Gibbs Reaction. Part 1. Reduction of Benzoquinone *N*-Chloroimines to Benzoquinone Imines

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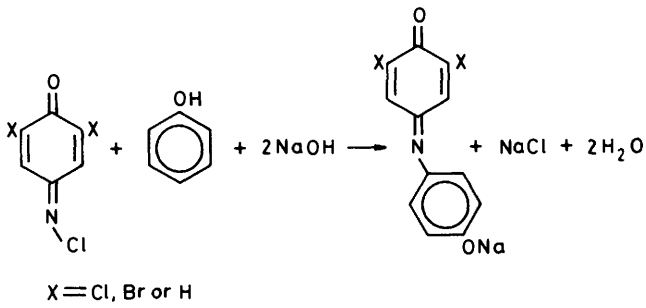
The behaviour of benzoquinone *N*-chloroimines under neutral, acidic, and basic conditions has been studied. Although these compounds are stable under neutral conditions they are hydrolysed in acidic solution to the corresponding benzoquinone derivatives. In the presence of base and alcohols, they are reduced to benzoquinone imines. Kinetic investigation of the reaction suggested an ionic mechanism, in which cleavage of the C_{α}–H bond of the alcohol is the rate-determining step.

Since the introduction of the Gibbs phenol assay method[1,2] several authors have tried to establish the mechanism of the reaction.

In his original paper Gibbs reported the reactions of 2,6-dibromobenzoquinone *N*-chloroimine and 2,6-dichlorobenzoquinone *N*-chloroimine (TQI) with equivalent amounts of phenols unsubstituted in the *para*-position (Scheme 1). As direct electrophilic substitution by TQI on the aromatic nucleus was considered by Gibbs and later authors as highly improbable, several alternative explanations of the reaction were considered. Gibbs proposed a rearrangement *via* an oxime ether, while Ziegler and Gartler,[3] for the reaction with benzoquinone *N*-chloroimine, suggested an electrophilic attack by the benzoquinone iminium cation. Svobodova *et al.*,[4,5] on the other hand, assumed that in alkaline medium TQI was hydrolysed to 2,6-dichlorobenzoquinone imine (DQI) and hypochlorite, and that this DQI, which was substantially more active than TQI, reacted with the phenolic partner as studied in detail by Corbett.[6,7] In contrast to Gibbs, these authors found that one mole of phenol reacted with two moles of the reagent, in good agreement with the reaction of DQI. These contradictory results prompted us to reinvestigate the Gibbs reaction and the transformations of TQI systematically.



Scheme 1.

Results

Behaviour of TQI in Aqueous Solution.—In neutral aqueous solution protected from light, TQI is stable; its u.v. spectrum shows absorptions at 303 and 312 nm.[4] When stored in acidic solution (pH < 2) the u.v. spectrum indicates decompositions, characterized by an isosbestic point (Figure 1), yielding 2,6-dichlorobenzoquinone as the end product. This finding contradicts the results of Harfoush *et al.*,[8] who attributed this change erroneously to simple protonation. However, the spectrum of TQI does not change with pH (7 > pH > 0); only the decomposition rate changes.

In alkaline aqueous solution TQI undergoes rapid decomposition. The decomposition rate generally increases with increasing pH (in 10^{-1}M-NaOH the decomposition is instantaneous; in 10^{-3}M-NaOH $t_{\frac{1}{2}}$ is about 2 min), but depends also on the type of buffer applied (at pH 9.2 in 2×10^{-3} mol dm^{-3} $Na_2B_4O_7$ buffer $t_{\frac{1}{2}}$ is 100 min; in 2×10^{-3} mol dm^{-3} NH_4OH–NH_4Cl buffer at the same pH, $t_{\frac{1}{2}}$ is 50 min). The first step of the decomposition results in an isosbestic point in the u.v. spectrum, and the product undergoes further decomposition (Figure 2). Although the $\lambda_{max.}$ value of the product formed during the first step of the decomposition is identical with that of DQI,[4] the product is not DQI, as the various other characteristics of the spectrum (molar extinction coefficient, position of the minimum, etc.) are not identical;[6] further the product does not give a positive indophenol reaction with phenols. It seems probable that this decomposition is analogous to that reported for benzoquinone imines,[9] namely a hydrolysis to 2,6-

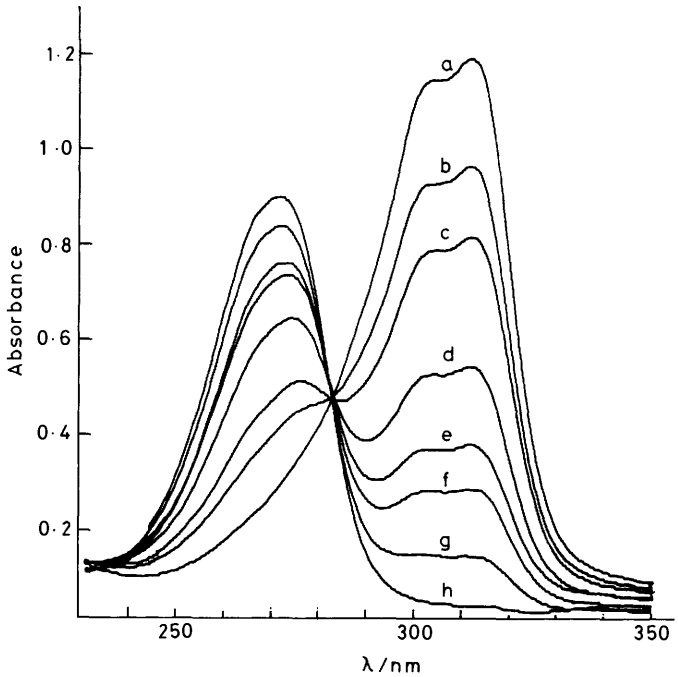


Figure 1. The spectrophotometric course of the decomposition of TQI (6.2×10^{-5}M) in 2M-HCl (reaction times a—h: 2, 20, 40, 80, 105, 135, 160, 185 min)

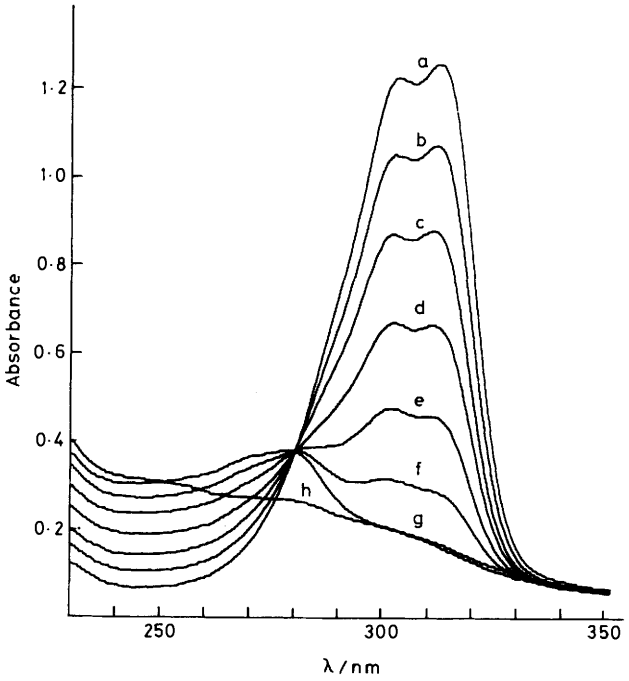


Figure 2. The spectrophotometric course of the decomposition of TQI (6.2×10^{-5}M) in $Na_2B_4O_7$ buffer solution at pH 9.2 (reaction times a—h: 5, 35, 65, 95, 130, 175, 210, 300 min)

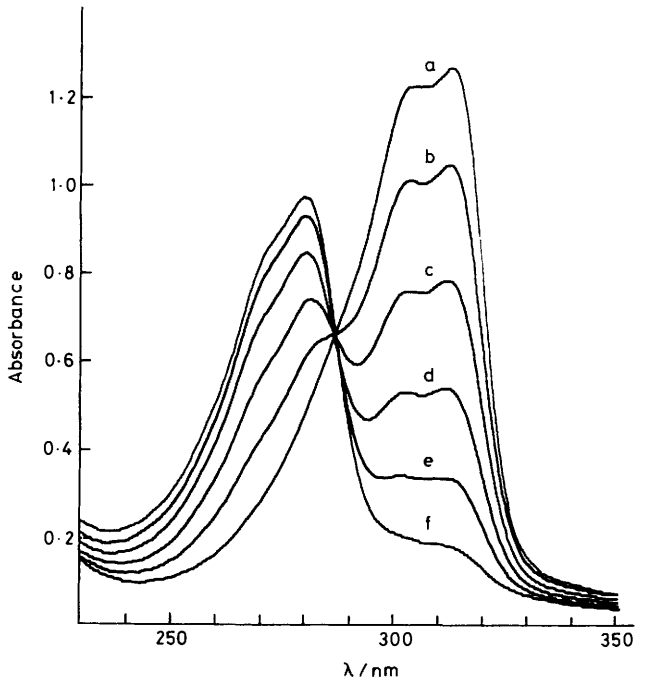


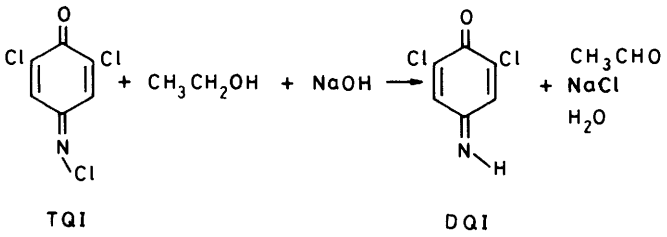
Figure 3. The spectrophotometric course of the reduction of TQI (6.2×10^{-5}M) in $Na_2B_4O_7$ solution containing 2% ethanol (reaction times a—f: 2, 6, 10, 14, 18, 22 min)

dichlorobenzoquinone, which undergoes further rapid decomposition in alkaline medium.

Behaviour of TQI in Aqueous Alcoholic Solutions.—During the study of the Gibbs reaction it was found that the rate of the reaction leading to an indophenol may be increased substantially by addition of sufficient amounts of a primary or a secondary alcohol. To elucidate the role of the alcohol in the reaction, the behaviour of TQI was studied in alkaline aqueous solutions in the presence of ethanol. The u.v. spectra (Figure 3) showed that TQI was reduced to DQI (Scheme 2).

As both the spectrum and the higher reactivity of DQI are well known,[1,6] the TQI ⟶ DQI transformation seemed to afford a satisfactory explanation for the aforementioned phenomenon. As the reduction process requires the presence of an alcohol, it is evident that the alcohol itself is the reducing agent in the redox reaction. When the reaction was performed in the presence of benzyl alcohol, the formation of an equimolar amount of benzaldehyde could be detected by u.v. spectrophotometry and by t.l.c. Experiments were carried out to discover whether the alcohol was oxidized by TQI directly, or whether hydrolysis (assumed by Svobodova *et al.*[5]) occurred and was rendered irreversible by reaction of the hypochlorite formed with ethanol (the solution used by Svobodova contained ethanol). It was found that the presence of an equimolar amount or an excess of hypochlorite had no influence on the reaction rate, and furthermore that hypochlorite (in the absence of TQI but in equivalent amount) scarcely oxidized benzyl alcohol under identical conditions. Hence the possibility of an indirect oxidation could definitely be ruled out.

Kinetics of the Redox Process.—By performing the reaction in anhydrous ethanol, and using base (butylamine) and TQI in about equimolar amounts, it was found that the reaction was of the second order (first order in each reactant) (Table 1), *i.e.* $v = k_a[TQI][:B]$. The kinetic partial order of the alcohol was determined in aqueous solution in the presence of an amine as



Scheme 2.

base according to the method usually applied in solvolytic reactions (Figure 4), as the alcohols always had to be used in large excess (1.5×10^2 to 5.5×10^4 mol equiv. depending on their oxidizability), to suppress side reactions (hydrolysis and aminolysis of TQI and DQI) (Table 2).

Figure 4 shows that in the equation the alcohol concentration participates as a first-order component. Thus the complete equation is $v = k[TQI][:B][Alc]$. The kinetic isotope effect was determined to elucidate whether during the oxidation of the alcohol the C_α–H bond is cleaved in the rate-determining step. By carrying out the reaction in aqueous CD_3CD_2OH and $(CH_3)_2CDOH$, k_H/k_D values of 4.6 and 5.6 were obtained, respectively.

The thermodynamic parameters of the reactions were determined in anhydrous ethanol by using three amines as bases (Table 3). The data demonstrate that the more bulky bases (of equal basicity; basicities were compared according to a literature method[10]) result in higher activation energies and hence lower reaction rates.

Redox Behaviour in Low Polarity Medium.—When the reaction was performed in both polar and apolar aprotic organic solvents, under conditions similar to those applied in the aqueous reaction (same amounts of alcohol and base), the reaction rate was substantially lower than that observed under

Table 1. Temperature dependence of the second-order rate constants for the transformation of TQI (1.188×10^{-4} mol dm^{-3}) into DQI in absolute ethanol in the presence of various amines

	Butylamine		Dibutylamine		Tributylamine	
T/K	k/dm^3 mol^{-1} s^{-1}	δ	k/dm^3 mol^{-1} s^{-1}	δ	k/dm^3 mol^{-1} s^{-1}	δ
299.5	6.18	0.25	2.65	0.16	0.315	0.019
308.0	9.53	0.39	4.63	0.24	0.650	0.039
312.0	11.07	0.45	5.50	0.25	0.890	0.040
316.5	12.51	0.62	6.60	0.22	1.100	0.040
326.5	18.41	0.89	10.30	0.52	1.850	0.098

Table 2. Pseudo-first-order rate constants for the reduction of TQI (6.18×10^{-5} mol dm^{-3}) with various alcohols in $Na_2B_4O_7$ buffer (pH 9.2) at 300 K

	[Alc.]/mol dm^{-3}	10^{-4} k/s^{-1}
Ethanol	0.343	8.25
Propan-2-ol	0.343	38.5
2,2,2-Trifluoroethanol	3.47	1.44
Benzyl alcohol	0.0175	19.3
2-Chloroethanol	3.47	3.85

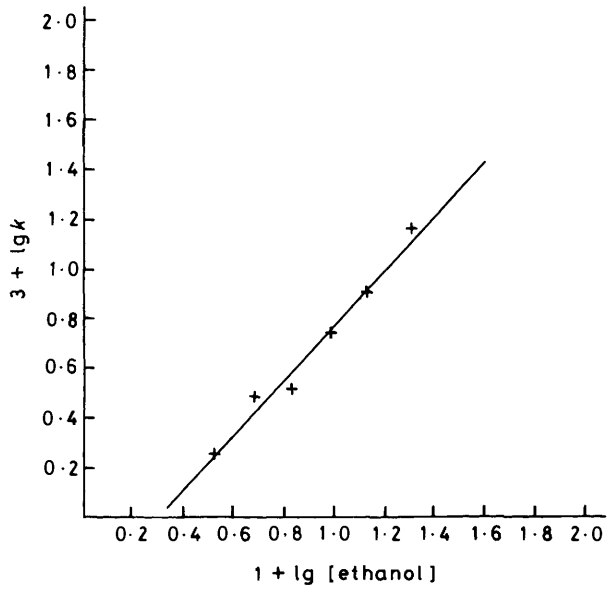


Figure 4. Plot of lg c *vs.* lg k for the determination of the kinetic order of the alcohol

protic conditions. The rate increased with increasing polarity of the solvent [in 8:2 acetonitrile–ethanol, in the presence of butylamine at 308 K, $k = 0.75$ mol^{-1} dm^3 s^{-1}, $\Delta S^{\ddagger} = 92$ J mol^{-1} K^{-1}, $\Delta H^{\ddagger} = 49$ kJ mol^{-1}; in 5:3:2 chloroform–acetonitrile ethanol $k = 0.48$ mol^{-1} dm^3 s^{-1}, $\Delta S^{\ddagger} = -148$ J mol^{-1} K^{-1}, $\Delta H^{\ddagger} = 31$ kJ mol^{-1}; use of $(CH_3)_2CDOH$, CD_3CD_3OH, and (CH_3) CHOD in chloroform solution gave $k_H/k_D = 1.75$, 1.60, and 1.0, respectively]. Crown ethers affect the reaction rate by solvating the amine hydrochlorides formed. The extent of this influence depends on both the size of the cavity and the size of the amine (Table 4).

Without amine as base and without alcohol, solid sodium ethoxide, dissolved in an aprotic solvent with 15-crown-5, affords DQI at a measurable reaction rate [in $CHCl_3$, in the presence of a 25 molar excess of sodium ethoxide (2.97 mmol dm^{-3}), $t_{\frac{1}{2}} = 31$ min; in acetonitrile, in the presence of an 8 molar excess of sodium ethoxide (0.95 mmol dm^{-3}), $t_{\frac{1}{2}} = 3$ min]. In an analogous experiment, when an amine base was added to the reaction as well as sodium ethoxide, the reaction rate was increased, revealing that the base does not accelerate the reaction by promoting dissociation of the alcohol. In the foregoing solvents the reaction rate was increased by the bases in the order tributylamine > dibutylamine > butylamine (the reverse order to that observed in protic solvents must be due to the fact that in aprotic solvents the basicities change in a similar order;[10] this is why the increase in bulk of the bases did not result in further change).

Use of Other Reducing Agents.—TQI may be reduced by other reducing agents, and also by electrochemical methods.[11] In alkaline medium 4-amino-2,6-dichlorophenol reacts with an equimolar amount of TQI instantaneously to afford two moles of DQI.[12] More vigorous reducing agents (*e.g.* ascorbic acid, phenylhydrazine, hydroquinone, α-tocopherol) in a two-fold molar excess reduce TQI to 4-amino-2,6-dichlorophenol. When only one equivalent of the reducing agent was used, only 0.5 mol equiv. of TQI was reduced to 4-amino-2,6-dichlorophenol, which reacted immediately with the excess of TQI to give 1 mol equiv. of DQI. In acidic medium this reaction was slower; hence the simultaneous presence of TQI and the aminophenol could be detected when the reduction was carried out with ascorbic acid at pH 4 (when the solution was made alkaline, DQI was formed immediately).

Other Benzoquinone N-*Chloroimines.*—The transformations described for TQI were generally the same for other derivatives, too, though substantial differences were found in reactivities (TQI ~ 2,6-dibromobenzoquinone *N*-chloroimine ≫ benzoquinone *N*-chloroimine > benzoquinone bis-*N*-chloroimine.)* The change in reactivity was in good agreement with the polarographic half-wave potentials (in the above order: −0.15, −0.16, −0.27, and −0.34 V).

Discussion

The benzoquinone *N*-chloroimines are sparingly soluble in water. To expedite their dissolution, organic solvents, mainly aliphatic alcohols (ethanol, propan-2-ol) have been applied by several authors.[4,13–34] Unfortunately they failed to consider the possibility of reduction of the benzoquinone *N*-chloroimines by these alcohols. Since the resulting benzoquinone imines exhibit a different reactivity and stoicheiometry in reactions with phenols, the published results should be revised according to whether the formation of benzoquinone imines as intermediates can definitely be ruled out.

In contrast with the results of Harfoush *et al.*,[8] we found that the spectrum of TQI, measured in ethanol, was almost identical ($\Delta\lambda_{max.}$ 2 nm) with that recorded in an apolar, aprotic medium (CCl_4, $CHCl_3$) [the spectrum remains unchanged even in the

* Reduced to benzoquinone di-imine.

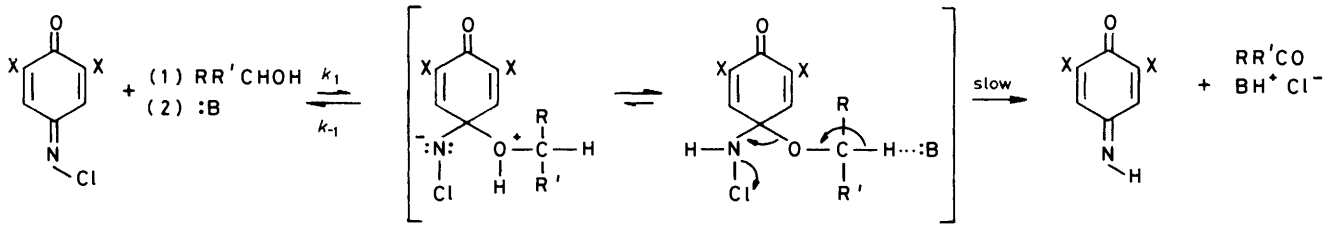
Table 3. Activation parameters for the reduction of TQI in absolute ethanol

Base	k^a/mol^{-1} dm^3 s^{-1}	$\Delta H^{\ddagger b}$/kJ mol^{-1}	$\Delta S^{\ddagger c}$/J mol^{-1} K^{-1}	$\Delta G^{\ddagger}$/kJ mol^{-1}
Butylamine	9.53	30	−130	70
Dibutylamine	4.63	39	−107	72
Tributylamine	0.67	50	−86	77

[a] At 308 K. [b] Estimated error ±2 kJ mol^{-1}. [c] Estimated error ±8 J mol^{-1} K^{-1}.

Table 4. Ratios of rate constants measured with and without crown ethers in $CHCl_3$–ethanol (8:2) (TQI concn. 1.188 × 10^{-4} mol dm^{-3})

Crown ether	10^{-4} [crown ether]/ mol dm^{-3}	Butylamine	Dibutylamine	Tributylamine
18-Crown-6	1.188	5.3	1.3	1.0
	11.88	15.8	1.7	1.2
Dicyclohexyl-18-crown-8	1.188	6.1	1.8	1.0
	11.88	17.0	3.4	1.5
Dibenzo-24-crown-8	5.94	2.1	1.2	2.4
15-Crown-4	1.188	1.0	1.0	1.0
	11.88	1.6	1.0	1.0
12-Crown-4	11.88	1.0	1.0	1.0



(I)

R, R' = H, alkyl or aryl
:B = OH^- or amine base

Scheme 3.

mixtures (chloroform–ethanol or carbon tetrachloride–ethanol) used by Harfoush]. The u.v. spectrum published by these authors is in fact the spectrum of a mixture of DQI and TQI; consequently their suggestion of the formation of a molecular complex is not justified under the given experimental conditions, and TQI is reduced to DQI instead. Gibbs[1] as well as Scudi[35] presumed that during alkaline hydrolysis of TQI 2,6-dichlorobenzoquinone oxime was formed. Reproducing the process of Ramart-Lucas and Martynoff,[36] we prepared 2,6-dichlorobenzoquinone oxime, which proved to be stable under the conditions of the alkaline decomposition of TQI. As no oxime was detected during the decomposition of TQI (Figure 1), the nucleophilic attack by the hydroxide ion was presumably directed towards C-4 and not towards the N atom, as in the reaction of CN^- ions with TQI,[37] and the decomposition presumably proceeded through 2,6-dichlorobenzoquinone, analogously to the decomposition of DQI.[9]

Mechanism.—The rate equation, the considerable negative activation entropy, and the solvent dependence of the reaction rate suggest that the reaction is of ionic character, and that in the rate-determining step a trimolecular transition state is formed with the participation of TQI, the base, and the alcohol. It can be assumed that in the first step of the reaction a nucleophilic attack is initiated by the O atom of the alcohol on the C=N–Cl system of TQI in a equilibrium reaction (Scheme 3).

The behaviour of TQI with other nucleophiles (CN^- addition, hydrolysis) suggests that the attack is directed towards the C atom of the same bond system. This hypothesis is supported by electron-density calculations, according to which C-4 is the most positive atom in this system (see Experimental section). As suggested by the isotope effect observed, and by the increase in reaction rate brought about by crown ethers, which can easily solvate ammonium ions, in the rate-determining step the C_α-hydrogen atom of the alcohol is abstracted by the base as a proton, following transfer of the proton of the oxonium ion to the nitrogen atom. It might also be presumed that the base could either form alkoxide with the alcohol in a pre-equilibrium step, or that the base would split off the alcoholic hydrogen from the transition state (I) in a rapid reaction before the rate-determining step. These possibilities can, however, be excluded, because in these cases the base concentration would be a second-order component in the kinetic equation; furthermore it was also observed that the reaction rate is increased by the amine base even if the reaction partner is RO^- instead of ROH.

When these possibilities are ruled out, the mechanism shown in Scheme 3 can be described by equation (1), which has been confirmed experimentally.

$$d[DQI]/dt = Kk_2[TQI][Alc][:B], \text{ where } K = k_1/k_{-1} \quad (1)$$

It has often been discussed[38–40] whether, in the ionic

oxidation of alcohols, the C_α-hydrogen atom leaves in the form of H^+ or H^-. In our opinion in the transition state (I) the C_α–H is abstracted by the base in the form of a proton. If in the transition state a hydride shift from C_α occurred towards the chloronium ion cleaved from N–Cl, or towards the nitrogen bearing an electron sextet, following loss of the Cl^- ion, the base would not be involved in the rate-determining step; *cf.* the foregoing deductions concerning alkoxides.

It is remarkable that the present reaction terminates at DQI, despite the fact the DQI is more readily reduced than TQI. This may be due to the fact that this reversible reduction cannot take place if the redox potential of the 'reducing' agent is more positive than the potential of the DQI–4-amino-2,6-dichlorophenol redox system, but the TQI ⟶ DQI reduction can proceed because of the irreversibility of this reaction itself. This presumption was confirmed by the experimental finding that in $Na_2B_4O_7$ buffer at pH 9.2 the *p*-benzoquinone–*p*-hydroquinone system ($E_{\frac{1}{2}}$ −0.02 V) did not reduce *p*-benzoquinone imine to *p*-aminophenol ($E_{\frac{1}{2}}$ −0.07 V), but did reduce benzoquinone *N*-chloroimine to benzoquinone imine.

Experimental

Materials.—TQI and 2,6-dibromobenzoquinone *N*-chloroimine were commercial products (Merck); the crown ethers were purchased from Fluka. The alcohols used were of spectroscopic grade (Merck, Uvasol) or analytical grade (Reanal, Hungary). CD_3CD_2OD was a Merck (Uvasol) product, 98% deuteriated; $(CH_3)_2CHOD$ and $(CH_3)_2CDOH$ were prepared from acetone with $LiAlH_4$–D_2O or $LiAlD_4$–H_2O, respectively. Their purity was checked by ^1H n.m.r. spectroscopy. Benzoquinone *N*-chloroimine and benzoquinone bis-(*N*-chloroimine) were prepared by known methods.[41] Benzoquinone *N*-chloroimine showed δ_H (90 MHz; $CDCl_3$) 6.50 and 6.60 (2 × 1 H, 2 × dd, *J* 11 and 2 Hz, 2- and 6-H), and 7.23 and 7.73 (2 × 1 H, 2 × dd, *J* 11 and 3 Hz, 3- and 5-H); δ_C (25.2 MHz; $CDCl_3$) 186.5 (C-1), 167.3 (C-4), 137.5 and 134.7 (C-3 and C-5), and 130.9 and 127.2 (C-2 and C-6). Benzoquinone bis-(*N*-chloromine) showed δ_H 7.03 (2 H, dd, *J* 11 and 3 Hz) and 7.40 (2 H, dd); δ_C 167.4 (C-1 and C-4), and 135.2 and 122.0 (C-2, -3, -5, and -6).

4-Amino-2,6-dichlorophenol.—A solution of ascorbic acid (3.70 g, 21 mmol) in water (25 ml) was poured into a solution of TQI (2.00 g, 9.5 mmol) in acetone (25 ml). The solution was stirred for 5 min at room temperature, then was extracted with chloroform (2 × 25 ml). The pH of the aqueous layer was adjusted to 6—7 with saturated $NaHCO_3$ (with cooling in ice), and the white precipitate was filtered off and washed with water (under protection from light), then dried (P_2O_5); yield 1.16 g (68%); $\lambda_{max.}$ (96% ethanol) 239 (lg ε 3.820) and 312 nm (3.500); $\lambda_{max.}$ (10^{-2}M-NaOH; N_2 atm.) 244 (lg ε 3.862) and 324 nm (3.630); $\lambda_{max.}$ (10^{-1}M-HCl) 279 and 285 nm (lg ε 3.345); δ_H [90 MHz; $(CD_3)_2SO$; DSS standard] 3.3—5.8 (3 H, exchangeable) and 6.6 (2 H s); δ_C [25.2 MHz; $(CD_3)_2SO$; DSS standard] 144.7 (C-1 or C-4), 141.1 (C-4 or C-1), 125.4 (C-2 and C-6), and 115.8 (C-3 and C-5).

Detection of Benzaldehyde.—(*a*) *Thin-layer chromatography.* TQI (20 mg, 0.0952 mmol) was dissolved in benzyl alcohol (3.50 ml, 34 mmol), then distilled water (60—70 ml) and diethylamine (4.90 ml from 4 × 10^{-2} mol dm^{-3} aqueous solution; in portions) were added within 2 min. The solution was made up with distilled water to 100.0 ml and the mixture was extracted with diethyl ether (30 ml) after 2 min. The extract (0.05 ml) was immediately spotted on the plate [Kieselgel F_{254} (Merck); solvent chloroform; spots located with 2,4-dinitrophenylhydrazine and u.v. light at 254 nm (R_F 0.82)].

(*b*) *U.v. spectrophotometry.* A 2.376 mmol dm^{-3} solution of TQI in acetonitrile (0.62 ml) was pipetted into a volumetric flask; water (5.00 ml), a solution of benzyl alcohol (0.9711 mol dm^{-3}) in acetonitrile (0.50 ml), and finally a solution of diethylamine (11.88 mmol dm^{-3}) in water (0.50 ml) were added, and the mixture was immediately made up to 25.00 ml with acetonitrile. The solution was studied by spectrophotometry in 0.5 cm cuvettes, and the results were plotted as a function of time. The reference solution contained the same amount of benzyl alcohol. The TQI ⟶ DQI conversion was quantitative in 35—40 min at room temperature, $\lambda_{max.}$ benzaldehyde 246 nm, $\lambda_{max.}$ DQI 278 nm (shoulder at 267 nm).

Kinetics.—The kinetic and stability measurements were performed with a 0.1188 mmol dm^{-3} solution of TQI in a suitable solvent or solvent mixture. TQI consumption was monitored by u.v. spectrophotometry in a Unicam SP8-100 apparatus, at 313 nm.

Polarographic measurements were carried out with a PAR 174/A Polarographic Analyzer (glassy carbon PT and SCE electrodes) with a 1.224 × 10^{-4} mol dm^{-3} solution of the test compound in water buffered with $Na_2B_4O_7$ at d.c. operation.

Net Electron Densities (CNDO/2 Method).—TQI: C-1 0.2209, C-2 0.0813, C-3 −0.0320, C-4 0.1345, C-5 −0.0261, C-6 0.0835, N −0.0437, (N)–Cl −0.1153, C(3)H 0.0531, C(5)H 0.0412, C(2)Cl −0.0995, C(6)Cl −0.0959, C(1)O −0.2021.

Benzoquinone *N*-chloroimine: C-1 0.2412, C-2 −0.0421, C-3 −0.0011, C-4 0.1231, C-5 0.0047, C-6 −0.0391, N −0.0432, (N)–Cl −0.1273, C(3)H 0.0352, C(5)H 0.0222, C(2)H −0.0421, C(6)H −0.0391, C(1)O −0.2358.

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