Acta Chemica Scandinavica B 33 (1979) 413—417

Oxidation by Quinones. Mechanistic Aspects of Aromatic Side-chain Acyloxylation by 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

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DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in acetic acid at reflux temperature has been shown to oxidize methylaromatic compounds, yielding benzylic acetates. The results of competition experiments of substituted toluenes support a mechanism involving hydride abstraction in the rate-controlling step.

High-potential quinones, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) are versatile oxidation reagents in organic chemistry.[1] One useful reaction type is the side-chain (α) oxidation of alkylaromatic compounds ($ArCH_3$) which normally is believed to proceed *via* hydride ion transfer from the α position to the quinone.[1a,2] Suggestions about other possible mechanisms, *e.g.* hydrogen atom abstraction or electron transfer followed by proton loss from $(ArCH_3)\cdot^+$, have been made occasionally,[1a,3] but have never been fully substantiated.

Previous work on the α acetoxylation of methylaromatic compounds has shown that other strong oxidants, such as the anode,[4] manganese(III),[5] silver(II)[6] and the sulfate radical ($SO_4^{\cdot-}$),[7] presumably react *via* an electron transfer mechanism[8] which in the terminology of electrochemistry is an ECE mechanism (eqns. 1 – 3).

$$ArCH_3 + Ox \rightleftharpoons (ArCH_3)\cdot^+ + Ox^- \quad (1)$$

$$(ArCH_3)\cdot^+ \xrightarrow{\text{Base}} ArCH_2^{\cdot} + H^+ \quad (2)$$

$$ArCH_2^{\cdot} + Ox \longrightarrow ArCH_2^+ + Ox^- \quad (3)$$

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0302-4369/79/060413-05$02.50

In view of the rather strong oxidizing power of DDQ, we were curious to see if it might oxidize methylaromatic compounds *via* an ECE mechanism too, especially since radical cations had been reported to form during quinone oxidation of aromatics in acidic media.[9] We here report that DDQ indeed reacts with alkylarenes, such as mesitylene, in refluxing acetic acid to give benzylic acetates. We also report a mechanistic study of the reaction in order to test the validity of the electron transfer mechanism in this particular case.

RESULTS

Preparative experiments. Mesitylene was reacted with DDQ under different conditions (see Table 1), the main product being 3,5-dimethylbenzyl acetate in most cases. Addition of strong acid, *e.g.* trifluoroacetic or trifluoromethanesulfonic acid (expts. 4 and 10) did not affect the yield significantly. Longer reaction periods increased the yield (expts. 6 and 7) whereas lower reaction temperatures lowered it (expts. 5 and 10). The optimum temperature appeared to be the reflux temperature of acetic acid (117 °C) since runs in refluxing propionic acid (140 °C) gave lower yields (expts. 12 and 13).

The dehydrodimer formed in expts. 4, 8 and 9 was 2,4,6,3′,5′-pentamethyldiphenylmethane, no other types of dimers, *e.g.* bimesitylene or bis-1,2-(3,5-dimethylphenyl)ethane, being detectable.

Table 1. Acyloxylation of mesitylene with DDQ under different conditions.[a]

Experiment	Additive (amount)	Yield of side-chain acyloxy products/% [b]	Other products
1	–	17	
2 [c]	–	32 [d]	
3 [e]	–	22	
4	TFA (5 ml)	23	Dehydrodimer [j] (< 1 %)
5 [f]	TFA (5 ml)	6	
6 [g]	TFA (5 ml)	41	
7 [g]	TFA (10 ml)	42	
8 [h]	TFA (10 mmol)	Low yield	Dehydrodimer [j] (< 1 %)
9 [i]	TFA (50 ml)	Low yield	Dehydrodimer [j] (< 1 %)
10 [f]	TFMA (5 ml)	7	
11	DCA (5 ml)	Several products in low yield	
12 [i]	EtCOOH (50 ml)	Trace	
13 [i]	EtCOOH (50 ml)/TFA (5 ml)	21	

[a] TFA = trifluoroacetic acid, TFMA = trifluoromethanesulfonic acid, DCA = dichloroacetic acid. Reaction conditions, unless otherwise noted: mesitylene (10 mmol), DDQ (10 mmol), glacial acetic acid (50 ml), reflux temperature, 4 h reaction period. [b] GLC yield based on consumed amount of substrate. [c] 20 mmol mesitylene. [d] Yield based on DDQ. [e] 20 mmol DDQ. [f] Reaction temperature 80 °C. [g] Reaction period 8 h. [h] In benzene (50 ml) without glacial acetic acid. [i] Without glacial acetic acid. [j] 2,4,6,3′,5′-Pentamethyldiphenylmethane.

Also other methylbenzenes could be acetoxylated in one α position in refluxing acetic acid (see Table 2). These substrates are all activated by at least two electron-donating groups. Toluene itself did not give any benzyl acetate under these conditons, whereas strongly activated compounds, *e.g. m*-toluidine and *p*-methylphenol, reacted very fast but gave no acetoxylated products. Oxidation of substrates without any α hydrogen available for substitution (anisole, benzene and chlorobenzene) did not give any detectable (GLC) products.

Competition experiments. Since toluene was unreactive against DDQ, the relative reaction rates of a number of substituted toluenes were instead determined with *p*-xylene as reference. The results are shown in Fig. 1 as a plot of log k_{rel} *vs.* the substituent constants [10] σ_m and σ_p^+ ($\varrho^+ = -4.3$, $r = 0.98$). If the same data are plotted *vs.* σ_m and σ_p the correlation is not significant ($r = 0.83$); use of the unified σ° scale developed by Sjöström and Wold [11] gave the same result ($r = 0.02$).

Isotope effects. Previous work [3,12,13] has shown that hydrogen abstractions by quinones exhibit large isotope effects. We determined the isotope effect for the DDQ α acetoxylation reaction by allowing DDQ to react with a large excess of an equimolar amount of protiated and deuterated compound. By determining the deuterium content of the benzylic acetate (MS)

Table 2. Acyloxylation of aromatic compounds with DDQ under different conditions.[a]

Experiment	Compound	Yield of side-chain acetates/% [b]
1	*p*-Xylene	44
2 [c]	*p*-Xylene	40
3	*m*-Xylene	10 [d]
4	Hexamethylbenzene	80
5 [e]	Hexamethylbenzene	84
6 [f]	Hexamethylbenzene	74
7	*p*-Methoxytoluene	80
8	*m*-Methoxytoluene	8
9	*p*-Phenoxytoluene	40
10	*p-tert*-Butyltoluene	15 [d]
11 [g]	2-Methylthiophene	25
12 [g,h]	2,5-Dimethylthiophene	28

[a] Reaction conditions, unless otherwise noted Aromatic compound (10 mmol), DDQ (10 mmol), glacial acetic acid (50 ml), reflux temperature, 4 h reaction period. [b] GLC yield based on consumed amount of the aromatic compound. [c] Reaction period 15 h. [d] GLC yield based on initial amount of aromatic compound. [e] Additive NaOAc (10 mmol). [f] Reaction temperature 80 °C, additive TFA (5 ml). [g] Small amounts of bithienylmethane were formed. [h] Isolated yield 23 %.

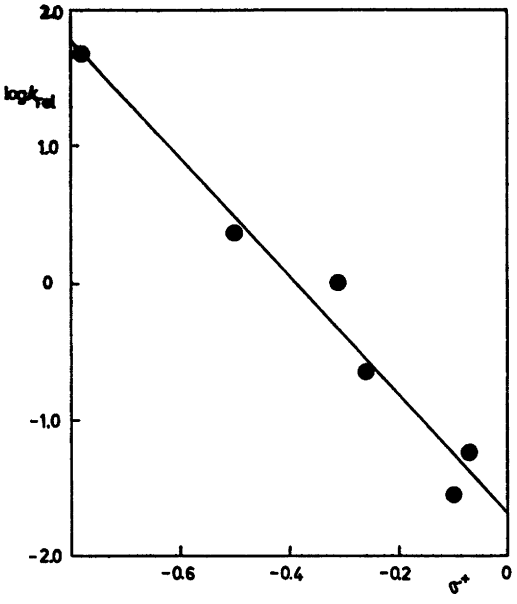

Fig. 1. Plot of log k_{rel} *vs.* substituent constant (substituent, σ^+, log k_{rel}: *p*-MeO, −0.78, 1.67; *p*-PhO, −0.5, 0.34; *m*-CH_3, −0.07, −1.24; *p*-CH_3, −0.31, 0; *p*-*t*-Bu, −0.26, −0.66; *m*-*t*-Bu, −0.1, 1.55). Values of log k_{rel} have been corrected for statistical factors.

the k_H/k_D ratio could be calculated. For *p*-methoxytoluene and *p*-xylene k_H/k_D then was determined to be 3.7 ± 0.2 and 2.5 ± 0.2, respectively.

ESR spectroscopy. ESR studies on solutions of DDQ (1 mM) and *p*-di-*t*-butylbenzene, 1,3,5-tri-*t*-butylbenzene or hexamethylbenzene (1 mM) in glacial acetic acid/trifluoroacetic acid failed to give any evidence for radical cations being produced.

DISCUSSION

The rate data correlate well with σ^+ (Fig. 1), ϱ^+ being −4.3. Table 3 compares this value with ϱ^+ values from typical cases of three other reaction types, *viz.* solvolysis, hydrogen atom transfer, and electron transfer. It is obvious that ϱ^+ for DDQ oxidation falls within the same range as those of the solvolysis reactions and that it is significantly more negative than those of the other processes. This implies high sensitivity toward strong ±M-substituents, indicative of a transition state with carbocationic character. Thus we see no reason to deviate from previous mechanistic proposals of hydride transfer being the rate-determining step (eqn. 5), preceded by fast reversible formation of a charge transfer complex (eqn. 4).

$$DDQ + H_3CAr \rightleftharpoons (DDQ \cdots\cdots H_3CAr) \quad (4)$$

$$(DDQ \cdots H_3CAr) \xrightarrow{\text{Slow}} DDQH^- + H_2\overset{+}{C}Ar \quad (5)$$

The use of acetic acid as a solvent suppresses the concentration of the quinol anion ($DDQH^-$) which otherwise is known to react with carbocations.[3]

The rather modest primary kinetic isotope effect observed can, of course, easily be accommodated within this mechanism. A comparison with other reactions involving hydride transfer to DDQ shows that the range of isotope effects is wide, from cycloheptatriene[12] (k_H/k_D 4.0) to the remarkably strong effects determined for hexamethylbenzene[14] (12) and tris(4-dimethylaminophenyl)methane (7).[3]

As a final remark, we note that the products that are normally observed in electron transfer

Table 3. Values of ϱ^+ for some side-chain reactions of substituted toluenes.

Reactions	ϱ^+	Ref.
$ArC(CH_3)_2Cl \rightarrow ArC(CH_3)_2^+ + Cl^-$	−4.5	15
$Ar(Ph)CHCl \rightarrow Ar(Ph)CH^+ + Cl^-$	−4.1	16
$ArCH_2OTs \rightarrow ArCH_2^+ + OTs^-$	−4.6[a]	16
$ArCH_3 + t\text{-}Bu^\cdot \rightarrow ArCH_2^\cdot + t\text{-}BuH$	0.99	17
$ArCH_3 + t\text{-}BuOO^\cdot \rightarrow ArCH_2^\cdot + t\text{-}BuOOH$	−0.56	18
$ArCH_3 + Br^\cdot \rightarrow ArCH_2^\cdot + HBr$	−1.38	18
$ArCH_3 + {}^\cdot CCl_3 \rightarrow ArCH_2^\cdot + HCCl_3$	−1.46	19
$ArCH_3 + {}^\cdot CH_2COOH \rightarrow ArCH_2^\cdot + CH_3COOH$	−0.63	20
$ArCH_3 + Co(III) \rightarrow ArCH_3^{\cdot+} + Co(II)$	−2.4	21
$ArCH_3 + SO_4^{\cdot-} \rightarrow ArCH_3^{\cdot+} + SO_4^{2-}$	−1.9	7

[a] Electron-donating substituents.

oxidation (anodic,[4] metal ion [6] or sulfate anion radical [7]) of alkylaromatics in addition to the benzylic substitution products were not detected in the DDQ reaction. Especially for electron transfer oxidation of mesitylene are these products (2,4,6-trimethylphenyl acetate and bimesitylene) highly characteristic.[4]

EXPERIMENTAL

Materials. All chemicals used were either purchased in the highest quality available or synthesized by known procedures. *p*-Phenoxytoluene was prepared by an Ullman-type reaction.[22] 2-Methylthiophene and 2,5-dimethylthiophene were synthesized by standard methods.[23] Perdeuterated *p*-xylene was purchased from CIBA AG, Basel, Switzerland. [α,α,α-^{2}H]-*p*-Methoxytoluene was prepared according to a literature method and had an isotopic purity of 96 %.[24] The substituted benzyl acetates were available from earlier work [4,7] or isolated from reaction mixtures.

Small-scale acyloxylation procedure. A mixture of the aromatic compound, DDQ and additive in glacial acid was stirred for different periods and at different temperatures. The mixture was worked up by addition of saturated sodium hydrogen carbonate solution followed by ether extraction. The competition experiments were carried out in the following way: 5 mmol of each substrate was heated at reflux temperature (117 °C) in a solution of glacial acetic acid (50 ml) with DDQ (1 mmol) for 1 h. The work-up procedure was the same as above.

Preparative scale acetoxylation procedure. A solution of 9.2 g (50 mmol) of *p*-phenoxytoluene and 12 g (50 mmol) of DDQ in glacial acetic acid (250 ml) was refluxed for 4 h. The reaction mixture was worked up by addition of water (250 ml) and extraction by dichloromethane (250 ml). The water/acetic acid layer was extracted with two additional 50 ml portions of dichloromethane. The combined extracts were washed with water and sodium hydrogen carbonate solution, and finally dried with magnesium sulfate. After filtration and evaporation, the residue was subjected to column chromatography on silica gel. The starting material was eluted with carbon tetrachloride. To isolate *p*-phenoxybenzyl acetate a mixture of carbon tetrachloride – chloroform (3:1) was used. Acetoxylation of 2-methylthiophene and 2,5-dimethylthiophene and isolation of the corresponding thenyl acetates were carried out under the same conditions. All products from preparative scale acetoxylations were identified by ^{1}H NMR spectroscopy and mass spectroscopy. *p*-Phenoxybenzyl acetate: ($CDCl_3$) δ 2.1 [3 H, s, $OCOCH_3$], 5.0 [2H, s, CH_2], 7.2 [9H, m, aromatic protons]. 2-Thenyl acetate: (CCl_4) δ 2.1 [3H, s, $OCOCH_3$], 5.2 [2H, s, CH_2], 7.1 [3H, m, aromatic protons]. 5-Methyl-2-thenyl acetate: (CCl_4) δ 2.1 [3H, s, $OCOCH_3$], 2.5 [3H, s, CH_3], 5.2 [2H, s, CH_2], 6.7 [2H, m, aromatic protons].

Analysis. Yields and isomer distributions were determined using a Varian 1400 gas chromatograph, equipped with an electronic integrator (Hewlett-Packard 3380 A) on a 2 m × 3 mm 5 % NPGS on Chromosorb W column. The yield was determined using an internal standard calibrated against authentic samples. The identification of products was based on GLC/MS comparison (LKB 9000 system) with authentic samples. NMR spectra were recorded on a Varian A 60 spectrometer. The ESR measurements were recorded on a Varian E-3 spectrometer.

Acknowledgements. This work was supported by grants from the Swedish Natural Science Research Council and the Royal Physiographic Society of Lund. We thank Dr. J. W. Verhoeven, University of Amsterdam, The Netherlands, for giving us access to unpublished material, and Mrs. Kerstin Pettersson for the preparation of methylthiophenes.

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Received February 20, 1979.