C=O), 1692 cm^{-1} (quinonoid C=O); UV-vis (CH_3CN) λ_{max} 227 (ϵ = 18 800), 267 (ϵ = 21 200), 306 nm (12 400 M^{-1} cm^{-1}); ^1H NMR (270 Hz, DMSO-d_6) δ 3.97 (3 H, s, $COOCH_3$), 3.98 (3 H, s, $COOCH_3$), 7.61 (1 H, d, J = 7.4 Hz, H-5), 7.68 (1 H, t, J = 7.4 Hz, H-7), 7.81 (1 H, dt, J = 1.8, 7.4 Hz, H-6), 8.15 (1 H, dd, J = 1.8, 7.4 Hz, H-8), 8.35 (1 H, s, H-3); ^{13}C NMR (DMSO-d_6) 53.1 (OCH_3), 53.8 (OCH_3), 127.0, 128.1, 129.5, 131.1, 131.7, 132.2, 132.4, 135.0, 139.7, 146.9, 148.4, 164.0 (ester C=O), 168.0 (ester C=O), 176.5 (dd, $^3J_{CH}$ = 1.5 Hz, $^4J_{CH}$ = 4.1 Hz, C-9), 177.9 ppm (s, C-10); MS (EI) m/z 327 (M^+ + 2; characteristic peak for *o*-quinone compounds); exact mass for $C_{17}H_{11}NO_6$ calcd 325.0586, found 325.0592. Anal. Calcd for $C_{17}H_{11}NO_6$: C, 62.77; H, 3.41; N, 4.31. Found: C, 62.52; H, 3.38; N, 4.31.

Acetone Adduct Formation (General Procedure). To a solution of the quinone (10 mM) in acetone was added triethylamine (100 mM) through a microsyringe under N_2. The reaction was followed by TLC (SiO_2). When the quinone disappeared completely, acetone and the excess of triethylamine were removed under reduced pressure. Recrystallization from $CHCl_3$ and *n*-hexane gave the acetone adduct products.

Trimethyl 4-oxo-5-acetonyl-5-hydroxy-4,5-dihydro-1-methylpyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (8): isolated yield 93%; mp 99–101 °C; IR (KBr) 3452 (OH), 1732 (ester C=O), 1690 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 2.24 (3 H, s, $COCH_3$), 3.30 (2 H, s, CH_2CO), 3.78 (3 H, s, NCH_3), 3.89 (3 H, s, $COOCH_3$), 3.99 (3 H, s, $COOCH_3$), 4.02 (3 H, s, $COOCH_3$), 3.9–4.1 (1 H, br, OH), 7.49 (1 H, s, H-3), 8.40 (1 H, s, H-8); MS (EI) m/z 444 (M^+).

Dimethyl 9-oxo-10-acetonyl-10-hydroxybenzo[*f*]quinoline-2,4-dicarboxylate (9): isolated yield 83%; mp 142–144 °C; IR (KBr) 3412 (OH), 1732, 1702 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$) δ 2.31 (3 H, s, $COCH_3$), 3.01 (1 H, d, J = 14.9 Hz, C*H*HCO), 3.26 (1 H, d, J = 14.9 Hz, CH*H*CO), 3.91 (3 H, s, $COOCH_3$), 4.02 (3 H, s, $COOCH_3$), 7.51 (1 H, dd, J = 1.4 and 8.7 Hz, H-5, an NOE of 2.7% was detected when the methyl ester group at the 4-position (δ 3.91 ppm) was irradiated), 7.59 (1 H, dt, J = 1.4 and 8.7 Hz, H-7), 7.66, (1 H, dt, J = 1.6 and 8.7 Hz, H-6), 8.02 (1 H, dd, J = 1.6 and 8.7 Hz, H-8), 8.22 (1 H, s, H-3, an NOE of 2.4% was detected when the methyl ester group at the 4-position (δ 3.91 ppm) was irradiated); MS (EI) m/z 383 (M^+). Anal. Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.84; H, 4.40; N, 3.62.

Reaction of 3 and 4 with Phenylhydrazine. To a solution of quinone **3** or **4** (4 mM) in CH_3CN was added phenylhydrazine (1.1 equiv) through a microsyringe under argon. The reaction mixture was stirred at room temperature for 80 min. Removal of the solvent under reduced pressure gave the corresponding quinols, $3H_2$ and $4H_2$. The ^1H NMR spectra of those products were identical to those of the authentic samples prepared by the reported method.[24] $3H_2$: ^1H NMR (270 MHz, DMSO-d_6) δ 3.81 (3 H, s, NCH_3), 3.89 (3 H, s, $COOCH_3$), 3.99 (3 H, s, $COOCH_3$), 4.02 (3 H, s, $COOCH_3$), 7.55 (1 H, s, H-3), 8.18 (1 H, s, H-8); MS (EI) m/z 388 (M^+). $4H_2$: ^1H NMR (270 MHz, DMSO-d_2) δ 4.00 (3 H, s, $COOCH_3$), 4.07 (3 H, s, $COOCH_3$), 7.63 (1 H, dd, J = 7.1 and 8.4 Hz, H-6), 7.77 (1 H, dd, J = 7.1 and 8.1 Hz, H-7), 8.10, (1 H, d, J = 8.4 Hz, H-5), 8.13 (1 H, s, H-3), 8.32 ppm (1 H, d, J = 8.1 Hz, H-8), 9.18 (1 H, br s, OH), 10.23 (1 H, br s, OH); MS (EI) m/z 327 (M^+).

Aerobic oxidation of benzylamines was performed as described elsewhere.[19a]

Acknowledgment. The present study was financially supported in part by a Grant-in-Aid for Encouragement of Young Scientists (02855205 and 03855187) from the

(20) Duine, J. A.; Jongejan, J. A. *Annu. Rev. Biochem.* **1989**, *58*, 403.
(21) Janes, S. M.; Mu, D.; Wemmer, D. E.; Smith, A. J.; Kaur, S.; Maltby, D.; Burlingame, A. L.; Klinman, J. P. *Science* **1990**, *248*, 981.
(22) McIntire, W. S.; Wemmer, D. E.; Chistoserdov, A.; Lidstrom, M. E. *Science* **1991**, *252*, 817.
(23) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: Elmsford, NY, 1966.
(24) Itoh, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1911.

Ministry of Education, Science, and Culture and also by Foundation "Hattori Hokokai" and "Asahi Glass Foundation". Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining ^{13}C-NMR spectra on a Brucker AM-600 spectrometer and mass spectra on a JEOL JMS-DX303 spectrometer.

Supplementary Material Available: ^{1}H NMR spectra of $3H_2$, $4H_2$, and 8 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Investigation of a Model for 1,2-Asymmetric Induction in Reactions of α-Carbalkoxy Radicals: A Stereochemical Comparison of Reactions of α-Carbalkoxy Radicals and Ester Enolates

David J. Hart* and Ramanarayanan Krishnamurthy

Department of Chemistry, The Ohio State University, 120 West 18th Avenue, Columbus, Ohio 43210

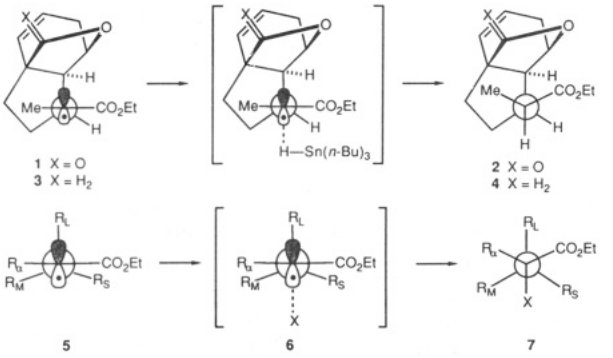
Received March 26, 1992

The stereochemical course of reductions and allylations of α-carbalkoxy radicals with chiral centers at the β-position are reported. Radicals without polar substituents, with alkoxyl or acetoxyl groups, and with hydroxyl groups at the β-position were examined. Reactions showed selectivities ranging from low (50:50) to high (99:1). The results are discussed in terms of transition-state models that emphasize the importance of (1) allylic conformational analysis (minimization of $A^{1,3}$ and $A^{1,2}$ strain), (2) torisonal strain (minimization of eclipsed interactions), and (3) stereoelectronic effects.

Introduction

Asymmetric stereoselection in free-radical reactions is a topic of current interest. For example, notable advances toward controlling absolute stereochemistry in radical additions to α,β-unsaturated amides and esters have been reported by the groups of Porter, Giese, and Curran.[1] High levels of asymmetric induction have also been observed by Hamon and Crich in reactions between α-carbalkoxy radicals and trialkyltin hydrides, allylic stannanes, and thiopyridones.[2] Another area of activity has been the development of reactions in which asymmetry at the β-position of an α-carbalkoxy radical influences the stereochemical course of an intermolecular reaction (1,2-asymmetric induction). For example, the Guindon group has reported reductions and allylations of β-alkoxy-α-carbalkoxy radicals that proceed with high diastereoselectivity.[3,4] Our own efforts, which have focused on the 1,2-symmetric induction problem, were stimulated by an observation recorded while undertaking a total synthesis of pleurotin. We discovered that radical **1** was reduced by tri-*n*-butyltin hydride to afford **2** with 16:1 diastereoselectivity.[5] We later noted that radical **3** was also reduced to **4** with 10:1 diastereoselectivity.[6] We rationalized these observations using the model set forth in Scheme I.[6] This model has the following features: (1) We assumed that the α-carbalkoxy radical was delocalized and thus subject to the conformational analysis usually applied to allylic systems. This assumption is supported by C_α—C(=O) rotational barriers reported for α-carbalkoxy and α-keto radicals.[7] (2) We suggested that the conformation leading to the lowest energy transition state was that in which $A^{(1,3)}$ interactions were minimized (H_β vs OEt or O•) and the largest allylic substituent was orthogonal to the π-bond. Placing the largest substituent orthogonal to the π-bond also minimized $A^{(1,2)}$ interactions. This suggestion seemed reasonable based on the role played by allylic strain in a variety of diastereoselective processes.[8,9] (3) We suggested

Scheme I



(1) (a) For a recent overview of progress in the area of acyclic stereocontrol in free-radical reactions, including a discussion of 1,2-asymmetric induction, see: Curran, D. P.; Giese, B.; Porter, N. A. *Acc. Chem. Res.* **1991**, 296. (b) Also see: Porter, N. A.; Lacher, B.; Chang, V. H.; Magnin, D. R.; *J. Am. Chem. Soc.* **1989**, *111*, 8309. Giese, B.; Zehnder, M.; Roth, M.; Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. Porter, N. A.; Swann, E.; Nally, J.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6740. Giese, B.; Zehnder, M.; Roth, M.; Zeitz, H.-B. *J. Am. Chem. Soc.* **1990**, *112*, 6741. Scott, D. M.; McPhail, A. T.; Porter, N. A. *Tetrahedron Lett.* **1990**, 1679. Porter, N. A.; Wu, W.-X.; McPhail, A. T. *Tetrahedron Lett.* **1991**, 707. Porter, N. A.; Breyer, R.; Swann, E.; Nally, J.; Pradhan, J.; Allen, T.; McPhail, A. T. *J. Am. Chem. Soc.* **1991**, *113*, 7002.

(2) Crich, D.; Davies, J. W. *Tetrahedron Lett.* **1987**, 4205. Hamon, D. P. G.; Massey-Westropp, R. A.; Razzino, P. *J. Chem. Soc., Chem. Commun.* **1991**, 332. Hamon, D. P. G.; Razzino, P.; Massey-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 722.

(3) Guindon, Y.; Yoakim, C.; Lemieux, R.; Boisvert, L.; Delorme, D.; Lavallee, J.-F. *Tetrahedron Lett.* **1990**, 2845.

(4) Guindon, Y.; Lavallee, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, 27.

(5) Hart, D. J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, 3749.

(6) Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(7) Strub, W.; Roduner, E.; Fischer, H. *J. Phys. Chem.* **1987**, *91*, 4379.

(8) Johnson, R. *Chem. Rev.* **1968**, *68*, 375.

(9) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

0022-3263/92/1957-4457$03.00/0