BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 50 (10), 2704—2713 (1977)

The Oxidative Solvolysis of Durohydroquinone Monobenzoates. A Study of the Mechanism

Makoto TAKAGI, Masato TAZAKI, and Tsutomu MATSUDA

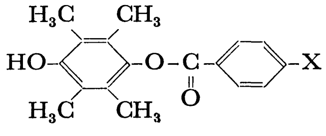
Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812

(Received February 25, 1977)

Durohydroquinone mono(*p*-substituted benzoate)s (**1a**—**1e**) were oxidized by DDQ in CH_3OH/CH_2Cl_2 at room temperature. The products were duroquinone dimethyl acetal **4** and *p*-substituted benzoic acids (**5a**—**5e**). None of the methyl esters **3** was formed. The details of the mechanism of a series of reactions, which start with the one-electron oxidation of **1**, is elucidated by the isolation and characterization of the intermediates as well as by a kinetic study in an acetonitrile solution. The relation between the mode of oxidation, whether it is a one-electron or two-electron process, and the activation of the acyl group was explicitly discussed in terms of the mechanism. Two-electron oxidation is suggested to offer a better chance for acyl activation. Some generalization of the mechanism is made for other oxidation-induced acyl, phosphoryl and sulfuryl activating systems.

The oxidation of hydroquinone monoesters is of considerable interest as models for biological energy conversion, wherein the free energy associated with redox reaction is conserved in such "energy-rich" bondings as phosphoric or carboxylic anhydrides. Research efforts have especially been focussed on the phosphate esters since some hydroquinone phosphates are believed to be involved in biological phosphorylation.[1–3] The oxidation of hydroquinone phosphates can generate a phosphorylating agent and the reaction mechanism, as well as the synthetic application, has been examined extensively.[4,5] The carboxylates behave similarly, and several implications of the mechanism involved have been made by Wieland and Aquila,[6] Bunton and Hellyer,[7] and Clark *et al.*[8] Thanassi and Cohen[9] have proposed a phosphate-free energy conservation cycle based on the ubihydroquinone monocarboxylate ester in mitochondria.

From the point of view of the mechanism, there have been controversial observations of this oxidation-assisted activation of phosphoryl and acyl groups, since both O–C(aryl) and O–P or O–C(acyl) bond fissions have been observed depending on the oxidation conditions.[4–12] The mode of oxidation, whether it is a one- or two-electron process, and the nature of the specific ionic species involved in the case of phosphate esters should be explicitly formulated in the delineation of the reaction mechanism which links oxidation to the phosphoryl and acyl transfer processes. There has been, however, little work along this line which traces back to the characterization of the reaction intermediates involved and studies the detailed behavior in the isolated state. As a substrate for a study of the mechanism involved the carboxylate has some advantages over the phosphate in that they do not dissociate under ordinary conditions and the physical-organic chemistry of the acyl group in general is much better founded than that of the phosphoryl group. In the present investigation, the mechanism of oxidation of durohydroquinone mono(*p*-substituted benzoate)s (**1**)[13a] by dichlorodicyano-*p*-benzoquinone ((DDQ) was studied by product analysis and by intermediate isolation and characterization, as well as by kinetic measurements. The one-electron oxidation process which does not lead to acyl activation[13b] has been elucidated, and the mechanism has been discussed in comparison with the two-electron oxidation process by bromine or NBS which was found to bring about acyl transfer.



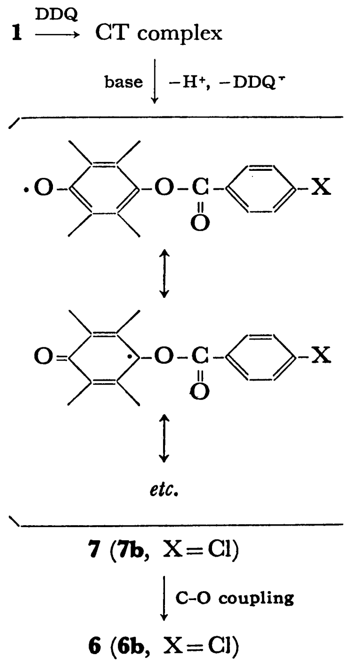
1a: X=H
1b: X=Cl
1c: X=NO_2
1d: X=CH_3
1e: X=OCH_3

Results

Oxidation Products. Substrate **1** reacted with equimolar amounts of DDQ in CH_3OH/CH_2Cl_2 (50/50, v/v) at 30 °C, and the mixture was analyzed directly using GLC for duroquinone (**2**), methyl *p*-X-benzoate (**3**), duroquinone dimethyl acetal (**4**) and *p*-X-benzoic acid (**5**). The results are shown in Table 1. It is obvious that the nature of the products and their yields are the same, irrespective of the *p*-substituent on the benzoyl nucleus. About 90% of the durohydroquinone moiety was recovered as **4**, and 6 to 8%, as **2**. The combined yield accounts for more than 94% of the starting substrate. The benzoyl portions were almost quantitatively converted into the benzoic acids, and methyl benzoates were formed only in trace amounts. After work up, $DDQH_2$ and **5** were isolated in about 90% yield, and the combined yield of isolated **2** and **4** accounted for over 90% of the starting durohydroquinone ester. However, no methyl benzoate **3** was detected. Thus, the reaction can be formulated as

$$\mathbf{1} + DDQ + 2CH_3OH \xrightarrow[1\,h]{r.t.} \mathbf{4} + \mathbf{5} + DDQH_2. \qquad (1)$$

Isolation of Reaction Intermediates. Dissolution of DDQ and **1b** in benzene produced a 1:2 (DDQ: **1b**) molecular complex as black-violet crystalline powder, having an IR spectrum very close to the superposition of those of **1b** and DDQ. Since the IR spectrum of the anion radical, $DDQ^{\bar{\cdot}}$ (potassium salt[14]), was quite different, the structure of this molecular complex appears to involve the usual charge transfer (CT) interaction rather than an ionic or dative one with complete electron transfer. Similar CT complexes were isolated using other nonpolar solvents (1:1 or 1:2 stoichiometry). Recently, McNelis[15] reported a 1:1 CT complex between naphthalenediol monoacetate and DDQ.



Scheme 1.

When **1b** reacted with DDQ in benzene (CT complex formation) and was then treated with a 2 M NaOH solution, 4-(4-chlorobenzoyloxy)-4-[4-(4-chlorobenzoyloxy)-2,3,5,6-tetramethylphenoxy]-2,3,5,6-tetramethyl-2,5-cyclohexadienone **6b** was produced in a 90% yield as colorless crystals. The ^1H NMR spectrum is illustrated in Fig. 1. The assignment is based on a comparison with other structurally-related compounds synthesized in the present study, which are included together in the figure. The formation of **6** from the CT complex upon treatment with a base can be rationalized as follows. The base abstructed the phenolic proton from the CT complex.

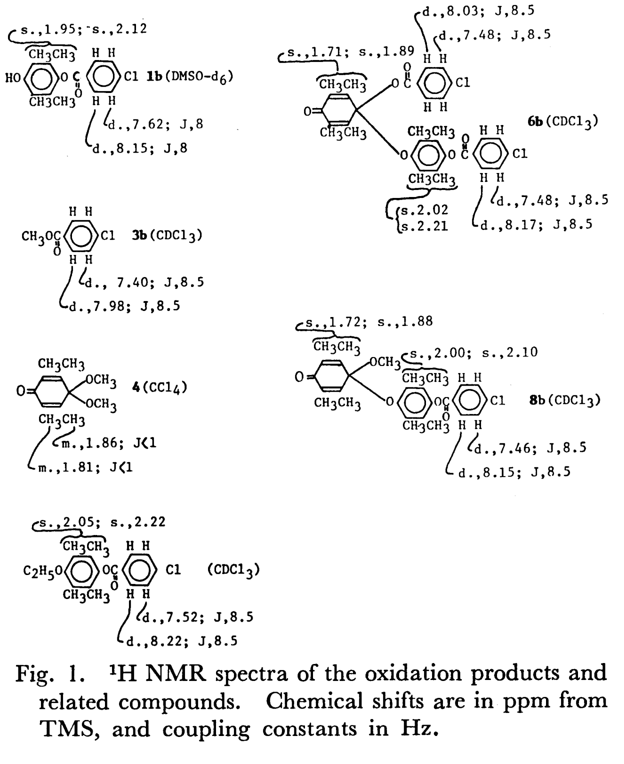
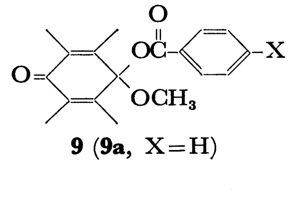


Fig. 1. ^1H NMR spectra of the oxidation products and related compounds. Chemical shifts are in ppm from TMS, and coupling constants in Hz.

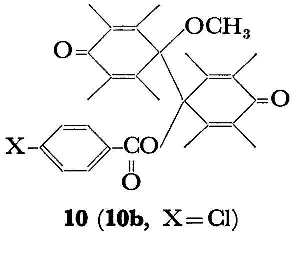
The CT interaction then proceeded to transfer an electron to form phenoxyl **7**, which in turn coupled bimolecularly at C- and O-terminals giving **6** (Scheme 1).

The reaction of **1** with DDQ in a medium containing alcohols as a major component proceeded rather rapidly (within 1 h) and gave **4**, **5** and $DDQH_2$ as final products (Reaction 1). However, when the reaction was quenched at a very early stage, the products were different. The oxidation of **1b** in $C_2H_5OH/CHCl_3$ (50/50, v/v) according to the similar procedure as described above for the reaction in benzene (1 min of reaction time before treatment with 2 M NaOH) produced **6b** in a 73% yield. In the alcoholic solvent, the CT complex is not a stable entity, but proceeds rapidly to further reactions. It is, therefore, uncertain whether **6b** was formed on contact with the added base (as is the case for the reaction in benzene) or was already being formed in the polar and hydroxylic reaction medium. The reaction mixture was quenched by aqueous ascorbate–sodium hydrogen carbonate. Then, the yield of **6b** was even higher (86%) in $C_2H_5OH/CHCl_3$, while in benzene no **6b** was obtained, and **1b** was recovered quantitatively. This indicates that the ascorbate anion reduced DDQ in the CT complex and completely suppressed the base promoted transformation of the CT complex to *p*-benzoyloxyphenoxyl (**7b**) and $DDQ^{\cdot-}$. These results strongly support the hypothesis that the reactions in Scheme 1 are under way in the initial phase of the reaction in the polar and hydroxylic mediums, such as CH_3OH/CH_2Cl_2 or $C_2H_5OH/CHCl_3$. On the other hand, the reaction does not proceed beyond the CT stage in the benzene solvent.

Scheme 1 describes the one-electron oxidation of **1** by DDQ. The oxidation was carried out with typical one-electron oxidizing agents for comparative purposes. The oxidation of **1b** with potassium hexacyanoferrate(III) in 2 M NaOH produced **6b** in a 70% yield. Oxidation with cerium(IV) ammonium nitrate in methanol turned out to be somewhat different, giving 4-[4-(4-chlorobenzoyloxy)-2,3,5,6-tetramethylphenoxy]-4-methoxy-2,3,5,6-tetramethyl-2,5-cyclohexadienone **8b** (yield 84%). Clark *et al.*[8] conducted a similar cerium(IV) oxidation experiment with **1a** and isolated a yellow solid for which the structure **9a** (X=H) was suggested. The ^1H NMR spectra of the preparation reported here (Fig. 1, **8b**) is not in accord with this type of structure. Another structure, **10b**, which is isomeric to **8b**, was excluded on the basis of a detailed comparison of the ^1H NMR chemical shifts of the related compounds in Fig. 1. The product difference between hexacyanoferrate(III) oxidation and cerium(IV) oxidation can be rationalized by the lability of **6b** under acidic conditions.



9 (**9a**, X=H)



10 (**10b**, X=Cl)

Table 1. DDQ oxidation of **1** in CH_3OH/CH_2Cl_2[a]

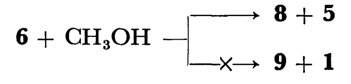
Substrate	Product, % yield			
	2	**3**	**4**	**5**
1a	6	<1	92	~100
1b	8	<1	92	~100
1c	6	<1	88	b)
1d	—	<1	88	~100
1e	6	<1	88	~100

a) $[\mathbf{1}]_0=[DDQ]_0=0.05$ M, CH_3OH/CH_2Cl_2 (50/50, v/v), 30 °C, 1 h. b) Not determined.

The reaction medium for cerium(IV) oxidation was rather strongly acidic, and it was shown in a control experiment that, under such circumstances, **6b** is readily converted into **8b**.

Chemical Transformations of Reaction Intermediates. The intermediates isolated in the foregoing section were found to be eventually transformed into the final products, **2**, **4**, and **5**, under the reaction conditions described in Table 1. In this context, the behavior of the isolated intermediates was studied with respect to the reactivity of the acetal linkages. Two types of reaction, *i.e.*, heterolytic and homolytic cleavages, were observed.

The acetal **6b** dissolved in $CHCl_3/CH_3OH$ (10/90, v/v) was maintained at 0 °C overnight. Work up of the mixture gave no recoverable **6b** but did give **8b** (in a 83% yield without purification) and *p*-chlorobenzoic acid, **5b**. No evidence was obtained for the formation of **1b**, which should be readily detectable from its characteristic IR absorption (ν_{OH}, 3415 cm^{-1}). This indicates that the acetal linkage C–OCOAr is much more labile than C–OAr′ under neutral to weakly acidic conditions (Reaction 2). Prolonged treatment of **6b** with methanol resulted in a complex mixture containing **2** and **4**, in addition to **5** and **8**. The reaction in ethanol proceeded similarly, but slowly in comparison with that in methanol:



$$\mathbf{6}+CH_3OH \left\{\begin{array}{l}\longrightarrow \mathbf{8}+\mathbf{5}\\ \overset{\times}{\longrightarrow} \mathbf{9}+\mathbf{1}\end{array}\right. \qquad (2)$$

The time dependence of the ^1H NMR spectrum of a mixture of durohydroquinone monomethyl ether (**11**, 0.10 mmol) and DDQ (0.11 mmol) in $CD_3OD/CDCl_3$ (50/50, v/v, 400 μl) was inspected. The spectra in Fig. 2 indicate that, after 2 h, methyl trideuteriomethyl acetal of duroquinone, **12** (the compound **4** in which one of the CH_3O groups is replaced by CD_3O), was formed quantitatively. After 4 days, the CH_3O group in the acetal **12** was completely exchanged to CD_3O by further reaction with the solvent. A considerable amount of duroquinone was also formed by a reaction with the moisture in the solvent. The first phase of the reaction was very rapid, and the formation of **12** was, in fact, complete within 5 min according to the NMR measurement. The reaction of **11** and DDQ under alkaline conditions gave a quite different product. Thus, the solution of **11** and DDQ in benzene, after treatment with aqueous alkali, afforded 4-methoxy-4-(4-methoxy-2,3,5,6-tetramethylphenoxy)-2,3,5,6-tetramethyl-2,5-cyclohexadienone **14** as colorless crystals (yield, 75%). The latter could also be prepared using an alkaline hexacyanoferrate(III) solution as the oxidizing agent.[16] Compound **14** was not only labile to acid forming **4** and **11** in acidified methanol (by the addition of $DDQH_2$) but also readily oxidizable (within 5 min) by DDQ in $CD_3OD/CDCl_3$ to give the acetal **12**. These facts indicate that **14** would be of only transient existence, even if it were formed in the DDQ oxidation of **11** in $CD_3OD/CDCl_3$. The ^1H NMR spectrum of **14** contained unusually broad resonance signals, which were barely assignable to the proposed structure. The ESR measurements made on the solution in benzene/toluene (Fig. 3)

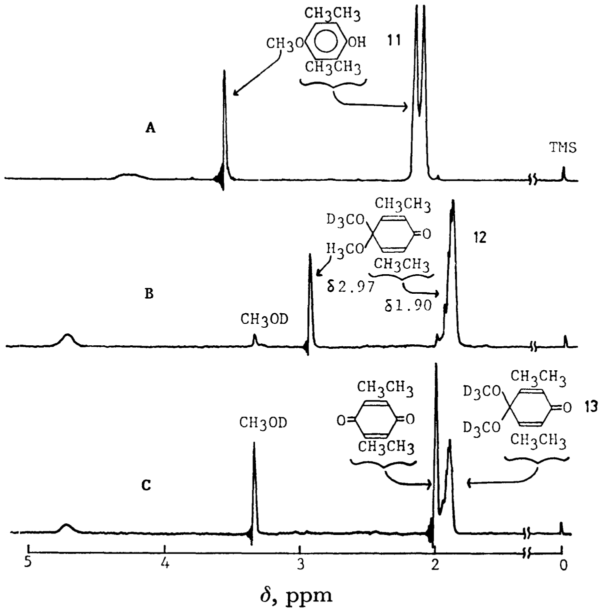


Fig. 2. DDQ oxidation of **11** (0.10 mmol) in $CD_3OD/CDCl_3$ (50/50, v/v, 400 μl) at room temperature. ^1H NMR spectra. A, **11** in $CDCl_3$; B, reaction mixture after 2 h; C, after 4 days.

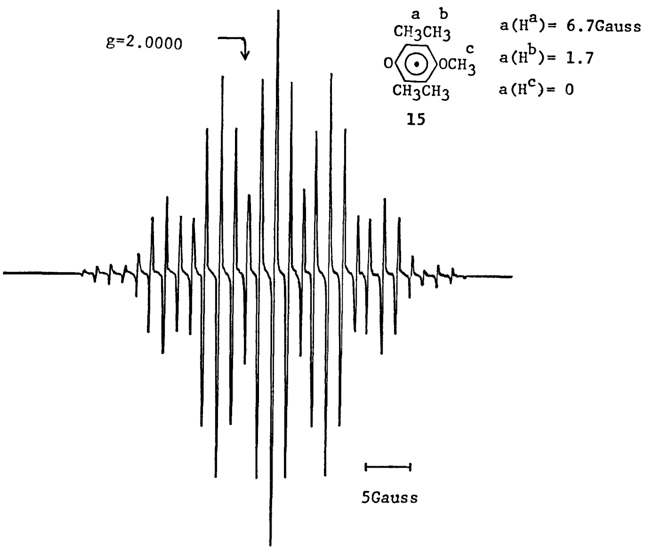
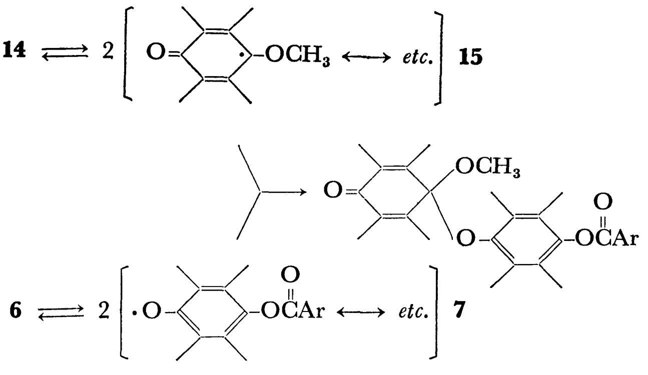


Fig. 3. The ESR spectrum of **14** in $C_6H_6/C_6H_5CH_3$ (40/60, v/v). $[\mathbf{14}]=0.67M$, room temperature. $\mathbf{14}\rightleftharpoons 2\cdot\mathbf{15}$.

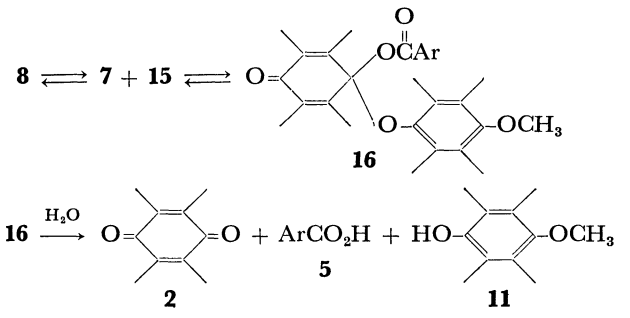
clearly indicate the presence of phenoxyl **15** in equilibrium with **14**. Similar behavior has been reported for a related compound.[17]

An equimolar mixture of **6b** and **14** was found to be converted into **8b** simply by dissolving the former in benzene followed by concentration under reduced pressure. This observation indicates that the radical dissociation of **6b** should be considered in addition to that of **14**. The reaction is illustrated in Scheme 2.



Scheme 2.

The intermediate **8** also appears to undergo facile homolytic cleavage of the acetal linkage, evidence for which has come from the attempted purification of **8b** by column chromatography on silica gel. On elution with benzene/ether, **8b** (1 mmol, contaminated with **5b**) decomposed to **1b** (0.55 mmol), **2** (0.89 mmol), **5b** (0.79 mmol) and **11** (0.26 mmol). Degradation accounts for the difficulty encountered in obtaining **8b**, and, in fact, it was this finding which prompted the examination of the DDQ oxidation of **11**. The reaction can be rationalized by the process illustrated in Scheme 3. A hydrolysis of acetal **8b** to **1b** and **2** should also be considered.



Scheme 3.

Kinetic Study in Dilute Solutions. In the preceeding sections, the chemical events after the completion of one-electron oxidation on the substrate were considered. Now, information is treated regarding the oxidation step using a kinetic method in dilute solutions. The oxidation for the kinetic study was carried out conveniently in CH_3CN or AcOH, and most of the kinetic runs presented herein involve the former as a solvent. When **1a** (0.5 mM) reacted with DDQ (0.5 mM) in dry CH_3CN at room temperature, the electronic spectra indicated the formation of $\mathrm{DDQ}^{\bar{\cdot}}$, in addition to $DDQH_2$ (Fig. 4). In accordance with the acid dissociation and redox equilibrium between DDQ, $DDQH_2$, and $\mathrm{DDQ}^{\bar{\cdot}}$,[18] the relative $\mathrm{DDQ}^{\bar{\cdot}}$ and $DDQH_2$ concentrations formed during the oxidation reactions varied with the acidity of the medium. For example, upon the addition of excess trifluoroacetic acid, no $\mathrm{DDQ}^{\bar{\cdot}}$ was detected, and in the presence of equimolar 2,6-lutidine, $\mathrm{DDQ}^{\bar{\cdot}}$ was the sole product in the oxidation. The presence of basic material (*e.g.*, 2,6-lutidine, pyridine *N*-oxide or lithium acetate) not only affected the nature of the product (*i.e.*, increased the ratio of $\mathrm{DDQ}^{\bar{\cdot}}/DDQH_2$) but also drastically accelerated the oxidation rate. For instance, oxidation in the presence of equimolar 2,6-lutidine was instantaneous at room temperature, while the presence of several molar excess amounts of water, methanol, acetic acid or trifluoroacetic acid showed no measurable influence on the rate (*vide infra*). Base-assisted oxidation, which is in accord with Scheme 1, will be more fully treated in a separate communication.

$$2\mathrm{DDQ}^{\bar{\cdot}} + 2\mathrm{H}^+ \rightleftharpoons \mathrm{DDQ} + \mathrm{DDQH_2}, \qquad (3)$$

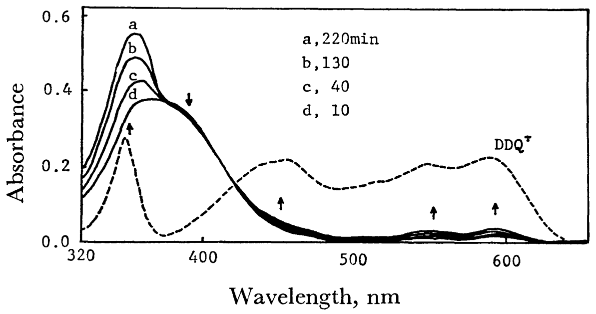


Fig. 4. The variation of electronic spectra accompanying the reaction of DDQ with **1a**. $[\mathrm{DDQ}]_0=[\mathbf{1a}]_0=$ 0.5 mM, CH_3CN, 30 °C.

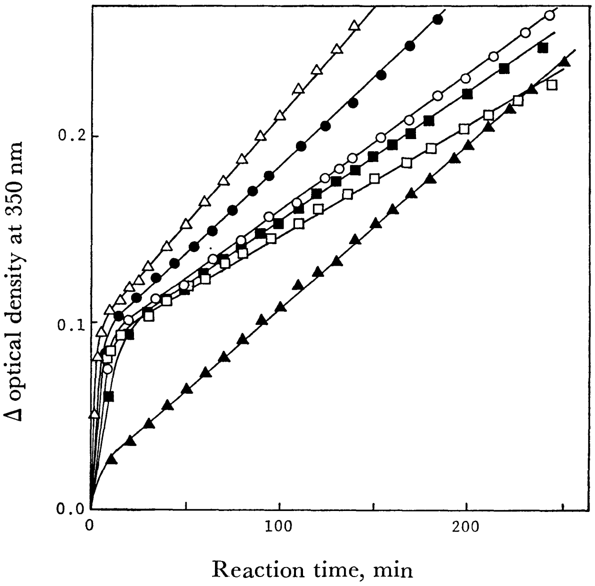


Fig. 5. The time dependence of the increase in absorption at 350 nm in CH_3CN at 30 °C. $[\mathrm{DDQ}]_0=[\mathbf{1a}]_0$ =0.5 mM.
—■—, without additive; —○—, 0.06 M CH_3OH; —●—, 0.31 M CH_3OH; —△—, 0.61 M CH_3OH; —□—, 0.22 M AcOH; —▲—, 0.22 M CF_3COOH.

In Fig. 5, the increase in the absorbance at 350 nm, which corresponded to the formation of $DDQH_2$, was plotted against time for the oxidation of **1a** in CH_3CN. A small absorption due to $DDQ^{\cdot-}$ was observed under these conditions, except for the case in which trifluoroacetic acid was present as an additive, but this constituted only a trivial correction to the amount of $DDQH_2$ formed on reduction by substrate **1a**. No sign of CT complex formation was observed in the spectra at the low concentration ranges of DDQ and **1a** utilized. Figure 5 exhibits the unusually fast production of $DDQH_2$ at the very early stages of the reaction ($<2.5\%$ conversion of DDQ), which was followed by a region (up to $\approx 8\%$) with a constant rate (pseudo-zero order kinetics). The first phase of the reaction was probably due to the presence of a small amount of basic impurity in the CH_3CN solvent, although it was carefully purified. The addition of trifluoroacetic acid eliminated most but not all of this irregular region. The relative reaction rates estimated from the slope of the second linear portion of the plots in Fig. 5 are 1.00 (without the additive), 0.83 (AcOH, 0.22 M), 1.23 (CF_3COOH, 0.22 M), 1.06 (CH_3OH, 0.06 M), 1.34 (CH_3OH, 0.31 M), and 1.69 (CH_3OH, 0.61 M). The small effect of the additives on the reaction rate even in the presence of a molar excess of **1a** of 1000 is more likely due to the change in the nature of the medium rather than to the specific effect of the additives. Thus, neither a nucleophilic process nor an acidic catalysis is involved in the rate-determining step of the formation of $DDQH_2$ (or $DDQ^{\cdot-}$, refer to Reaction 3). The reaction products from **1** are probably similar to those mentioned in previous sections, but were not identified under the present reaction conditions. Where no nucleophilic additive was intentionally applied, a trace of water in the solvent might have assumed the role of a nucleophile.

Kinetics in acidified CH_3CN (0.16 M CF_3COOH) were studied. The initial concentration of DDQ was maintained constant at 0.5 mM and that of **1a** was varied between 0.25 and 3.99 mM. The pseudo-zero order rates, v_0, for the production of $DDQH_2$ in the early stages of the reaction ($<7\%$ conversion of DDQ) were obtained from the slopes of the plots similar to that shown in Fig. 5 and are plotted against the **1a** concentration in Fig. 6. The linear plot with a 1.0 slope indicates the first-order dependence of the rate on [**1a**]. The other series of experiments, in which DDQ (initial concentration, 0.1 mM) reacted with a large excess (4—7 mM) of **1a**, showed that the dependence on DDQ was also of the first order (pseuso-first order production of $DDQH_2$ with up to 90% conversion of DDQ), although the reactions for such low concentrations of DDQ were less reliable in this experiment. Kinetic studies with glacial acetic acid as the solvent also indicated a first-order dependence on both [DDQ] and [**1a**]. The calculated second-order rate constant k ($M^{-1}\ min^{-1}$), according to the expression $d[DDQH_2]/dt=k[\mathbf{1a}][DDQ]/2$, was 1.6 in CH_3CN (30 °C) and 2.0 in CH_3COOH (25 °C).

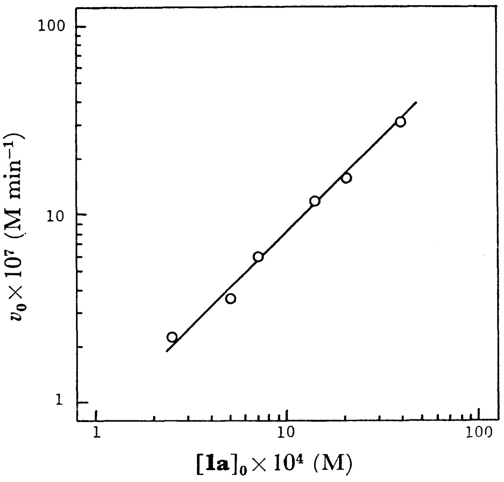


Fig. 6. The dependence of the initial rate of $DDQH_2$ formation on the substrate (**1a**) concentration. $[DDQ]_0=0.5$ mM, $[CF_3COOH]=0.16$ M, CH_3CN, 30 °C.

The effect of a *p*-substituent in the benzoyl group on the rate was investigated. The substrate (**1a**—**1e**, 0.5 mM) was oxidized by DDQ (0.5 mM) at 30 °C in acetonitrile containing 0.16 M trifluoroacetic acid. The previous initial rates were obtained, and the logarithm of the rate ratio was plotted against σ and σ^+ (Fig. 7).

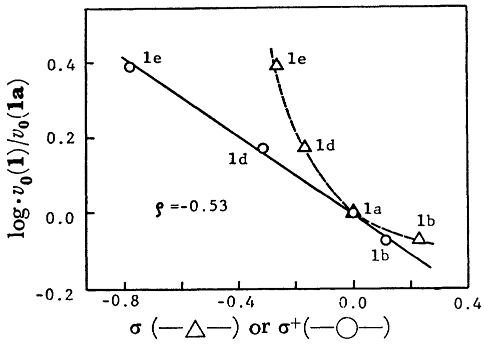


Fig. 7. Hammett's plot of the initial rate for the oxidation of **1a**—**1e** by DDQ. $[DDQ]_0=[1]_0=0.5$ mM, $[CF_3COOH]=0.16$ M, CH_3CN, 30 °C.

The plot against σ^+ gave a straight line with a slope $\rho=-0.53$. This indicates that a positive charge develops on substrate **1** in the transition state of the rate-limiting step. This is in accord with the expectation that the transition state involves electron transfer or charge separation between **1** and DDQ. The small value of ρ reflects that the substituents are situated rather remote from the durohydroquinone nucleus which suffers oxidation.

Discussion

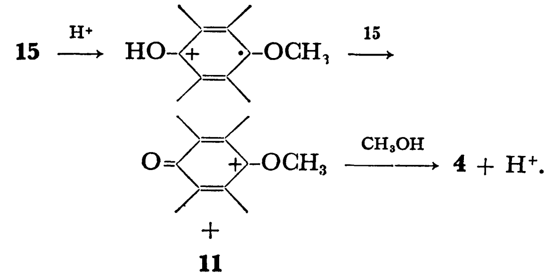
Reaction Products and Intermediates in DDQ Oxidation. The oxidation products in an alcoholic medium indicated that no activation of an acyl group or acyl transfer occurs (Reaction 1). Even the trace of **3** detected in direct GLC analysis could be an artifact due to the subsequent analytical operation. However, in their extensive study on the oxidation of hydroquinone monocarboxylates, Clark *et al.*[8] reported the activation of an acyl group in a system closely related to that studied here. In their experiment, **1a**, **1c**, and **1e** reacted separately with DDQ in $C_2H_5OH/CHCl_3$ (50/50, v/v) at room temperature, and the formation of **2** and **3′** (ethyl esters) was observed in yields of 80—95 and 4—33%, respectively, by analyzing the reaction mixture directly using GLC. This reaction was re-examined and their results were reproduced (except for the production of **4**, which they did not mention) but only under subtly specific reaction conditions. Thus, when the GLC analysis was performed immediately after the dissolution of the reactants, the yield of **3′** was much higher than those reported. Analyses at various reaction times indicated a decreasing yield of **3′** with time. Analyses after the conventional work up indicated that no **3′** was formed throughout the reaction. Their results, therfore, do not appear to reflect the real progress of the reaction in the reaction vessel. Quite similar behavior was in fact observed also in the present system (reaction in $CH_3OH/CHCl_3$) and, under suitable conditions, a yield of **3** of more than 60% was realized by direct GLC analysis. These facts obviously indicate that the starting material, or more probably some reaction intermediates therefrom, reacted to give **3** at the high temperature in the injection part of the instrument. The behavior of reaction intermediate **6** was studied in this context. When a solution of **6b** in CH_3OH/CH_2Cl_2 or $C_2H_5OH/CHCl_3$ was injected onto a GLC column, no benzoate, neither **3b** nor **3b′**, was formed. Upon the addition of DDQ to the solution, the formation of 2—4% of the ester was indicated, which could be eliminated by treating the reaction mixture with aqueous sodium ascorbate before injection. Thus, the combination of **6** and DDQ partially simulate the reaction of **1** with DDQ to give benzoates. However, this is obviously not sufficient to explain the origin of the high yield (10—60%) of **3** at the initial stage of the oxidation reaction. It is most likely that the CT complex of **1** and DDQ is responsible for this reactivity:

$$\underset{\text{CT complex}}{\mathbf{1}\cdot\text{DDQ}_n} + \text{CH}_3\text{OH} \xrightarrow{\text{high temp}} \mathbf{2} + \mathbf{3} + \text{DDQH}_2 + (n-1)\text{DDQ}. \quad (4)$$

The strongly blackish coloration at the onset of the reaction and the isolation of the CT complex support this view.

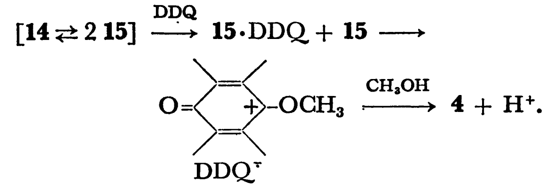
Hageman *et al.*[15] have studied the oxidation of 2,3-dimethyl-1,4-naphthalenediol monoacetate by manganese dioxide and DDQ to give an oxidatively dimerized product and have suggested that the dimer is formed *via* an *o*-quinone methide intermediate. In the present system, no evidence for the presence of such an intermediate could be obtained, even after all attempts including the possible cyclo-addition of the intermediate with butyl vinyl ether. These same authors[15] have further assumed that the foregoing intermediate was preceeded by still other intermediates, the naphthoxyl and its dimer, which were in equilibrium. This supposition appears to be substantiated by the isolation of **6b** in the present study. Clark *et al.* have mentioned that the oxidation of hydroquinone monobenzoates with cerium(IV) ammonium nitrate produced an oxidatively dimerized compound with concurrent nitration.[8] The structure of this compound was not elucidated, but it could be similar to **6**.

Mechanism of Oxidative Solvolysis. It is reasonable to suppose that ordinary acid catalyzes the acetal exchange process for the degradation of **14** to **4** and **11** in methanol.[16] However, in consideration of the homolytic fission of **14**, it appears also possible to delineate the alternative radical mechanism, in which **15** is first protonated and the subsequent electron transfer results in the net heterolytic cleavage of the acetal bond of **14**:[19]



(5)

Another possibility would be the disproportionation of **15** involving a quinone methide intermediate.[17] In the presence of DDQ, still another modification can occur due to the Lewis acidity (or CT interaction) of DDQ. The protonated radical in Reaction 5 is then replaced by the CT complex, which subsequently decomposes into DDQ$^{\overline{\cdot}}$ and the carbonium ion,[19] thus:

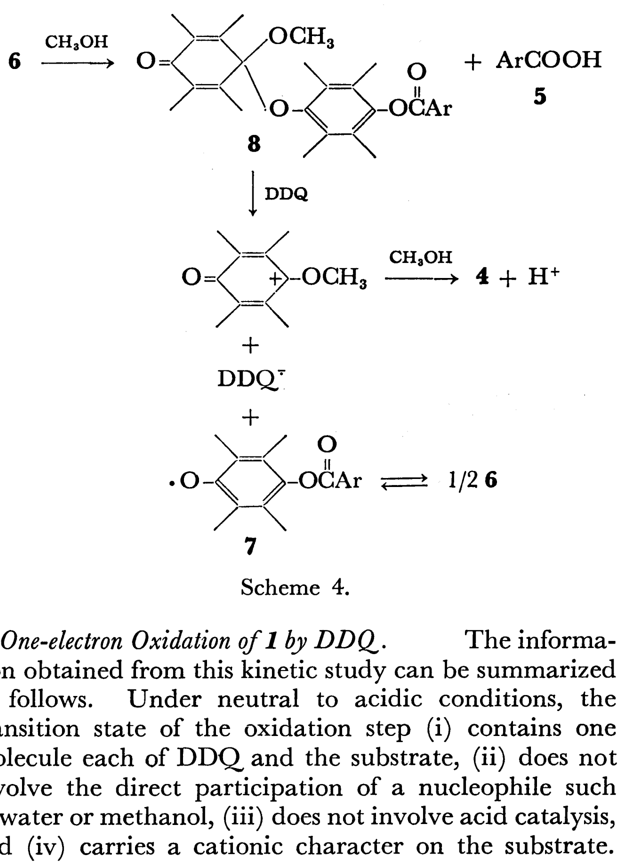


(6)

As has been noted, the oxidation of **11** and **14** by DDQ in $CD_3OD/CDCl_3$ is very rapid and is complete within 5 min at room temperature. The acid ($DDQH_2$) catalyzed degradation of **14** into **4** and **11** in the same solvent was also rapid and complete within 5 min under the conditions of the NMR spectral measurements (37 °C). Thus, under the present conditions, it was not possible to assign the major route of degradation of **14** from the alternative oxidation path (giving **4** and **15**, Reaction 6) and acid catalyzed paths (giving **4** and **11**, *e.g.*, *via* Reaction 5).

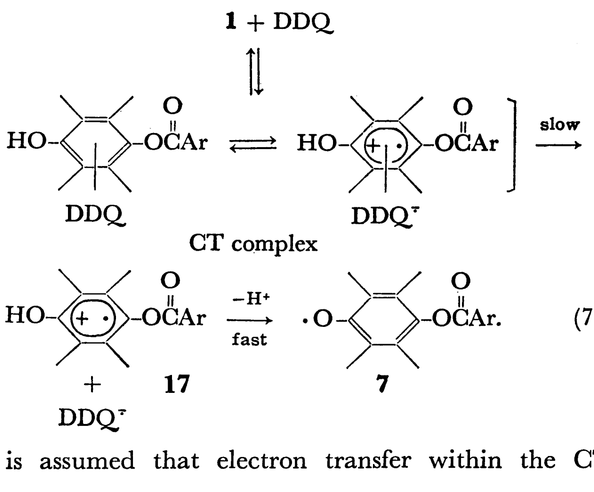
The homolytic scission of the acetal linkage of **8** poses a question similar to the case of **14** as regards the detailed mechanism of the acid catalyzed solvolytic reaction of **8** in methanol giving the dimethyl acetal **4** and **1** (a reaction similar to Reaction 5). The presence of DDQ here again introduces the possibility of an oxidation route, *i.e.*, the oxidative degradation of **8** to produce **4** and the *p*-aryloxyl radical **7** (which is in equilibrium with **6**) in a manner similar to that in Reaction 6. The data on hand show that both the acid catalyzed path and the oxidation path are again very rapid under the conditions for the NMR spectral measurements (complete within 5 min at 37 °C) and, therefore, it is difficult to determine which path is the major one under the reaction conditions given in Table 1. However, it is interesting to note that **6b** was very labile to acid, but not to DDQ. An equimolar mixture of DDQ and **6b** in $CD_3OD/CDCl_3$ showed no reaction after 5 min, although after 10 min, the NMR spectra implied the onset of the reaction, which was followed by a great increase in the rate. After 20 min, the reaction was complete and the products were **4** and **5b**. In the presence of $DDQH_2$ (an acid catalyst), **6b** was rapidly converted into **4**, **5b**, and **1b** (within 5 min). The insensitivity of **6b** to DDQ is deemed to reflect the reluctance of **1b** to undergo two-electron oxidation by DDQ.

The chemical events after the formation of **6** (Scheme 1) can now be delineated as in Scheme 4 (in which only the oxidation path is shown for the conversion of **8** into **4** and **7**), thus completing the overall reaction of Reaction 1.



Scheme 4.

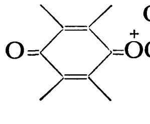
*One-electron Oxidation of **1** by DDQ.* The information obtained from this kinetic study can be summarized as follows. Under neutral to acidic conditions, the transition state of the oxidation step (i) contains one molecule each of DDQ and the substrate, (ii) does not involve the direct participation of a nucleophile such as water or methanol, (iii) does not involve acid catalysis, and (iv) carries a cationic character on the substrate. The following mechanism is consistent with these facts:



(7)

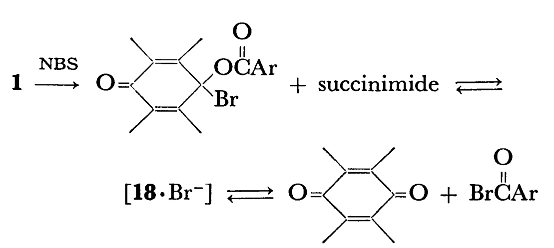
It is assumed that electron transfer within the CT complex is rapid and its dissociation into the solvated radical ion pair is rate determining. The degradation of the CT complex should be strongly facilitated in the presence of a base, since the phenoxyl **7** rather than its conjugate acid **17** can result from the interaction between the base and the CT complex. This view conforms to experimental observation. That the increase in the concentration of methanol in acetonitrile brought about rate enhancement suggests the solvation of the transition state by methanol molecules effectively acting as bases. For the oxidation of phenols by DDQ, both one-electron (as in Scheme 1 and Reaction 7) and two-electron (hydride abstraction mechanism) processes have been proposed,[17,20] and experimental distinction, in many cases, is difficult. The present kinetic evidence itself by no means excludes the alternative hydride abstraction mechanism. The preference for the one-electron oxidation with prior CT complex formation (Reaction 7) is in compliance with the results in the previous sections.

One- and Two-electron Oxidations and the Mechanism of Acyl Activation. Concerning the process of acyl activation *via* oxidation, it would be reasonable to suppose that, as a consequence of oxidation, the hydroquinone moiety of the ester should be converted into a group which exhibits an improved capacity to accommodate the negative charge. For the oxidation of **1** with DDQ, it was shown that **1** is first transformed into the phenoxyl **7** *via* a one electron process. The much stronger acidity of durosemiquinone (pK_a, 4.9—5.9[21]) than that of durohydroquinone (pK_a, 10.5, a guess from Ref. 22) renders the conjugate base of the former much more stable as a product anion. Therefore, from a comparison between the structures of **1** and **7**, we would expect the activated acyl group from **7**, rather than that from **1**. This type of activation should account for somewhat more than the difference in reactivities between phenyl (pK_a (C_6H_5OH)=10.6) and *p*-nitrophenyl (pK_a (*p*-NO_2–C_6H_4OH)=7.2) benzoates. The enhanced reactivity of the benzoyl group in **7**, however, could not be observed experimentally because of the involvement of other facile processes, which are initiated by the dimerization of **7** to **6** (Scheme 4). Since the dimerization of radicals is inevitable under ordinary reaction conditions, it is concluded that the acyl activation of hydroquinone monoester cannot generally be expected, when the oxidation is effected by the one-electron process. However, there is a prerequisite for this conclusion in that radical **7** dimerizes to **6** and the latter does not undergo further one-electron oxidation, which would lead in effect to the two-electron oxidation of the substrate, **1**. If the dimerization process is inhibited by certain factors, the expected activation should be observed. The unimolecular conditions (with respect to the substrate) imposed in enzymic reactions or possibly in reaction in a polymer matrix would qualify to be such factors. Concerning two-electron oxidation, there is no evidence up to now that either **6** or **7** is further one-electron oxidized by DDQ. Such a process would produce the very reactive hypothetical cation intermediate:



18

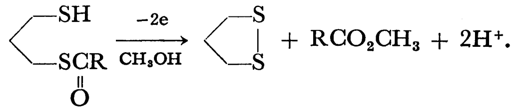
If **18** or a similar species which can conveniently be formulated as **18** on the basis of its reactivity is formed in the reaction mixture, a nucleophilic attack by methanol would be possible at two reactive sites, *i.e.*, at the acyl carbon and the carbonyl carbon of the quinone nucleus. The former gives methyl carboxylate, while the latter would lead eventually to dimethyl acetal (**4**) and carboxylic acid (**5**). Thus, the production of **18** is not necessarily equivalent to experimentally observable acyl activation. The literature indicates that the acyl activation (acyl transfer) has been verified successfully utilizing bromine, NBS, *etc.*, which are apparently two-electron oxidizing agents.[6,8,9] Some of these results were confirmed for the present substrate, **1**. A preliminary study on the mechanism suggests the intervention of **18** or a similar species. Thus, when **1b** reacted with equimolar NBS in benzene at room temperature, *p*-chlorobenzoyl bromide was obtained in a 10% yield, which was identified by IR spectroscopy and its derivation to the anilide. The reaction may be formulated as:


(8)

A similar process has been inferred previously.[8,10,23] The reaction with bromine gave similar results, but extensive bromination of the side chain of duroquinone occurred concurrently (acid catalysis by HBr).

It is reasonable to suppose that the actual structure of the intermediate in the two-electron oxidation process can vary according to the nature of the specific oxidizing agent. For NBS, the two electrons are abstracted directly from the hydroquinone nucleus through C–Br bonding (Reaction 8), while the formation of O–I[7,24] and O–Tl[8,25] bonding are assumed for oxidation with periodate and thallic salt, respectively. The efficiency of the nucleophilic attack on the acyl carbon in **18** is also dependent on these variations. A detailed study has yet to be made of this aspect. It is interesting to note in passing that the thermolysis of the CT complexes of **1** and DDQ produced methyl benzoates in a fairly high yield (up to 60%). The mechanism is by no means clear, but it is possible that the thermal decomposition of the CT complex resulted in a net two-electron oxidation and gave an intermediate of type **18**.

Generalization of the Mechanism. As is obvious from the foregoing discussion, two-electron oxidants have a greater probability of activating the acyl group than do one-electron oxidants. This proved also true of the oxidative acyl transfer observed in the reaction of 1,3-dithiol mono carboxylates:[26]


(9)

While iodine was the most effective oxidizing agent for the acyl activation, one-electron oxidizing agents lead to the linear disulfide (dimerization of the intermediate thiyl radical) without activating the acyl group. However, if we leave the carboxylate and proceed to the phosphates and sulfates, a different consideration has to be made. The essential difference between the acyl group displacement and that of the phosphoryl and sulfuryl groups resides in the fact that the acylium ion intermediate can never be formed under ordinary conditions, while the corresponding intermediates the metaphosphate anion[5,27] and sulfur trioxide,[28,29] respectively, are of a more realistic entity. There have been reports, although small in number, of one-electron oxidation processes resulting in the observable activation of the phosphoryl group (phosphoryl transfer).[4,11] This means that the radical intermediate corresponding to **7** evolves the metaphosphate anion, the semiquinone anion radical acting as an effective leaving group.[11,12] It is reasonable to assume in these cases that the dimerization of the radical intermediate was inhibited because of the unfavorable charge and steric effects. A similar process may also be possible for the sulfate.[28,30] On the other hand, much of the same above discussion applies to the two-electron oxidation of the phosphates and the sulfates except for allowance for the intervention of metaphosphate and sulfur trioxide intermediates, respectively.

Experimental

General. The melting points were determined on a hot-stage apparatus and are uncorrected. The infrared spectra were recorded in Nujol mulls on a Jasco IR-E instrument unless otherwise noted. The ultraviolet and visible spectra were measured on a Shimazu UV-200 spectrometer, and the NMR spectra were recorded with a Varian A-60 spectrometer for solutions in $CDCl_3$, CCl_4 or deuterated DMSO, using TMS as an internal standard. The ESR spectra were obtained on a Jasco ME-3X X-band spectrometer. The magnetic field was calibrated with Mn^{2+}: MgO. All solvents were purified by standard techniques. The acetonitrile for the kinetic study was retained over 3A Molecular Sieves after a final distillation from K_2CO_3. Kinetic measurements were made in a thermostatically-controlled cell, having an optical path of 10 mm and which was capped with silicone rubber and placed in the spectrometer. The solution was prepared in a nitrogen atmosphere and introduced by means of syringe. The reaction temperature was reproducible to within ± 0.2 °C.

Materials. DDQ (reagent grade, purchased from the Tokyo Kasei Kogyo Co.) was repeatedly recrystallized from benzene, and the CT complex therefrom was decomposed under reduced pressure to give pure DDQ. Durohydroquinone was synthesized according to the reported procedure.[31] The durohydroquinone mono *p*-X-benzoates, **1a**, **1c**, and **1e** were prepared according to the literature[8,32] and purified by repeated recrystallization from benzene and then methanol. **1a**: Yield (after purification), 20%; mp 227—228 °C (lit, 221—223°C[32]); IR 3420, 1710, 1292, 1250, and 1097 cm^{-1}; Found: C, 75.65; H, 6.72%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%. **1c**: Yield, 15%; mp 231.5—233.0 °C (lit, 231 °C[8]); IR 3440, 1720, 1536, 1350, 1290, 1245 and 1093 cm^{-1}; NMR (DMSO-d_6) δ 1.95 (6H, s), 2.15 (6H, s), 8.36 (4H, s); Found: C, 64.65; H, 5.51; N, 4.55%. Calcd for $C_{17}H_{17}NO_5$: C, 64.76; H, 5.43; N, 4.44%. **1e**: Yield, 16%; mp 239—241 °C (lit, 237 °C[8]); IR 3400, 1708, 1290, 1245, and 1100 cm^{-1};

NMR ($CDCl_3$) δ 2.06 (6H, s), 2.15 (6H, s), 3.89 (3H, s), 6.97 (2H, d, $J=9$ Hz), 8.18 (2H, d, $J=9$ Hz); Found: C, 71.96; H, 6.71%. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71%. The substrates **1b** and **1d** were prepared similarly. **1b**: Yield, 33%; mp 240—241 °C; IR 3415, 1715, 1290, 1245, and 1095 cm^{-1}; NMR, Table 1: Found: C, 67.07; H, 5.71%. Calcd for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62%. **1d**: yield, 32%; mp 253.5—255.5 °C; IR 3410, 1712, 1290, 1245 and 1095 cm^{-1}; NMR (DMSO-d_6) δ 1.95 (6H, s), 2.15 (6H, s), 2.41 (3H, s), 7.36 (2H, d, $J=8$ Hz), 8.03 (2H, d, $J=8$ Hz); Found: C, 76.06; H, 7.16%. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%. Durohydroquinone monomethyl ether (**11**) was synthesized according to the literature[23] and purified by repeated recrystallization from CCl_4/petroleum ether. Yield, 14%; mp 117—118 °C (lit, 115—116 °C[33]); IR 3330, 1242, 1076, and 1008 cm^{-1}; NMR ($CDCl_3$) δ 2.11 (6H, s), 2.16 (6H, s), 2.59 (3H, s), 4.2—4.5 (1H, broad). Durohydroquinone monoethyl ether was synthesized similarly (mp 122.5—124.5 °C; IR 3370, 1240, 1080, and 1030 cm^{-1}). 4-Ethoxy-2,3,5,6-tetramethylphenyl *p*-chlorobenzoate was prepared in a manner similar to that described for **1** by the reaction of *p*-chlorobenzoyl chloride with durohydroquinone monoethyl ether. Yield, 39%; mp 152—154 °C; IR 1738, 1269, 1235, and 1090 cm^{-1}; NMR, Table 1; Found: C, 68.25; H, 6.35%. Calcd for $C_{19}H_{21}ClO_3$: C, 68.57; H, 6.36%.

The Oxidation of 1b by DDQ in Methanol. A mixture of 0.05 mmol of **1** and DDQ in 1 ml of CH_3OH/CH_2Cl_2(50/50, v/v) was stirred at 30°C for 1 h. The initially blackish mixture gradually faded to a brownish and then a reddish-orange color. After 40 min, no further reaction was visually observed, and the reaction mixture was analyzed directly on a GLC column for **2**,**3**,**4**, and **5**. Silicone SE 30 (10% on Celite) was utilized for the former three products (with dinitrodurene as the internal standard), and Polyester FA (10% on Celite) was used for the latter (with dinitrodurene or dimethyl phthalate as the standard). The yield of **2** was dependent on the analytical GLC conditions, and when Polyester FA was utilized, instead of Silicone SE 30, the yield increased to 32—34% at the expense of a decrease in the yield of **4**. This indicates hydrolytic decomposition of **4** during the GLC analysis and, thus, the values for **2** in Table 1 may be considered to be the upper limits of **2** present in the actual reaction mixture. The reddish-orange coloration of the final reaction mixture was caused by the displacement of the chloride atom on DDQ by CH_3OH, although this constituted only a minor side reaction since the reaction was carried out under neutral to acidic conditions.

The reaction was carried out on a preparative scale with 304 mg (1 mmol) of **1b** and 227 mg (1 mmol) of DDQ in 5 ml of CH_3OH at room temperature in a nitrogen atmosphere. After 24 h, the reaction mixture was concentrated under reduced pressure and extracted with 5 ml of CCl_4. The insoluble residue was found to be an approximately equimolar mixture of $DDQH_2$ and **5b** from an inspection of the IR spectrum, which accounted for $\approx$88% of the DDQ and **1b** utilized. The CCl_4 soluble portion was subjected to chromatography on silica gel to give 39 mg (24%) of **2** and 144 mg (69%) of **4**. The combined yield corresponded to 93% of the starting durohydroquinone ester. No methyl benzoate **3b** was detected. The yields of **2** and **4** were again dependent on the separation conditions, but the combined yield remained constant for duplicate runs. **4**: mp 48—54°C (lit, 56 °C[16]); IR 1678, 1638, 1075, and 1030 cm^{-1}; NMR (CCl_4) δ 1.81 (6H, m, $J<1$ Hz), 1.86 (6H, m, $J<1$ Hz), 2.88 (6 H, s). The corresponding diethyl acetal was synthesized according to the known procedure.[16] Mp 88—89.5 °C (lit, 68 °C[16]); IR 1686, 1650 and 1058 cm^{-1} NMR ($CDCl_3$) δ 1.19 (6H, t, $J=7.0$ Hz), 1.92 (12H, s), 3.05 (4H, q, $J=7.0$ Hz).

Reaction Intermediates. *CT Complex*: Upon the addition of DDQ (450 mg, 2 mmol) to a solution of **1b** (304 mg, 1 mmol) in benzene (50 ml), a black-violet crystalline powder (220 mg, dec 107 °C) was immediately separated out. The preparation as obtained gave reasonably good analysis for a 1:2 (DDQ: **1b**) molecular complex. Found: C, 61.35; H, 4.19; N, 3.41%. Calcd for $C_{42}H_{34}N_2Cl_4O_8$: C, 60.30; H, 4.10; N, 3.35%. The complex was unstable in the presence of moisture. **6b**: A mixture of **1b** (102 mg, 0.33 mmol) and DDQ (350 mg, 1.5 mmol) in benzene (20 ml) was stirred for 10 min, and the resultant suspension of the CT complex was treated with a cold 2M NaOH solution. The organic layer which immediately turned colorless was separated from the yellow aqueous solution after further addition of 30 ml of benzene. The organic layer was repeatedly washed with 2M NaOH until the latter became colorless. After the final washing with water, the benzene solution was filtered through dry filter paper and evaporated under reduced pressure. The pale yellowish residue gave **6b** as colorless crystals (92 mg) after purification by reprecipitation from CCl_4/hexane. Yield, 90%; mp 145 °C (dec); UV $\lambda_{\max}$ (CH_3CN) 244 nm (ε 29000); IR (Jasco DS-403G, KBr pellet) 1732, 1720, 1676, 1639, 1594, 1269, 1228, 1088, 1070, 1012, 898, and 759 cm^{-1}; NMR, Table 1; Found: C, 67.32; H, 5.30%. Calcd for $C_{34}H_{32}Cl_2O_6$: C, 67.22; H, 5.31%. **8b**: The compound was isolated according to the procedure outlined in the text. After the addition of $NaHCO_3$, the reactions mixture ($CH_3OH/CHCl_3$) was concentrated under reduced pressure, and the residue was extracted twice with 20 ml of ether. After filtration through fine filter paper, the ether solution was evaporated to dryness, and the residue was purified by reprecipitation from CCl_4/petroleum ether giving colorless crystals of **8b**. Spectral data indicated the presence of *p*-chlorobenzoic acid as a minor contaminant, the complete elimination of which was not successful under the present conditions (also see text). Yield, 84%; mp 131 °C (dec); UV $\lambda_{\max}$ (CH_3CN) 240 nm (ε 36000); IR (Jasco DS-403G, KBr pellet) 1743, 1673, 1636, 1594, 1265, 1229, 1085, 1046, 1010, 948, and 759 cm^{-1}; Found: C, 68.63; H, 6.44%. Calcd for $C_{28}H_{31}ClO_5$: C, 69.63; H, 6.47%. **14**: To a solution of methyl ether **11** (180 mg, 1 mmol) in benzene (20 ml) was added DDQ (650 mg, 2.4 mmol), and the mixture was stirred for 10 min at room temperature. The resultant solution was washed with 2M NaOH until the washing became colorless. Workup of the organic layer in a manner similar to that reported[16] afforded **14** in a 75% yield. White crystals; mp 100—101 °C (lit, 101 °C[16]); IR 1678, 1643, 1247, 1085, 1045, 1010, and 945 cm^{-1}; NMR ($CDCl_3$) δ 1.5—2.3 (24 H, broad), 2.75—3.15 (3H, broad), 3.4—3.8 (3H, broad).

The authors are grateful to Dr. Yoshihisa Matsuda for ESR measurement.

References

1) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. II, ed by W. A. Benjamin, New York (1968), p. 91.

2) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, **89**, 1269 (1967).

3) P. G. Phillips, B. Revsin, E. G. Drell, and A. F. Brodie, *Arch. Biochem. Biophys.*, **139**, 59 (1970).

4) W. Dürckheimer and L. A. Cohen, *Biochemistry*, **3**, 1948 (1964).

5) R. J. Brooks, C. A. Bunton, and J. M. Hellyer, *J. Org. Chem.*, **38**, 2151 (1973), and references cited therein.

6) Th. Wieland and H. Aquila, *Chem. Ber.*, **102**, 2285 (1969).

7) C. A. Bunton and J. Hellyer, *J. Am. Chem. Soc.*, **89**, 6252 (1967).

8) V. M. Clark, M. R. Eraut, and D. W. Hutchinson, *J. Chem. Soc., C*, **1969**, 79.

9) J. W. Thanassi and L. A. Cohen, *J. Am. Chem. Soc.*, **89**, 5733 (1967); *Biochim. Biophys. Acta*, **172**, 389 (1969).

10) A. Lapidot and D. Samuel, *J. Am. Chem. Soc.*, **86**, 1886 (1964); *Biochim. Biophys. Acta*, **65**, 164 (1962).

11) C. A. Chambers and J. Q. Chambers, *J. Am. Chem. Soc.*, **88**, 2922 (1966).

12) E. P. Meier, J. Q. Chambers, C. A. Chambers, B. R. Eggins, and C.-S. Liao, *J. Electroanal. Chem.*, **33**, 409 (1971).

13) a) Suffixes **a**—**e** are used throughout this paper to denote the *p*-substituent in the benzoyl group. b) "Acyl activation" or similar terminology in this paper refers to the process in which nucleophilic displacement at the acyl carbon is facilitated as a consequence of oxidation . The process in which the O–C (alkyl) bond is cleaved, even though it mey be accelerated, is not apparent.

14) Y. Matsunaga, *J. Chem. Phys.*, **41**, 1609 (1964).

15) L. Hageman and E. McNelis, *J. Org. Chem.*, **40**, 3300 (1975).

16) C. Martius and H. Eilingsfeld, *Justus Liebigs Ann. Chem.*, **607**, 159 (1957).

17) H.-D. Becker, *J. Org. Chem.*, **30**, 982 (1965).

18) J. Q. Chambers, "The Chemistry of the Quinoid Compounds," Part 2, ed by S. Patai, John Wiley & Sons, New York (1974), pp. 737—791.

19) The formation of the carbonium ion in Reaction 5 or 6 should not be conceived literally as it stands therein. For instance, the nucleophilic attack by methanol on the duroquinone nucleus may take place on the CT complex in Reaction 6.

20) P. D. McDonald and G. A. Hamilton, "Oxidation in Organic Chemistry," Part B, ed by W. S. Trahanovsky, Academic Press, New York (1973), p. 97.

21) E. Hayon and M. Simic, *Acc. Chem. Res.*, **7**, 114 (1974).

22) "Constants of Organic Compounds," ed by M. Kotake, Asakura Publishing Co., Tokyo (1963), pp. 644—651.

23) V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. Todd, *J. Chem. Soc.*, **1961**, 715.

24) E. T. Kaiser and S. W. Weidman, *J. Am. Chem. Soc.*, **86**, 4354 (1964).

25) A. McKillop, B. P. Swann, M. J. Zelesko, and E. C. Taylor, *Angew. Chem.*, **82**, 84 (1970).

26) M. Takagi, S. Goto, R. Ishihara, and T. Matsuda, *J. Chem. Soc., Chem. Commun.*, **1976**, 993.

27) J. Rebek and F. Gavine, *J. Am. Chem. Soc.*, **97**, 3221 (1975).

28) S. W. Weidman, D. F. Mayers, D. R. Zaborsky, and E. T. Kaiser, *J. Am. Chem. Soc.*, **89**, 4555 (1967).

29) S. J. Benkovic and R. C. Hevey, *J. Am. Chem. Soc.*, **92**, 4971 (1970), and references cited therein.

30) Prof. Kaiser, who had studied the oxidation of quinol sulfate,[28] shared this view when he visited this laboratory. We thank him for these discussions.

31) a) L. I. Smith, *Org. Synth.* Coll. Vol. II, 254 (1943). b) T. H. James and A. Weissberger, *J. Am. Chem. Soc.*, **60**, 98 (1938).

32) F. Bergel, A. R. Todd, and T. S. Work, *J. Chem. Soc.*, **1938**, 253.

33) T. H. James, J. M. Snell, and A. Weissberger, *J. Am. Chem. Soc.*, **60**, 2084 (1938).