Solvolytic Elimination and Hydrolysis promoted by an Aromatic Hydroxy Group. Part 1. The Reaction of 2,6-Dibromo-4-dibromomethylphenol and of 2,6-Dibromo-4-bromomethylenecyclohexa-2,5-dienone with Water in 95% 1,4-Dioxane

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The reaction of 2,6-dibromo-4-dibromomethylphenol with water to give the quinone methide, 2,6-dibromo-4-bromomethylenecyclohexa-2,5-dienone, together with 2,6-dibromo-4-hydroxybenzaldehyde has been studied in 95% 1,4-dioxane. U.v. spectroscopy has been used to study the kinetic form of the reaction. At very low acidities, rapid conversion into the quinone methide occurs through the aryl oxide ion, and is followed by addition and replacement to give the aldehyde. At acidities greater than 10^{-3}M, reaction of the un-ionised phenol is dominant and follows a conventional S_N1 pathway through a mesomeric carbocationic intermediate. Subsequent loss of a proton from this intermediate to give the quinone methide is competitive with its capture by the solvent (to give in several steps the related aldehyde) and by bromide ion (to give starting material). The mass-law constant for capture of the carbocation by bromide ion is very large (*ca.* 10^4 in this solvent), so that relatively small concentrations of hydrogen bromide convert the quinone methide back into the dibromomethylphenol by 1,6-addition. Solvent kinetic isotope effects on the individual reaction stages are reported. The rate of solvolysis of the phenol is much greater than would be predicted by the use of conventional linear free-energy parameters.

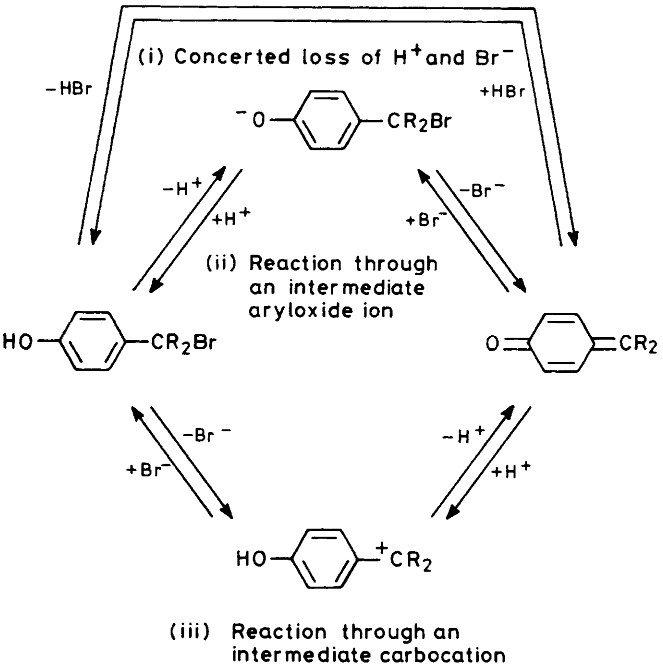
By comparison with the solvolyses of derivatives of benzyl halides, the reactions of the dihalogenomethylbenzenes with nucleophiles have been studied mechanistically rather little. Analogy with the reactions of dibromomethane and of diphenylmethyl bromide[1] suggest that their bimolecular reactions would be slow, in part because of steric hindrance. Their unimolecular reactions, however, would be likely to be readily accessible. Olivier and Weber[2] examined the reactions of several derivatives of dichloromethylbenzene with water in 50% acetone at 60 °C. The sequence of relative rates, *viz.* $C_6H_5{\cdot}CHCl_2 = 1$, $4\text{-}Cl{\cdot}C_6H_4{\cdot}CHCl_2 = 0.409$, $3\text{-}Cl{\cdot}C_6H_4{\cdot}CHCl_2 = 0.0115$, shows that the inductive effect of the chlorine substituent in the *meta*-position is reduced considerably when in the *para*-position. This pattern of substituent effects indicates that the reaction is a unimolecular rather than a bimolecular solvolysis, as was confirmed by showing that the rate was not accelerated by the presence of hydroxide ions. Kohnstam and his co-workers[3] reached the same conclusion; enhancement of the rate of solvolysis by a 4-methyl group by a factor of 79 for reaction at 25 °C indicated that the reaction has a high negative ρ-value. Hine and Rosscup[4] recorded a solvolytic rate for 4-dichloromethylanisole at 30 °C in the much less aqueous solvent 83.3% acetone, thus confirming the importance of conjugative electron release on the rate of these solvolyses. Quemeneur *et al.*[5,6] examined the reactions of both dichloromethylbenzenes and dibromomethylbenzenes in several mixtures of acetone and water; a large enhancement of rate by a 4-methyl group was found for the latter as for the former series. Their results show also that the reaction responds very markedly in rate to change in ionising power of the solvent, in the direction expected for a unimolecular ionisation of a neutral molecule. These authors noted also that the presence of strongly electron-withdrawing substituents was conducive to the incursion of a bimolecular component in the reaction.

In all of these cases, it can be presumed that the sequence of steps following the initial ionisation would be fast, and that the final product would be the aldehyde. Sequence equation (1) depicts what would be expected for the case of a dibromomethylbenzene. Mass-law effects established for some of these reactions[3,4] show that these carbocations are attacked by halide ions at rates which are competitive with their capture by solvent. Such ionic recombinations are known to be activated processes.[7]

$$Ar{\cdot}CHBr_2 \xrightleftharpoons[+Br^-]{-Br^-} Ar{\cdot}CHBr^+ \xrightarrow{+H_2O} Ar{\cdot}CH(Br){\cdot}OH_2^+ \xrightarrow{-H^+} Ar{\cdot}CH(Br){\cdot}OH \xrightarrow{-Br^-} Ar{\cdot}CH(OH)^+ \xrightarrow{-H^+} Ar{\cdot}CHO \quad (1)$$

New situations arise when the substituent in the 4-position is a hydroxy group. Under these conditions, 1,6-elimination can compete with solvolytic replacement and give a quinone methide. Three possible pathways are shown in Scheme 1.

Quinone methides are in general quite reactive compounds, and few have been fully characterised. Filar and Winstein[8] reported that many 4-hydroxybenzyl bromides can solvolyse in dilute solution to give such compounds. Lindemann[9] described the preparation of 2,6-dibromo-4-bromomethylenecyclohexa-2,5-dienone by the treatment of 2,6-dibromo-4-dibromomethylphenol in ether with aqueous sodium acetate, the success of this preparation depending apparently on the insolubility of the product. There seem to have been no mechanistic investigations, however, designed to establish which of the three pathways shown in Scheme 1 is taken in any particular case. If either pathway (ii) or pathway (iii) were adopted, then comparison of the rates with those of related reactions of compounds bearing other substituents would throw light on the electron-releasing power of the hydroxy and oxide-ion substituents. Our theoretical interest in these properties,[10,11] followed by the finding[12] that 2-bromo-4-dibromomethylphenol is exceptionally reactive in moist air, giving the corresponding aldehyde, has led us first to a detailed examination of the mechanisms of solvolysis of 2,6-dibromo-4-dibromomethylphenol. A preliminary report of some of the results has been given.[13]



Scheme 1. Possible reaction pathways in the formation of quinone methides from substituted 4-hydroxybenzyl bromides

Experimental

(a) *Materials and Methods.*—Proton nuclear magnetic resonance (^1H n.m.r.) spectra were recorded by using either a Varian T60 or a JEOL FX60 spectrometer, the solvent being CCl_4 or $CDCl_3$, with tetramethylsilane (Me_4Si) as internal reference; they are expressed as p.p.m. downfield shift from Me_4Si, and quoted as position, multiplicity, relative integration, and assignment. Infrared (i.r.) spectra were recorded by use of a Perkin-Elmer 397 spectrophotometer. For measurements of ultraviolet (u.v.) spectra, and for kinetic experiments, a Varian DMS90 spectrophotometer in conjunction with a Hewlett-Packard 7015B *x-y* recorder was used. Matched quartz spectral cells of volume *ca.* 2.5 ml, with Teflon stoppers, held at constant temperature by water circulated through were jackets surrounding the cells.

1,4-Dioxane (1 500 cm^3) for kinetic measurements was heated under reflux over $NaBH_4$ (8 g) for 24 h and then fractionally distilled by using a Vigreux column with a reflux still-head. The first *ca.* 100 cm^3 of distillate, collected slowly, was discarded. When the b.p. had risen to a constant value, *ca.* 101 °C, a fraction (*ca.* 1 200 cm^3) was collected more rapidly over a b.p. range of *ca.* 0.1 °C. This fraction was heated under reflux for 12 h over molten sodium (*ca.* 8 g), moisture being excluded. Portions of this purified dry solvent were fractionally distilled before use as required, and typically had b.p. 101.0—101.1 °C. Such material had negligible absorbance at wavelengths greater than 230 nm.

Bromine was purified by refluxing it with solid KBr for 4 h. It was then distilled, redistilled from P_2O_5, and stored in a dark bottle; b.p. 58 °C. Perchloric acid (AnalaR, 70% w/w) was used without further purification. It was standardized against sodium hydroxide solutions, themselves standardized against AnalaR potassium hydrogen phthalate. Lithium perchlorate was recrystallized twice from water to give the trihydrate, which was filtered off and dried in a desiccator containing silica gel. Lithium bromide was recrystallized (H_2O) and dried *in vacuo* at 100 °C; solutions were standardized by Volhard's method. Deuterium oxide (Baker) contained 99.75% atoms % D, and was used without further purification.

When a solvent is described as *X*% dioxane, a mixture of *X* volumes of dioxane with (100 − *X*) volumes of water taken at room temperature is implied. For determination of solvent deuterium isotope effects, however, care was taken to ensure that the deuterium-containing solvent contained the same molar proportion of D_2O as the proton-containing solvent had of H_2O.

2,6-Dibromo-4-methylphenol was prepared by dibromination of 4-methylphenol in acetic acid containing 20% water. The product was recovered and recrystallized from light petroleum; m.p. 46 °C (lit.,[14] 48 °C). When 2,6-dibromo-4-methylphenol (9.6 g) in dry CCl_4 (175 cm^3) was stirred with bromine (11.5 g) under strong illumination, reaction appeared to be complete after 2 h. The solvent was removed under reduced pressure to give 2,6-dibromo-4-dibromomethylphenol (1) as a crystalline solid, which was recrystallized from n-hexane to give 12 g (79%) of needles, m.p. 98—99 °C (lit.,[9] 98—101.5 °C). This compound, though sensitive to moisture, could be stored satisfactorily in a desiccator [Found: C, 20.0; H, 1.2; Br, 75.7; *M* (by titration), 422. $C_7H_4Br_4O$ requires C, 19.8; H, 0.95; Br, 75.4%; *M*, 424]. Its ^1H n.m.r. spectrum (CCl_4) had signals at δ 5.90 (s, 1 H, OH), 6.43 (s, 1 H, $CHBr_2$), 7.66 (s, 2 H, ArH).

Conversion of this into its methyl ether was carried out by treating it (12 g) with an excess of diazomethane, prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide in a conventional way.[15] Acetic acid (5 cm^3) was added to destroy the excess of diazomethane. Benzene was then added and evaporated off to remove traces of acetic acid. The residual oil was triturated with cold n-hexane, when it solidified and could be recrystallized from light petroleum (b.p. 30—40 °C) to give 2,6-dibromo-4-dibromomethylmethoxybenzene, m.p. 61—65 °C (lit.,[9] 60—64 °C). Its ^1H n.m.r. spectrum (CCl_4) had signals at δ 3.83 (s, 3 H, OMe), 6.36 (s, 1 H, $CHBr_2$), 7.55 (s, 2 H, ArH).

2,6-Dibromo-4-bromomethylenecyclohexa-2,5-dienone (2) when in solution reacts very rapidly with water, but it can be prepared easily by Lindemann's method.[9] Typically, a solution of 2,6-dibromo-4-dibromomethylphenol (1.4 g) in cold ether (5 cm^3) was shaken vigorously with aqueous NaOAc (10 cm^3, 2M) for 30 s. The product formed immediately and was filtered off, washed with water, and dried *in vacuo* (P_2O_5) for 3 h. Recrystallization ($CHCl_3$) gave 0.89 g of yellow-orange needles, m.p. 121 °C (decomp.) [lit.,[9] 120 °C (decomp.)]. Its ^1H n.m.r. spectrum ($CDCl_3$) had signals at δ 7.48 (d of d, *J* 0.86 and 0.61 Hz), 7.61 (d of d, *J* 2.44 and 0.61 Hz), 8.09 (d of d, *J* 2.4 and 0.86 Hz). Assignment is considered in the Discussion section, in conjunction with the characteristics of the corresponding ^{13}C n.m.r. spectra which were determined by using the JEOL FX60 spectrometer, Me_4Si being used as internal reference. Details of these spectra are recorded in Table 1. Because of the low solubility of this quinone methide in suitable inert solvents, we were unable to obtain a satisfactory single-resonance spectrum.

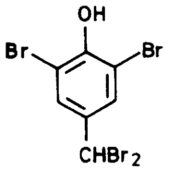
3,5-Dibromo-4-hydroxybenzaldehyde (3) was prepared by treatment of 4-hydroxybenzaldehyde with the required amount of bromine in 80% acetic acid. Water was then added and the product was filtered off and recrystallized from 50% aqueous ethanol; m.p. 183 °C (lit.,[9] 185 °C). Its ^1H n.m.r. spectrum [$(CD_3)_2CO$] had signals at δ 8.08 (s, 2 H, ArH), 9.80 (s, 1 H, CHO).

This was converted into its sodium salt by warming and shaking it with an excess of aqueous NaOH (2M) for 5 min. The salt was filtered off, washed (EtOH), dried *in vacuo*, and stirred with Me_2SO_4, the mixture being heated to 100 °C. Aqueous NaOH (20%) was then added and the mixture was

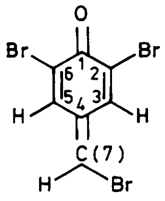
Table 1. ^{13}C N.m.r. spectra of 2,6-dibromo-4-bromomethylenecyclohexa-2,5-dienone[a] in $(CDCl_2)_2$. Results show the multiplicity in spectrum determined with decoupling indicated

		High-power single-frequency[c] on proton at δ			
δ[b]	Single frequency off-resonance	8.09 H(3)	7.61 H(5)	7.48 H(7)	Probable assignment
173.17	s	*d*	*d*	*d*	C(1)
139.21	d	d	s	s	C(5)
135.90	d	d[e]	d	d	C(3)
135.71	s	s	s	s	C(2), (4), or (6)
130.31	d	d	d (broad)	s	C(7)
127.33	s	s	s	s	C(2), (4), or (6)
122.72	s	s	s	s	C(2), (4), or (6)

[a] Numbering as in (2). [b] Signal position (δ, p.p.m. downfield from Me_4Si) in proton- and noise-decoupled spectrum. [c] Spectra were of weak intensity and rather poor resolution. [d] Signals were too weak to be detected. [e] Splitting was conspicuously smaller than when irradiation was on either of the other two protons.



(1)



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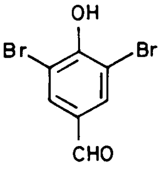


(3)

heated for 15 min. 3,5-Dibromo-4-methoxybenzaldehyde separated as a solid and was recrystallized from n-hexane to give plates, m.p. 87—88 °C (lit.,[9] 82—86 °C). Its ^1H n.m.r. spectrum (CCl_4) had signals at δ 3.97 (s, 3 H, OMe), 7.90 (s, 2 H, ArH), 9.70 (s, 1 H, CHO).

(b) *Kinetic Measurements*.—Rates of hydrolysis were determined spectrophotometrically at 34 °C. Known volumes (2.5 cm^3) of the freshly prepared solvent containing the necessary added electrolytes were allowed to equilibrate at 34 °C in cells in the spectrophotometer. Reaction was started by injecting into the cell by means of a syringe *ca.* 0.01 cm^3 of a solution of the required substrate in anhydrous dioxane. The cell was shaken, and absorbance readings were begun typically after 2 min. Concentrations of substrate after mixing were usually near to 1×10^{-4} mol l^{-1}. The change in solvent composition and concentration produced by adding 0.01 cm^3 to 2.5 cm^3 was neglected; it was very nearly constant throughout our comparisons.

Reference spectra from which concentrations could be calculated were determined for (1) and (2) in anhydrous dioxane; measurements could not be made in an aqueous solvent because hydrolysis was so rapid, but it was considered that any effect of change in solvent on the extinction coefficients for these compounds could be neglected. The spectrum of the aldehyde (3) was determined in 95% dioxane containing $>10^{-4}$M-$HClO_4$; at acidities less than this, the spectrum of (3) showed slight changes consistent with the presence of its phenoxide ion, but this did not result in any difficulty in the spectrophotometric rate-measurements, almost all of which involved initial acidities greater than 10^{-4}M.

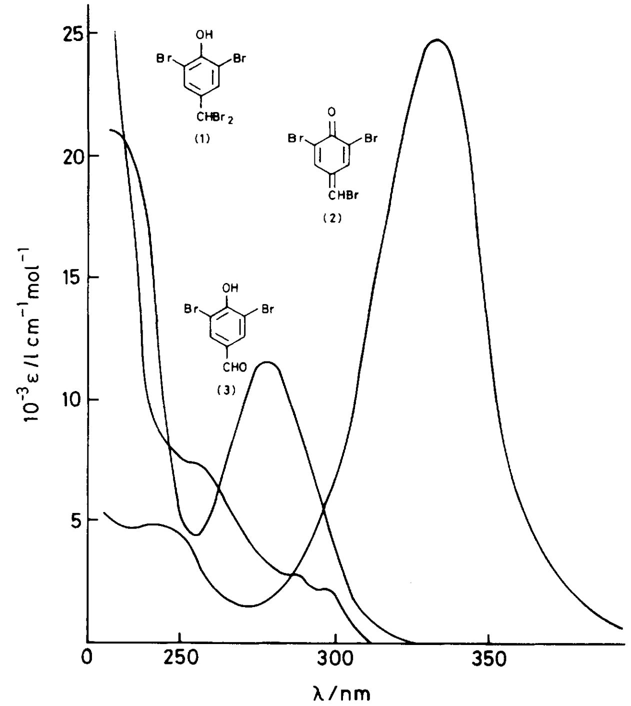


Figure 1. U.v. spectra of (1) and (2) in dioxane and of (3) in 95% dioxane

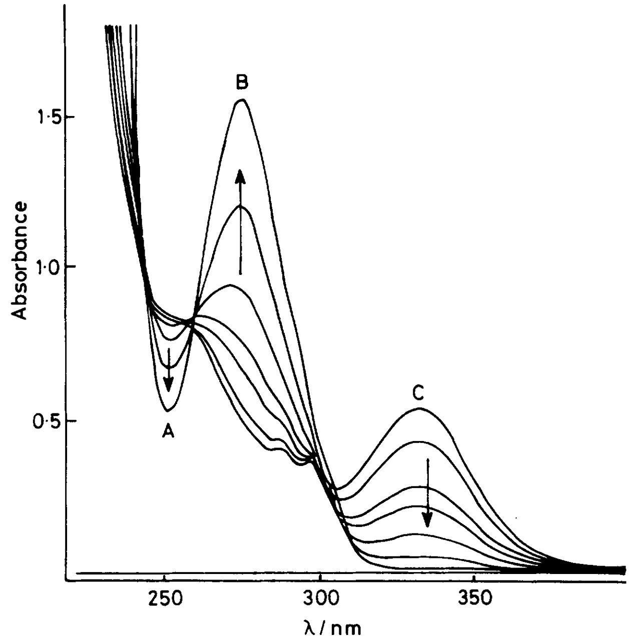


Figure 2. Successive u.v. spectra for solvolysis of 2,6-dibromo-4-dibromomethylphenol in 95% dioxane at 34 °C, with $H^+ = 8.308 \times 10^{-3}$M and ionic strength 2.00×10^{-2}M.

First scan, *t* = 10 min; final scan, *t* = 400 min. A, Starting material disappearing; B, aldehyde forming; and C, quinone methide formed rapidly before first scan, now disappearing

The u.v. spectra of the components of the reaction mixture are shown in Figure 1, from which it is clear that all three can be expected to be recognizable in mixtures, having maxima at well separated wavelengths. Figure 2 shows successive u.v. spectra for solvolysis of 2,6-dibromo-4-dibromomethylphenol

Table 2. Course of the reaction of 2,6-dibromo-4-dibromomethylphenol (1) with water in 95% dioxane at 34 °C, with initial ionic strength ($LiClO_4$), 2 × 10^{-2}M and $[H^+]_0$ = 8.308 × 10^{-3}M

t/min	10^5-[$CHBr_2$]/ M	10^5-[=CHBr]/ M	10^5-[CHO]/ M	10^5-$[Br^-]_{st}$ [a]/ M	10^5-$[H^+]_{st}$ [b]/ M
3.5	10.52	2.431	0.865 [c]	4.161	835.0
5	10.48	2.208	1.145	4.498	835.3
7	10.43	1.965	1.461	4.887	835.7
9	10.33	1.770	1.761	5.292	836.1
12	10.18	1.551	2.159	5.869	836.7
15	10.01	1.380	2.501	6.382	837.2
19	9.792	1.209	2.909	7.027	837.8
24	9.518	1.051	3.359	7.769	838.6
30	9.190	0.912	3.839	8.590	839.4
36	8.913	0.806	4.239	9.284	840.1
43.5	8.582	0.708	4.679	10.065	840.9
50	8.303	0.643	5.039	10.721	841.5
58	8.008	0.578	5.404	11.386	842.2
69	7.623	0.504	5.892	12.288	843.1
80	7.260	0.451	6.318	13.087	843.9
95	6.844	0.393	6.821	14.035	844.8
105	6.595	0.360	7.116	14.592	845.4
123	6.167	0.315	7.603	15.521	846.3
178	5.128	0.224	8.788	17.800	848.6
244	4.194	0.161	9.826	19.813	850.6
304	3.556	0.141	10.55	21.240	852.0
355	3.118	0.102	11.04 [c]	22.182	853.0

[a] $[Br^-]_{st}$ = [=CHBr] + 2[CHO] from the stoicheiometry of the hydrolysis. [b] $[H^+]_{st} = [H^+]_0 + [Br^-]_{st}$. [c] The total apparent concentration of the three components varied only slightly through the course of the run; the slight apparent rise, from 13.816 × 10^{-5} to 14.250 × 10^{-5}M, probably can be attributed to experimental error.

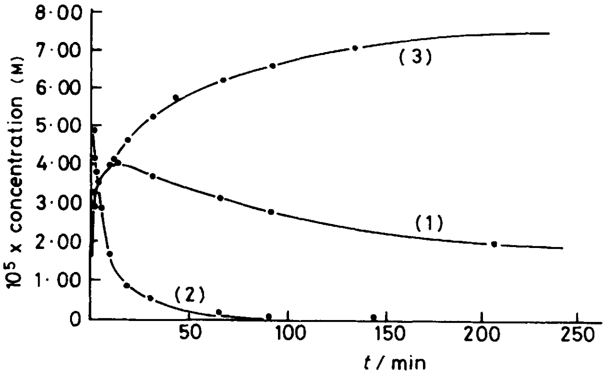


Figure 3. Course of the reaction of 2,6-dibromo-4-bromomethylenecyclohexa-2,5-dienone (2) (initially 9.5 × 10^{-5}M) with water in 95% dioxane at 34 °C with $HClO_4$ = 8.308 × 10^{-3}M and initial ionic strength, 2.00 × 10^{-2}M. (1), Dibromomethylphenol; (3), aldehyde

Table 3. Values of $k_{1\,(av.)}$ as a function of stoicheiometric concentration of hydrogen ion, $[H^+]_{st}$ for hydrolysis of (1) in 95% dioxane (ionic strength, 7 × 10^{-3}M) at 34 °C

$10^4[H^+{}_0]_{st}$/M [a]	$10^4[H^+]_{st,av.}$/M [b]	$10^3k_{1\,(av.)}$/min^{-1}
0	2.30	10.42
2.99	4.85	6.40
11.96	13.4	3.65
29.90	31.4	2.37
44.85	46.2	2.05
59.80	61.0	1.95

[a] Initial stoicheiometric concentration of $[H^+]$. [b] Average stoicheiometric concentration of H^+, taking into account HBr produced during the reaction.

Table 4. Dependence of $k_{1\,(av.)}$ on concentration of bromide ion for hydrolysis of (1) in 95% dioxane (ionic strength, 2.00 × 10^{-2}M) at 34 °C with $HClO_4$ = 8.3 × 10^{-3}M

$10^4[Br_0]$/M	$10^4[Br^-]_{av.}$/M	$10^4k_{1\,av.,\,OH}$/min^{-1}
0	1.60	33.8
1.75	3.05	19.3
3.51	4.61	11.0
7.02	7.83	7.07
14.04	14.60	4.10
24.57	24.90	2.46
28.08	28.50	2.34

(1) in 95% dioxane at 34 °C. These results show that the quinone methide (2) is formed initially very rapidly from (1), and that gradually both of these compounds are transformed into the aldehyde (3). The fact that successive scans pass only approximately through isosbestic points shows that (1) and (2) are not in constant ratio through the course of the measured reaction. No indication was found in these spectra for the presence of species other than (1), (2), and (3).

Kinetics of the reaction were then followed by monitoring the changes in absorbance at three wavelengths: 335, 275, and 250 nm. Ideally, these should have been recorded simultaneously at each time. This was not possible; instead, readings were taken in succession within an interval of not more than 8 s. The reactions were sufficiently slow that the error resulting from this procedure was very slight.

In Table 2, the symbols [$CHBr_2$], [=CHBr], and [CHO] are used to represent the concentrations of (1), (2), and (3), respectively, and values of the stoicheiometric concentrations of bromide ion ($[Br^-]_{st}$) and of acid ($[H^+]_{st}$) are tabulated also. This Table shows the course of reaction observed for the solvolysis of (1) at constant ionic strength and an excess of added perchloric acid, but with no added bromide ion. Under these circumstances the initial reaction, in which the quinone methide (2) is formed from the starting material, is associated with rapidly changing concentration of acid and of bromide ion. This part of the reaction, which could also be affected by incomplete mixing, is not able to be analysed kinetically from the results of a single run; but some further characteristics of the reaction can be deduced from Figure 3, which shows the course taken by the hydrolysis of the quinone methide (2) under initially similar conditions. Despite the fact that no bromide ion is present initially, a very rapid build-up of 2,6-dibromo-4-dibromomethylphenol is observed. Hydrogen bromide produced by hydrolysis must therefore add very rapidly to the quinone methide.

The values of the first-order rate-coefficients calculated on the disappearance of [$CHBr_2$] fell as the reaction proceeded, as would be expected for an ionisation of a neutral molecule subject to a substantial mass-law effect. Over a good part of the reaction, the fall was nearly linear; so to establish the effect of change in acidity and in bromide ion on this rate, we estimated for each run the average first-order rate-coefficient, k_1, corresponding with an average concentration of acid or of bromide ion. The results are shown in Tables 3 and 4.

With increasing acidity, k_1 is reduced, tending asymptotically to a non-zero value (Figure 4). Equation (2) fits the experimental values satisfactorily, as is shown by Figure 5 in

$$k_{1\,(av.)}/\text{min}^{-1} = 1.57 \times 10^{-3} + 2.37 \times 10^{-6}\,\text{mol l}^{-1}/[H^+] \quad (2)$$

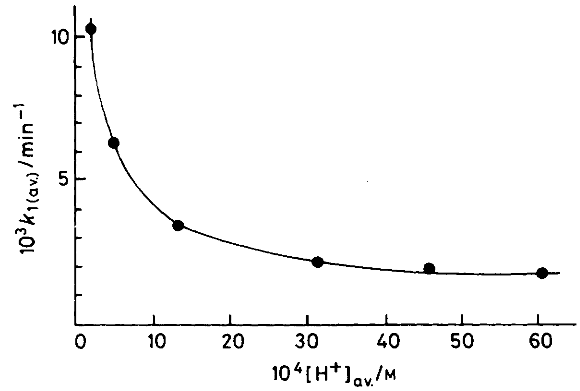


Figure 4. Dependence of the rate-coefficient for the hydrolysis of (1) on acidity (results of Table 3)

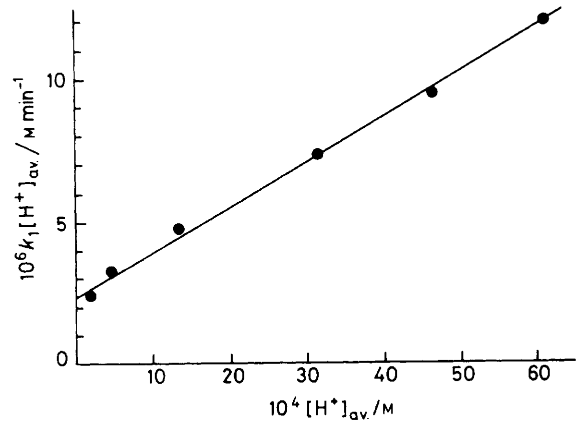


Figure 5. Plot of $k_{1\,(av.)}[H^+]_{av.}$ against $[H^+]_{av.}$ for the hydrolysis of (1) (results of Table 3)

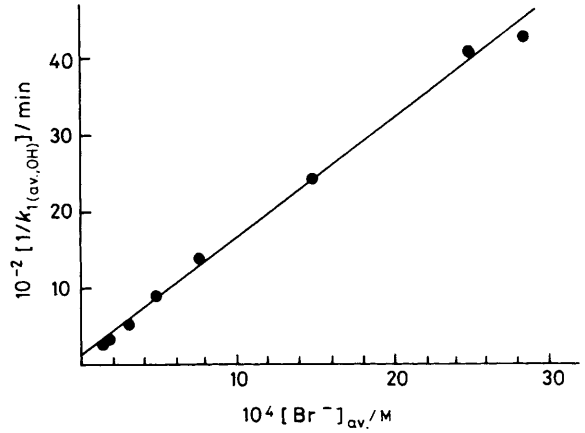


Figure 6. Plot of $1/k_{1\,(av.,\,OH)}$ against $[Br^-]_{av.}$ for the hydrolysis of (1) (results of Table 4)

Table 5. Effect of solvent on the course of solvolysis of (1), with added acid sufficient to suppress most of reaction through the phenoxide ion

H_2O (%)	$10^3[H^+]_0$/M	$10^3k_{1\,(av.)}$/min^{-1}	k^{II}/min^{-1}
5	3.3	1.7	0.03
8	4.8	15	0.12
10	6.0	37	0.20

which the equation has been transformed to put it into a linear form. The second term represents the rate of reaction through the phenoxide ion, present in small concentration, which is reduced with increased acidity. The first term is the average rate-coefficient, $k_{1\,(av.,\,OH)}$, for reaction through the phenol molecule under the average conditions of the run. It is reduced from its initial value by the mass-law effect of the bromide ion developing during the reaction. The effect of bromide ion was studied separately by varying its initial concentration, sufficiently high acidity being used to ensure that any reaction through the phenoxide ion was minimal. Under these circumstances, the dependence of the observed rate-coefficient, $k_{obs.}$, on $[Br^-]$ should be of the form shown in equation (3). The appropriate plot from which the parameters

$$k_{obs.} = k_{1\,(av.,\,OH)} = k_{1\,(OH)}/(\alpha[Br^-] + 1) \qquad (3)$$

of equation (3) can be obtained is shown in Figure 6. The initial rate could then be evaluated by extrapolating the results to zero bromide ion concentration. The result gives $k_{1\,(OH)} = 8.13 \times 10^{-3}$ min^{-1}, with the mass-law constant α = 12 400 l mol^{-1}. A concurrent, but in our view slightly less accurate, estimate could be obtained by extrapolating to zero time the results of a single kinetic run with no bromide ion added initially.

In order to measure a solvent deuterium isotope effect for this reaction, slightly different conditions had to be chosen in order that we could ensure that the final solvents used for the comparison contained the same molar proportions of H_2O and D_2O, and that the ionic strengths of the solution were the same. We chose the reaction at 34 °C with $HClO_4$ or $DClO_4$ 1.612×10^{-2}M, H_2O or D_2O 2.78M (*ca.* 5% v/v); the deuteriated solvent contained at least 98% of the aqueous component with D rather than H. The resulting rate-ratio, k_{H_2O}/k_{D_2O}, taken as an ' average ' rate-coefficient over a single run extending over the same proportion of the reaction, was 1.97; as a value extrapolated to $[Br^-] = 0$, the ratio was 1.90. The mass-law constant was slightly larger in the solvent containing D_2O than in the solvent containing H_2O.

The aldehyde formed as the final product of the reaction is derived mainly from the quinone methide. Consequently, the rate of this final stage of the reaction could be evaluated from successive values of [CHO] and [=CHBr] by using equation (4), in which $[=CHBr]_{av.}$ is the mean value of [=CHBr] in the interval Δt. These values were always substantially constant

$$k^{II} = \frac{1}{[=CHBr]_{av.}}\,\frac{\Delta[CHO]}{\Delta t} \qquad (4)$$

through the course of the reaction; for example from the results given in Table 2, successive values vary only over the range k^{II} = 0.076—0.082 (mean 0.080) min^{-1}, with no discernible trend as the reaction proceeded. They increased a little with increasing concentration of acid, being fitted by equation (5). They were essentially independent of the concentration of bromide ion, and at high acidity ($[HClO_4] = 1.61 \times 10^{-2}$M) showed a small inverse solvent deuterium isotope effect (k_{H_2O}/k_{D_2O} = 0.86).

$$k^{II}/\text{min}^{-1} = 0.0385 + 3.09[H^+]_{av.} \qquad (5)$$

The effect of change in solvent on the course and rate of reaction was examined only in preliminary experiments in which the ionic strength was not kept constant. Table 5 shows the results. These results, being composite of reaction through phenoxide ion and phenol, are quoted only to show that the rates of solvolyses are affected by solvent in the expected direction.

The conversion of 2,6-dibromo-4-dibromomethylanisole into 3,5-dibromo-4-methoxybenzaldehyde was very slow. An attempt was made to monitor the reaction of the anisole (0.550 g) in a solvent mixture of $(CD_3)_2CO$ (3.5 cm^3) and D_2O (1.0 g) at 34 °C by using the development of the ^1H n.m.r. signal for the aldehyde at δ 9.70. No signal in this region was detected until reaction had proceeded for 18 days, when no more than 3.5% of the starting material had been converted into aldehyde.

Discussion

The results presented in the tables show that in terms of stoicheiometry the reaction follows a relatively simple course, in which the dibromomethylphenol (1) is first converted into a mixture of this and the quinone methide (2), and that this mixture is then converted by a process of similar rate into the aldehyde (3). Kinetic analysis is made complicated by the fact that the rates of most of the processes concerned are affected by the concurrent development of $[H^+]$ and of $[Br^-]$; initial rates at zero and at high $[H^+]$ and at zero $[Br^-]$ need to be sought, and for the latter the extrapolation is longer than would be desired.

For the first stage of the reaction, the effect of acidity on the rate establishes that two pathways are followed. The first involves the rapid reversible loss of a proton from the phenol (1) followed by rate-determining loss of bromide to give the quinone methide (2), as in the central pathway in Scheme 1. This reaction is naturally inhibited by acid, and its contribution is reduced to zero at high acidity. If the dissociation constant of the phenol (1) in 95% dioxane were known, the observed rate of this reaction at low acidity could be used to determine the effect of the O^- group on the rate of solvolysis of the 2,6-dibromo-4-dibromomethylphenol, and hence by an appropriate comparison to estimate the σ^+ value for the O^- group. Discussion of this point is deferred.

In the second reaction, dominant at high acidity ($>10^{-3}$M), the hydroxylic proton is still present in the transition state, as would be consistent either with concerted loss of H^+ and Br^- (as in the top pathway in Scheme 1) or with reaction through an intermediate carbocation (as in the bottom route in Scheme 1). The form of the combined dependence of rate on bromide ion and on acid shows that it is the latter pathway which makes the major contribution (Figure 6). Thus a powerful mass-law effect of developing or added bromide ion is observed, even at acidities at which the rate has become nearly independent of the acidity.

The solvent deuterium isotope effect on the rate of the first stage of solvolysis ($k_1^{H_2O}/k_1^{D_2O} = 1.9$) is probably more consistent with reaction through an intermediate carbocation than with concerted loss of H^+ and Br^-. For the concerted reaction, a larger isotope effect would be expected, associated with breaking of the OH bond in the rate-determining step. The relatively small observed value can be attributed to a secondary effect of H–O hyperconjugation.[10,16] It is very similar to the effect found in the bromination of phenol,[16] and attributed similarly. The magnitude is rather greater than is customarily found for the hyperconjugative effect of one H–C bond,[17] as seems reasonable because of the greater extent of hydrogen-bonding by H–O than by H–C protons.

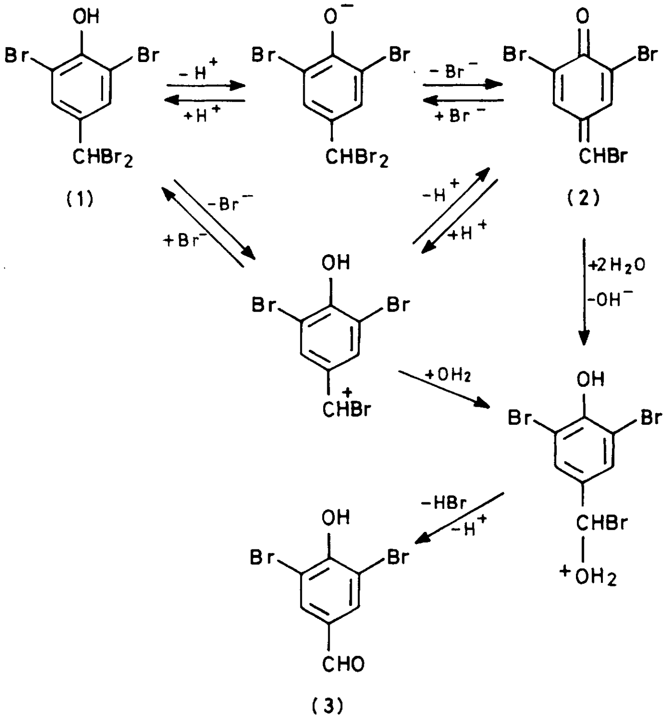
The back-reaction of the quinone methide with bromide ion is evidently very rapid. The mass-law constant for the solvolysis, which gives the ratio of overall forward reaction to recapture of bromide ion, was found to be very large (12 400 l mol^{-1}), under the conditions used for most of the measurements, and varied markedly with the ionic strength. It appeared to be subject to a reverse deuterium isotope effect ($\alpha_{H_2O}/\alpha_{D_2O} = 0.87$), as is consistent with a major component of reaction of the quinone methide (3) requiring a pre-equilibrium protonation before recapture by bromide ion.

It is qualitatively reasonable that the mass-law constant for the observed reaction should be high. The magnitude of this quantity has been taken[18] to reflect the stability of the carbocation on the basis of the principle that the longer its lifetime, the higher its selectivity should be in discriminating between two nucleophilic species. Thus for the hydrolysis of 4-dichloromethylmethoxybenzene in 83% acetone,[4] α is *ca.* 130 l mol^{-1}, whilst for chlorobis-(*p*-methoxyphenyl)methane,[19] with a more stabilized carbocation, α is 3 700 l mol^{-1}. In the present case, the carbocation is undoubtedly greatly stabilized; its back-reaction with bromide ion is in competition not only with capture by the solvent but also with proton-loss. Additionally, the fact that the solvent contains little water, and so may make much less than usual contribution to the solvation shell of the carbocation, may be a further factor in making the capture of the carbocation by bromide ion so unusually large.

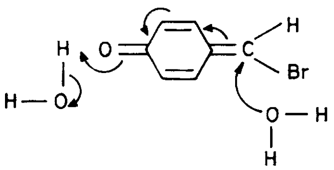
The mechanism of the final stage of the reaction, in which the mixture of quinone methide (2) and dibromomethylphenol (1) is converted into the aldehyde, has been studied only in outline. It includes a non-acid-catalysed component and an acid-catalysed process, which contributes about 60% to the total rate at the concentration of acid at which the solvent deuterium isotope effect was measured and found to be small and inverse ($k_{H_2O}^{II}/k_{D_2O}^{II} = 0.86$). The non-acid-catalysed reaction probably involves the concerted action of two water molecules (structure 4), having a normal solvent deuterium isotope effect, whilst the acid-catalysed component involves at least in part a pre-equilibrium formation of the carbocation. The overall reaction path, therefore, should be described according to Scheme 2. Evidence supporting this picture has been adduced for the acid-catalysed hydration of other quinone methides. In particular, Velek *et al.*[20] concluded that a route other than one involving a proton pre-equilibrium was involved in the hydration of (5) in water under acidic conditions, since the kinetic form of the reaction implicated general-acid catalysis.

Reactivity of the Phenol.—The expected rate of solvolysis of 2,6-dibromo-4-dibromomethylphenol can be estimated approximately by using calculations based on linear free-energy relationships and the additivity principle. The value of k_1 for $PhCHBr_2$ in 60% acetone at 25 °C is known[6] to be 8.3×10^{-5} min^{-1}, and the value of ρ for this system obtained by using the equation $\log_{10}(k/k_H) = \rho\sigma^+$ is -6.0 by comparison of the rates of solvolysis of this and its *p*-methyl derivative. Then by using the conventional values[21] $\sigma_{m\text{-}Br}^+ = +0.37$, $\sigma_{p\text{-}OH}^+ = 0.92$, we can estimate $\log_{10}k_1$ for (1) in 60% acetone at 25 °C as $-4.08 + [-6.0(0.74 - 0.92)] = -3.0$.

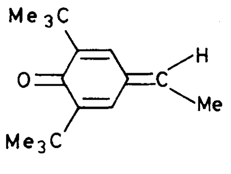
We must now correct for the solvent by using the trends of values of the solvent parameter, Y, with solvent composition, and the equation $\log_{10}k_s - \log_{10}k_{s'} = Y_s - Y_{s'}$. Values of $Y = -2.93$ for 95% dioxane and 0.80 for 60% acetone seem reasonable,[22] though the former involves considerable extrapolation. The expected rate in 95% dioxane at 25 °C would then be about 2×10^{-7} min^{-1}; and at 34 °C we could expect $k_1 = ca.\ 6 \times 10^{-7}$ min^{-1}. The observed rate, 1.7×10^{-3} min^{-1} (Table 5) is at least 10^3 times faster than this. Although the estimated value is subject to many uncertainties, the discrepancy is sufficiently great to warrant further consideration, which is deferred for comparison with the corresponding



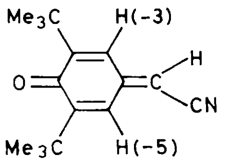
Scheme 2. Intermediates and reactions in the solvolysis of 2,6-dibromo-4-dibromomethylphenol, and in the hydration of 2,6-dibromo-4-bromomethylenecyclohexa-2,5-dienone



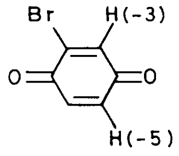
(4)



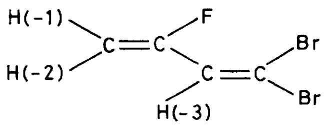
(5)



(6)

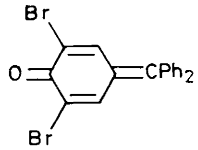


(7)



(8)

(9)



(10)

reaction of 2-bromo-4-dibromomethylphenol and its methyl ether.

N.m.r. Spectra.—Relatively few spectra of quinone methides have been recorded. The assignment of the three coupling constants apparent in the ^{1}H spectrum of (2) is not possible from the spectrum, but can be made by comparison with known analogues. Thus for (6),[23] $^4J_{\text{H-3,H-5}} = 2.4$ Hz, whilst for (7) [24] the value is 2.5 Hz. So the largest coupling constant of 2.44 Hz observed in the spectrum of (2) between the signals at δ 8.09 (' downfield ') and δ 7.61 (' middle ') protons almost certainly corresponds to this coupling. This means that the δ 7.48 (' upfield ') signal is that of H-7.

Distinction between H-3 and H-5 is a little more uncertain. Bothner-By and Koster [25] have reported values for $J_{1,3}$ and $J_{2,3}$ in the butadiene (8) of +0.54 and −0.31 Hz, respectively, whilst Lambert *et al.*[26] have shown that for various 1,3-dienes constrained in the s-*cis*-conformation (9) $|J_{1,2}|$ lies in the range 0.8—1.1 Hz. These results suggest that, of the two as yet unassigned coupling constants for (2), the larger (*viz.* 0.86 Hz), which is observed between the upfield and downfield protons, arises from the coupling of H-7 with H-3. The smaller value would then correspond with the coupling of H-7 with H-5. The signals then can be assigned as H-7, δ 7.48; H-5, probably δ 7.61; H-3, probably δ 8.09.

The noise-decoupled ^{13}C n.m.r. spectrum of (2) comprised seven distinct signals (Table 1), one of which can be assigned immediately to the carbonyl carbon (δ = 173.2). In the related molecule (10), the corresponding resonance [27] was at δ 174.6. The remaining signals for (2) fall in the expected range δ = 120—140, and those of the fully substituted carbons can be distinguished as shown in Table 1 from those carrying hydrogen atoms by their multiplicity in the single-frequency off-resonance decoupled spectrum. High-power irradiation at the frequencies of the three proton resonances selectively collapsed each of these doublets in turn; and, despite the weak intensity and poor resolution of the spectra, it was possible to identify in each case just one signal which collapsed most convincingly into a singlet. The assignment given in the table followed from these experiments.

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